METHODOLOGICAL GAPS IN GUIDELINES AND ADVANCING EVIDENCE SYNTHESIS

IDENTIFYING METHODOLOGICAL GAPS IN TREATMENT GUIDELINES AND ADVANCING EVIDENCE SYNTHESIS FOR EMPIRIC TREATMENT OF HOSPITAL- AND COMMUNITY-ACQUIRED PNEUMONIA

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A Thesis Submitted to the School of Graduate Studies in Partial Fulfilment of the Requirements for the Degree Doctor of Philosophy

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Abstract

Clinical practice guidelines provide recommendations to help clinicians, patients, and other relevant stakeholders make appropriate healthcare-related decisions. The Institute of Medicine (IOM) in 2011 proposed standards for developing trustworthy guidelines. Whether the trustworthiness of guidelines has improved since the release of IOM remains uncertain. In this thesis to address this question, we conducted a systematic survey comparing trustworthiness of guidelines released before versus after the introduction of IOM. We faced important challenges in assessing trustworthiness of guidelines in this study, as the available instrument – the National Guideline Clearinghouse Extent of Adherence to Trustworthy Standards (NEATS) – to evaluate adherence of guidelines to the IOM trustworthiness standards has limitations in addressing methodological quality of the guideline development process and lacks explicit instruction for reproducible assessments. To overcome these limitations, we developed modifications to the instrument and applied the modified NEATS instrument to assess trustworthiness of guidelines in our systematic survey.

The findings of our systematic survey revealed that adherence of post-IOM guidelines to the standards of systematic review of evidence, which is a crucial step in informing guideline recommendations, is suboptimal. This departure from the trustworthiness standards can be a source of conflicting guideline recommendations which is evident among guidelines developed to guide antibiotic selection for empiric management of non-ventilator-associated hospital-acquired pneumonia (HAP) and moderate to severe community-acquired pneumonia (CAP). Therefore, in subsequent

chapters of this thesis, we present two systematic reviews with network meta-analyses that adhere to the trustworthiness standards and address limitations in the existing evidence synthesis for antibiotics used in the empiric treatment of HAP and moderate to severe CAP.

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Declaration of Academic Achievement

This thesis is a "sandwich thesis" comprised of four individual projects published or submitted for publication in peer-reviewed journals. I am the principal contributor and first author of all the manuscripts contained in this dissertation.

Chapter 1 is unpublished. MG is the sole author.

Chapter 2 is published in the Journal of Clinical Epidemiology (pre-proof as of September 12, 2025). MG, GG, and RBP conceived and designed the study. MG, RC, CZ, JPL, SG, HM, WT, GBS, SM, HG, and NB identified and selected guidelines. MG, CZ, JPL, SG, HM, WT, GBS, SM, HG, and YS extracted data and assessed trustworthiness of the guidelines. MG analyzed the data. MG, GG, and RBP interpreted the results. MG drafted the manuscript. GG and RBP critically revised the manuscript. All authors reviewed and approved the final version of the manuscript.

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Chapter 1: Introduction of the thesis

Clinical practice guidelines, the end products of the knowledge creation funnel [1], provide recommendations to help clinicians, patients, and other relevant stakeholders make appropriate healthcare-related decisions [2]. The development of guidelines dates back to the 1970s when solely expert opinions informed recommendations [3]. The emergence of evidence-based medicine in the 1990s shifted the guideline development process toward basing recommendations on the available evidence of the balance of benefits and harms, as well as a host of other factors [4]. In the subsequent years, to improve the rigor of the guideline development process, clinical epidemiologists have produced a large body of guidance documents [2, 5-9]. The standards proposed in 2011 by the Institute of Medicine (IOM) have been among the key guides for developing trustworthy guidelines [2].

According to the IOM [2], a trustworthy guideline is developed by a multidisciplinary unconflicted panel who, using a rigorous systematic review of the available evidence and considering the trade-off of benefits and harms, certainty of the evidence, and value and preference of patients, formulates explicit and actionable recommendations [2]. A trustworthy guideline also undergoes external review by relevant stakeholders, presents a detailed plan for updating, and provides a transparent description of the development process and funding sources [2].

As guidelines can impact patient outcomes [10-12], an appropriate guideline development process has the potential to improve health outcomes, while untrustworthy guidelines can adversely affect patient care and resource use. Unfortunately, only a few guidelines that were published before the release of IOM adhered to the trustworthiness standards [13]. While the Trip Medical database [14] indexed 1,633 guidelines from pre-

IOM standards, this number increased to over 10,000 in the post-IOM era. This remarkable increase in the production of guidelines suggests an increased utility and thus profound influence guidelines can have on current clinical practice. However, whether post-IOM guidelines performed better than pre-IOM guidelines with respect to trustworthiness remains uncertain.

Chapter 2 of this thesis describes how our team addressed this question, which is to what extent trustworthiness, defined as adherence to IOM standards [2], has improved since the introduction of IOM. In this systematic survey, we focused on treatment guidelines and explored the degree to which overall adherence of treatment guidelines to trustworthiness standards has improved after the introduction of IOM. Moreover, we examined whether the proportion of guidelines with high trustworthiness has increased from pre-IOM criteria. We further evaluated trustworthiness at the individual standard level and identified limitations of post-IOM guidelines in adherence to each trustworthiness standard.

During the conduct of this study, we faced methodological challenges in assessing trustworthiness of guidelines. The National Guideline Clearinghouse, in 2019, developed the NGC Extent of Adherence to Trustworthy Standards (NEATS) instrument to assess adherence of guidelines to the IOM standards [15]. In using this instrument, we identified two major limitations. First, for assessment of conflict of interest of guideline development group members, systematic review process, rating the strength of recommendations, and guideline updating plan, the NEATS instrument [15] focused on the reporting quality and did not cover the appropriateness of the process for the domain under evaluation as

indicated by IOM standards [2]. This shortcoming can undermine the validity of the measurements [16] as the conclusion of our study would reflect the change in reporting quality rather than trustworthiness for these domains. Second, the instructions for the assessment of items, particularly ones rated on the 5-point Likert scale, are inadequate, and thereby the evaluation of these items is more vulnerable to subjective judgments than would be the case with more explicit instructions. This would be a particular problem when users of the instrument do not have expertise in the guideline methodology, which was the case with many members of the team in our study.

To overcome these limitations, we developed modifications to the NEATS instrument, which Chapter 3 describes. Our modifications of the NEATS instrument aimed to address the appropriateness of the guideline development process and improve the reproducibility of trustworthiness assessment across a range of users' levels of expertise in guideline methodology. We used our modifications of the NEATS instrument for the assessment of trustworthiness of treatment guidelines in the systematic survey presented in Chapter 2.

As emphasized by IOM, a crucial step in developing guidelines is conducting a systematic review of the available evidence on benefits and harms of alternative care options [2]. The findings of our systematic survey, described in Chapter 2, highlighted that after the introduction of IOM standards, there has been an improvement in the methodology of systematic review of the evidence that informed treatment recommendations. However, the adherence of post-IOM guidelines to the standards of search strategy, study selection, and synthesis of studies included in the systematic review – as specified by the IOM

committee on Standards for Systematic Reviews of Comparative Effectiveness Research [17] – remains suboptimal. This departure from the trustworthy systematic review standards can be a source of conflicting guideline recommendations, which is not uncommon [18].

For example, there are multiple guidelines developed by major organizations to guide healthcare providers in antibiotic selection for empiric management of non-ventilator-associated hospital-acquired pneumonia (HAP) [19, 20] and moderate to severe community-acquired pneumonia (CAP) [21-23]. These guidelines, however, provide conflicting treatment recommendations. For example, the American Thoracic Society and Infectious Diseases Society of America recommend a later-generation cephalosporin or β-lactam/ β-lactamase inhibitor combined with a macrolide or monotherapy with fluoroquinolone for moderate severity CAP [21], while a European guideline recommends monotherapy with amoxicillin and avoiding broad-spectrum antibiotics [23].

Evaluating the systematic reviews conducted in these guidelines revealed several limitations, including non-comprehensive and outdated searches, inadequate definition of eligibility criteria that directed the study selection process, and lack of duplicate screening of retrieved studies. Moreover, these guidelines used systematic reviews with pairwise meta-analysis to inform their recommendations. When multiple antibiotic options exist, which most lack direct evidence of comparative effects, network meta-analysis (NMA) offers advantages over pairwise meta-analysis.

Pairwise meta-analysis addresses the relative benefits and harms of only one intervention versus another that have been directly compared in randomized controlled

trials (RCTs). NMA, in contrast, via one or more common comparators, allows estimation of indirect comparisons between interventions that have not been compared head to head in RCTs and thereby enables decision-makers to choose optimal care from all available therapeutic options [24]. Moreover, when direct evidence is available, NMA uses simultaneous analysis of direct and indirect evidence to inform the overall effect estimate. This may result in greater precision than that of direct evidence alone [25].

Chapters 4 and 5 describe the conduct of trustworthy systematic reviews and NMAs of randomized controlled trials to inform comparative effects of antibiotic regimens for the empiric therapy of adults with HAP or moderate to severe CAP.

Chapter 6 summarizes the methodological challenges we faced in the process of performing this thesis and discusses the strategies we implemented to address these challenges. We further elaborate on the strengths and limitations of this thesis and highlight implications for practice and future studies.

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Chapter 2: Trustworthiness of treatment clinical practice guidelines has modestly improved since the introduction of Institute of Medicine standards: a systematic survey

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Trustworthiness of treatment clinical practice guidelines has modestly improved since the introduction of Institute of Medicine standards: a systematic survey

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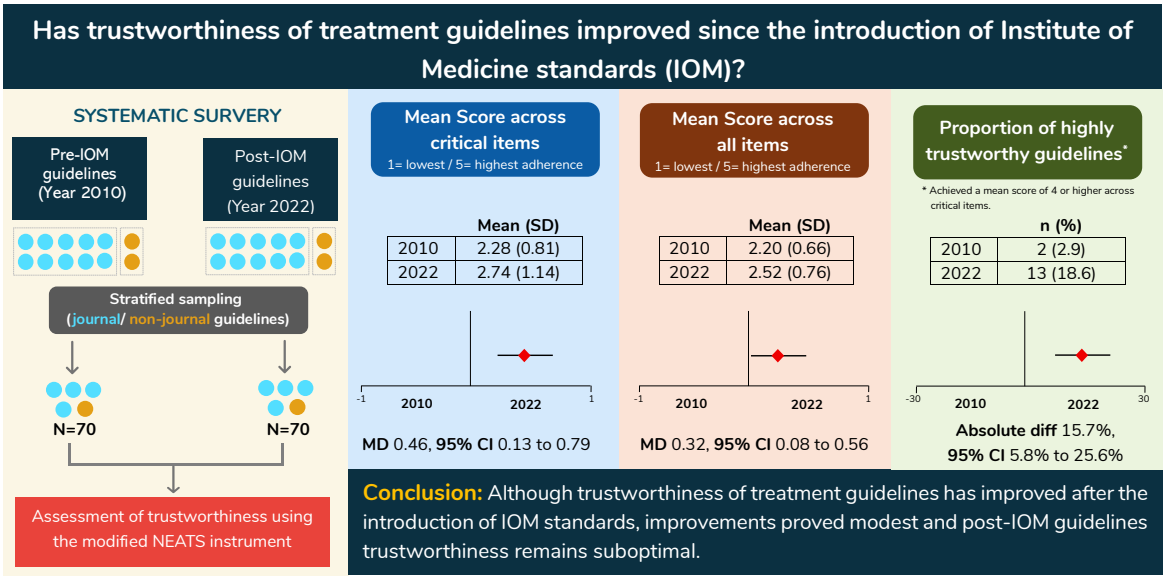
Graphical abstract



ABSTRACT

Objectives: To explore the extent to which trustworthiness of treatment guidelines has changed since the introduction of Institute of Medicine (IOM) standards.

Study Design and Setting: In this systematic survey, we searched Medline, Embase, PsycINFO, and Trip from January to December 2010 (pre-IOM) and 2022 (post-IOM) for guidelines that were informed by a systematic review of evidence, written in English, and included recommendations for treatment of any health conditions in individuals of any age. Using the 10-item modified National Guideline Clearinghouse Extent of Adherence to Trustworthy Standards (NEATS) instrument, paired reviewers independently assessed trustworthiness of 70 randomly selected guidelines from 2010 and 70 from 2022. We calculated mean difference (MD) and corresponding 95% confidence intervals (CI) comparing guidelines from 2010 with 2022 for mean score across four critical items, mean score across all items, and score of individual items on 5-point Likert scales in which 1 was least adherence and 5 highest adherence. We also explored change in the proportion of guidelines that achieved a mean score of 4 or higher across critical items.

Results: The average of mean scores increased from 2.28 to 2.74 (MD 0.46, 95% CI 0.13 to 0.79) across critical items and from 2.20 to 2.52 (MD 0.32, 95% CI 0.08 to 0.56) across all items. The proportion of guidelines with a mean score of 4 or higher across critical items increased from 2.9% to 18.6% (absolute difference: 15.7%, 95% CI: 5.8% to 25.6%). The items with greatest increase in the average score included disclosure of funding sources and disclosure and management of financial COIs, followed by smaller increase in

synthesis of evidence, study selection, and search strategy. Other items showed little to no change from 2010.

Conclusion: As assessed by the modified NEATS instrument, although trustworthiness of treatment guidelines has improved after the introduction of IOM standards, improvements proved modest and post-IOM guidelines trustworthiness remains suboptimal.

Keywords: Clinical practice guideline; Treatment; Trustworthiness; Methodological quality; IOM standards; Modified NEATS instrument

Running title: Trustworthiness of treatment guidelines

What is new?

Key findings

- This systematic survey found that despite a modest improvement in trustworthiness of treatment guidelines since the introduction of the Institute of Medicine (IOM) standards, post-IOM guidelines trustworthiness remains suboptimal.

What this adds to what was known?

- Evaluations of guidelines from pre-IOM standards reported most had major limitations particularly in addressing conflict of interests (COI), convening a multidisciplinary guideline panel, using a systematic review of evidence to inform recommendations, and rating the strength of recommendations.
- Studies on quality of post-IOM guidelines have reported mixed results, and no study has systematically addressed the extent of improved trustworthiness – if any – across a representative group of guidelines.
- This is the first systematic survey that across a representative group of guidelines addressed the extent to which trustworthiness of treatment guidelines has changed since the introduction of IOM standards.

What is the implication, what should change now?

- Findings from this study identify current methodological limitations in the guideline development process and may inform guideline developers regarding the steps that should be taken to improve the rigor of their process.

1. INTRODUCTION

Clinical practice guidelines are intended to aid decision-making and improve patient-important outcomes [1]. For optimal usefulness, the development of guidelines should implement rigorous methods, adhering to quality standards. In 2011, the Institute of Medicine (IOM) published standards for the development of trustworthy guidelines [1]. Based on IOM standards [1] a trustworthy guideline has an explicit disclosure of funding sources; is free from biases due to conflict of interests (COI) of members of the guideline development group (GDG); is developed by a guideline panel comprising relevant clinicians, methodological experts, and populations expected to be affected by the guideline; is informed by a systematic review of evidence that meets IOM standards for Systematic Reviews of Comparative Effectiveness Research [2]; provides an appropriate rating of the strength of recommendations; includes recommendations articulated in a clear standardized form; undergoes external review by relevant stakeholders; and presents adequate plans for updating.

Evaluations of guidelines from pre-IOM standards reported most had major limitations [3-7]. Fewer than half of the guidelines published between 2006 to 2011 met more than 50% of IOM standards with no apparent improvement over time [6]. The trustworthiness domains that suffered most frequently included addressing COIs, convening a multidisciplinary guideline panel, using a systematic review of evidence, and rating the strength of recommendations [3-7].

Since the introduction of IOM standards [1], over 9,000 guidelines have been released [8]. Studies on quality of post-IOM guidelines have reported mixed results [9-11],

and no study has systematically addressed the extent of improved trustworthiness – if any – across a representative group of guidelines. In this study, we therefore addressed the extent to which trustworthiness of guidelines as reflected in adherence to IOM standards has changed since their introduction.

2. METHODS

We conducted a systematic survey addressing trustworthiness of treatment guidelines released before versus after the introduction of IOM standards. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses that are relevant to this systematic survey [12].

2.1. Eligibility criteria

Eligible guidelines were written in English and included de novo or updated recommendations for pharmacologic or non-pharmacologic treatment of any health conditions in individuals of any age that were informed by a systematic review of evidence. To be identified as informed by a systematic review of evidence, guidelines met at least one of the following criteria: 1) explicitly stated that a systematic review of evidence informed the guideline; 2) presented a list of databases searched and search terms used; 3) described a study selection process that included number of studies identified through the search and number of studies included in the review; 4) provided a summary of inclusion and exclusion criteria; or 5) in the guideline development section, cited a methodology guidance paper that described conduct of a systematic review of evidence for developing guidelines. We excluded adaptation of existing guidelines.

2.2. Literature search

We searched Medline, Embase, and PsycINFO from January 2010 to December 2010 (pre-IOM), the year before IOM standards were published [1], and from January 2022 to December 2022 (post-IOM). An experienced health sciences librarian refined our search strategy for each database (Supplement 1). To identify guidelines that were not published in medical journals (i.e., only available through the guidelines developers' websites), we searched Trip database.

2.3. Sampling and guideline selection

Pairs of trained reviewers independently screened titles and abstracts, followed by full texts from the randomly ordered guidelines within each stratum of journal and non-journal guidelines, with disagreement adjudicated by a third reviewer (MG). We continued selection until we achieved the target sample size of 140 eligible guidelines which was determined based on feasibility considerations (70 from 2010 and 70 from 2022). Based on the proportion in each stratum in Trip database, 79% (n=55) of guidelines in each sample were published in journals and 21% (n=15) were from developers' websites.

2.4. Data extraction

Pairs of reviewers independently extracted data from each eligible guideline including country of origin, developing organization, population addressed, clinical condition (based on the International Classification of Diseases 11th Revision, ICD-11 [13]), and sources of funding. Reviewers resolved discrepancies by consensus and, when necessary, through discussion by a third reviewer (MG).

2.5. *Assessment of trustworthiness of guidelines*

We defined trustworthiness as the extent to which the guideline development process adhered to the methodological standards proposed by the IOM [1]. To improve the performance of the National Guideline Clearinghouse Extent of Adherence to Trustworthy Standards (NEATS) instrument, initially developed on the basis of IOM standards [14], we developed modifications of the instrument. The modified NEATS instrument [15] consists of ten items addressing disclosure of funding sources, disclosure and management of COIs, composition of the GDG, systematic review process (search strategy, study selection, and synthesis of evidence), rating the strength of recommendations, articulation of recommendations, external review process, and plans for updating. The item on disclosure of funding sources was rated using two response options (yes/no) and the item on the composition of the GDG was rated using three response options (yes/no/unknown). All other items were scored on a 5-point Likert scale (1= lowest adherence and 5= highest adherence to the item).

Paired reviewers, following an online training session and calibration exercises, independently assessed trustworthiness of each eligible guideline using the modified NEATS instrument [15]. Reviewers recorded their responses to the prompting questions for each item and corresponding score in pilot-tested extractions forms and resolved disagreements by consensus or in discussion with a third reviewer (MG).

We evaluated the first treatment recommendation from each guideline in our assessment of relevant items except for the "rating the strength of recommendations" item for which we evaluated the first five strong treatment recommendations. There exist different classification systems for the strength of recommendations. For example, the

Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach categorizes the strength of recommendation as strong or weak [16] while the American College of Cardiology and the American Heart Association categorize the strength of recommendation as strong, moderate and weak [17]. To ensure consistent evaluation across guidelines, we considered a recommendation as strong if the strength of the recommendation was stronger than weak.

2.6. Outcomes of interest

We chose as the primary outcome change in mean score across critical items from 2010 to 2022. Critical items included disclosure and management of COIs, study selection, synthesis of evidence, and rating the strength of recommendations [15]. Secondary outcomes included change in mean score across all items and change in the proportion of guidelines that achieved a mean score of 4 or higher across critical items from 2010 to 2022. We classified guidelines with a mean score of 4 or higher across critical items as high trustworthiness. A secondary outcome at the individual item level was change in the score of each item from 2010 to 2022. The score of each item ranged from 1 to 5; for items addressing disclosure of funding sources and GDG composition, we scored them as 1 if not met (rated "no" or "unknown") and 5 if met (rated "yes").

2.7. Statistical analysis

We summarized the distribution of continuous variables using mean and standard deviation (SD) and categorical variables as frequency and percentage. Using independent samples t-tests with equal variances, we calculated mean difference (MD) and corresponding 95% confidence interval (CI) comparing guidelines published in 2010

versus those from 2022 for mean score across critical items, mean score across all items, and score of individual items. Using multivariable linear regression models, we explored the following prespecified subgroups for the primary outcome: 1) guidelines focused on adults versus pediatrics may have greater improvement in trustworthiness; 2) guidelines developed by governmental agencies or the World Health Organization (WHO) versus professional societies or other groups may have greater improvement in trustworthiness. We found no evidence of departure from the assumptions of linear regression in the models. We planned to assess the credibility of any apparent difference in the subgroups (i.e., a p-value for the test of interaction of less than 0.1) using the ICEMAN tool [18]. We used Fisher exact test to compare the proportion of guidelines published in 2010 versus 2022 with a mean score of 4 or higher across critical items and implemented all analyses in Stata 17.0 (StataCorp., College Station, TX, USA).

3. RESULTS

Among the total sample of 429 full texts reviewed, we included 70 guidelines for the year 2010 and 70 guidelines for the year 2022. Supplementary Figures 1 and 2 present guideline selection flowcharts. Excluded full texts were often guidelines that did not use a systematic review of evidence (31.7%) (Supplementary Tables 1 and 2). Table 1 presents the characteristics of the included guidelines. The majority of guidelines were multinational (55/140, 39.3%), focused on the adult population (83/140, 59.3%), and targeted neoplasms (27/140, 19.3%). Professional societies predominantly developed the guidelines (100/140, 71.4%). Direct funding from pharmaceutical industries supported the development process of 13 (9.3%) guidelines. Supplementary Tables 3 and 4 present an

assessment of trustworthiness for each individual guideline with a summary of the assessments in Supplementary Figure 3.

3.1. Change in mean score across critical items

Figure 1A displays the distribution of mean scores across critical items. The average of mean scores across critical items was 2.28 in 2010 and increased to 2.74 in 2022 (MD 0.46, 95% CI 0.13 to 0.79) (Table 2).

3.2. Change in mean score across all items

Figure 1B presents the distribution of mean scores across all items. The average of mean scores across all items was 2.20 in 2010 and increased to 2.52 in 2022 (MD 0.32, 95% CI 0.08 to 0.56) (Table 2).

3.3. Change in the proportion of guidelines with high trustworthiness

The proportion of guidelines with a mean score of 4 or higher across critical items was 2.9% in 2010 and increased to 18.6% in 2022 (absolute difference: 15.7%, 95% CI: 5.8% to 25.6%) (Table 2).

3.4. Change in score at the individual item level

The items with greatest increase in the average score from 2010 to 2022 included disclosure of funding sources (MD 0.86, 95% CI 0.25 to 1.46) and disclosure and management of financial COIs (MD 0.84, 95% CI 0.20 to 1.48), followed by smaller increase in synthesis of evidence (MD 0.53, 95% CI 0.10 to 0.96), study selection (MD 0.49, 95% CI 0.04 to 0.93), and search strategy (MD 0.36, 95% CI -0.09 to 0.81).Other items showed little to no change from 2010 (Table 2). Supplementary Table 5 summarizes the limitations of guidelines in adherence to each item.

3.5. Other analyses

The subgroup analysis showed no apparent differences in the magnitude of change in mean score across critical items based on the target population or developers of the guidelines (Supplementary Figure 4).

4. DISCUSSION

4.1. Principal findings

This systematic survey found that overall adherence of treatment guidelines to the trustworthiness standards as assessed by the mean scores across critical items and all items of the modified NEATS instrument [15] has improved after the introduction of IOM criteria [1]. The improvement is, however, small and reflects moderate overall adherence to the trustworthiness standards among post-IOM guidelines. While the proportion of treatment guidelines demonstrating high trustworthiness has increased since IOM standards [1], fewer than 20% of post-IOM guidelines are of high trustworthiness.

Among the domains of trustworthiness, the greatest improvement occurred in adherence to disclosure of funding sources and disclosure and management of financial COIs. Improvement in COI domain mainly represents increased transparency in disclosing COI rather than more appropriate strategy to handle it. Adherence to the systematic review domain showed smaller improvement. Limited improvement in search strategy item reflects the challenge of keeping pace with the rapid growth of evidence, which might have hindered timely updates of the search. Within the study selection process, improvement occurred in defining eligibility criteria, while duplicate screening of retrieved studies decreased from pre-IOM, which might be due to time constraints and limited availability

of skilled reviewers amid an increased production of guidelines after IOM. Improvement in synthesis of evidence item mainly comes from a more appropriate rating of the certainty of evidence among post-IOM guidelines. Other domains of guideline trustworthiness proved little to no change from pre-IOM.

4.2. Strengths and limitations

This study has several strengths. First, to ensure a representative sample of guidelines, we included treatment guidelines published in journals as well as guidelines that were only available on the developers' websites. Second, to minimize bias, we performed selection of guidelines and assessment of trustworthiness in duplicate. Third, to address improvement in the overall adherence of guidelines to the trustworthiness standards, as the primary outcome, we focused on the domains with the most important role in developing trustworthy guidelines as judged by a consensus of team members with expertise in the guideline methodology [15].

This study also has limitations. First, for feasibility purposes, we sampled only guidelines from two time points, before (2010) and after IOM (2022). Given the possibility for year-to-year variations in trustworthiness of guidelines and potential impacts of coronavirus disease 2019 on guideline development, the observed improvement in trustworthiness may not be generalizable to all post-IOM years. Second, our judgment on critical items was subjective without a formal consensus process. We chose items that, in our view, if badly handled, are most likely to decrease trustworthiness. Third, we only assessed financial COIs and did not address intellectual COIs that can be a source of bias in the development of guidelines [1]. Intellectual COIs are prevalent [19-21] and have been

increasingly recognized in COI policies [1, 22-25] but remain less frequently addressed than financial COIs in the guideline development process [19, 20]. Therefore, it is possible that our assessment overrated guidelines in both years, likely more substantially in 2010, when addressing the "disclosure and management of COI" item. Consequently, the magnitude of improvement in adherence to this item from 2010 may have been underestimated in our study. Fourth, although we modified the NEATS instrument to capture trustworthiness of the guideline development process [15], limitations in reporting may have impacted our assessments for "disclosure and appropriate management of COI", "search strategy", and "study selection" items. For example, in the assessment of the "search strategy" item, the guidelines achieved the lowest adherence if there was no information on search terms. The authors of the guidelines may have used appropriate search terms that they failed to disclose. It is more likely that guidelines published in 2010 than in 2022 suffer from limited reporting (Supplementary Table 5); therefore, we may have overestimated the magnitude of improvement in adherence to these items from 2010. Fourth, we focused only on a group of recommendations and did not assess all the treatment recommendations in the guidelines. Therefore, it is possible that we overestimated scores for the "rating the strength of recommendations" and "articulation of recommendations" items in both years, however, the magnitude of change in the scores of these items from 2010 would probably remain unchanged.

4.3. Relation to other studies

Two other studies have explored the change in trustworthiness of guidelines after IOM standards [26, 27]. These studies focused on guidelines for specific clinical areas;

osteoporosis screening [26] and prescription of physical activity [27]. We adopted a broader scope and included guidelines for treatment of any health conditions.

While these studies evaluated trustworthiness as measured by adherence of guidelines to IOM standards which assumes guidelines are informed by a systematic review of evidence [1], they did not restrict the inclusion criteria to such guidelines. This makes the assessment of domains related to the appropriateness of the systematic review process irrelevant for guidelines that were not informed by a systematic review of evidence. We did not include such guidelines.

The assessment of trustworthiness in these studies [26, 27] had important limitations including failure to consider the relative importance of criteria under each IOM standard [1] in guideline trustworthiness, evaluating the reporting quality rather than trustworthiness for some standards, and vulnerability to subjective assessment. We addressed these limitations by using the rigorously developed modified NEATS instrument that addresses the appropriateness of the process relevant to each IOM standard using hierarchical algorithms with explicit prompting questions [15].

4.4. Implications of our findings

The findings of this study suggest that despite the improvement in trustworthiness of treatment guidelines since the introduction of IOM standards [1], post-IOM guidelines trustworthiness remains limited. Given the limitations of post-IOM guidelines in our study, guideline developers should focus on improving their process in a number of ways. These include first appointing at least one chair without financial COIs to lead the GDG. Second, recruiting a multidisciplinary GDG that includes methodologists and patient partners.

Third, improving the rigor of the systematic review of evidence that informs recommendations by performing an up-to-date search with an adequate selection of databases, defining specific and unambiguous eligibility criteria to direct the study selection, screening retrieved studies in duplicate and independently, presenting quantitative or qualitative synthesis of included studies, and rating the certainty of the evidence for each prioritized outcome. Fourth, rating the strength of recommendations using a structured framework of moving from evidence to recommendations that ideally implements the GRADE approach [28] and avoids issuing strong recommendations based on low or very low certainty evidence except in specific scenarios [28]. Finally, submitting draft guidelines for external review and devising plans for updating guidelines as soon as new practice-changing evidence becomes available to create "living" guidelines [29].

In addition, our findings suggest that guideline developers should provide greater transparency with respect to the reporting of their guideline development process. This particularly includes identifying the roles of GDG members including chair or co-chairs, describing the details of the systematic review process, and providing explicit statements for the GDG's justification on the balance of benefits and harms of intervention versus comparator(s) linked with the certainty of evidence that informed the strength of recommendations. To facilitate the implementation of recommendations in practice, guideline developers should explicitly identify population and comparators, in addition to the intervention of interest, when articulating recommendations.

Guideline publishers and databases of guidelines can play important roles in improving trustworthiness. Publishers could mandate adherence to IOM standards, whilst

databases could provide a public judgment on trustworthiness for individual guidelines and differentiate trustworthy from untrustworthy guidelines.

5. CONCLUSION

As assessed by the modified NEATS instrument, overall adherence of treatment guidelines to the trustworthiness standards and proportion of treatment guidelines with high trustworthiness have shown modest improvement after the introduction of IOM criteria. Despite the observed improvement, trustworthiness of treatment guidelines published after IOM standards remains suboptimal. Achieving uniformly high trustworthiness in practice guidelines will require considerable additional efforts in identifying and addressing existing barriers.

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CRediT authorship contribution statement

Maryam Ghadimi: Conceptualization, Methodology, Resources, Investigation, Data Curation, Formal analysis, Visualization, Validation, Writing – original draft, Writing – review and editing, Project administration. **Gordon Guyatt:** Conceptualization, Methodology, Supervision, Writing – review and editing, Funding acquisition. **Carlos Zaror:** Investigation, Data Curation, Writing – review and editing. **João Pedro Lima**: Investigation, Data Curation, Writing – review and editing. **Sana Gupta:** Investigation, Data Curation, Writing – review and editing. **Hamed Movahed:** Investigation, Data Curation, Writing – review and editing. **Wimonchat Tangamornsuksan:** Investigation, Data Curation, Writing – review and editing. **Gonzalo Bravo-Soto:** Investigation, Data Curation, Writing – review and editing. **Sahrish Masood:** Investigation, Data Curation, Writing – review and editing. **Huda Gomaa:** Investigation, Data Curation, Writing – review and editing. **Yanjiao Shen:** Investigation, Data Curation, Writing – review and editing. **Nima Behravan:** Investigation, Data Curation, Writing – review and editing. **Rachel Couban:** Resources, Writing – review and editing. **Romina Brignardello-Petersen:** Conceptualization, Methodology, Supervision, Writing – review and editing.

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Patient and public involvement: No patients or members of the public were involved in this work.

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Figure 1. Distribution of mean scores A) across critical items; B) across all items of the modified NEATS instrument. The reference horizontal lines represent the median of mean scores for each year. Critical items included disclosure and management of conflict of interest, study selection, synthesis of evidence, and rating the strength of recommendations.

NEATS: National Guideline Clearinghouse Extent of Adherence to Trustworthy Standards.

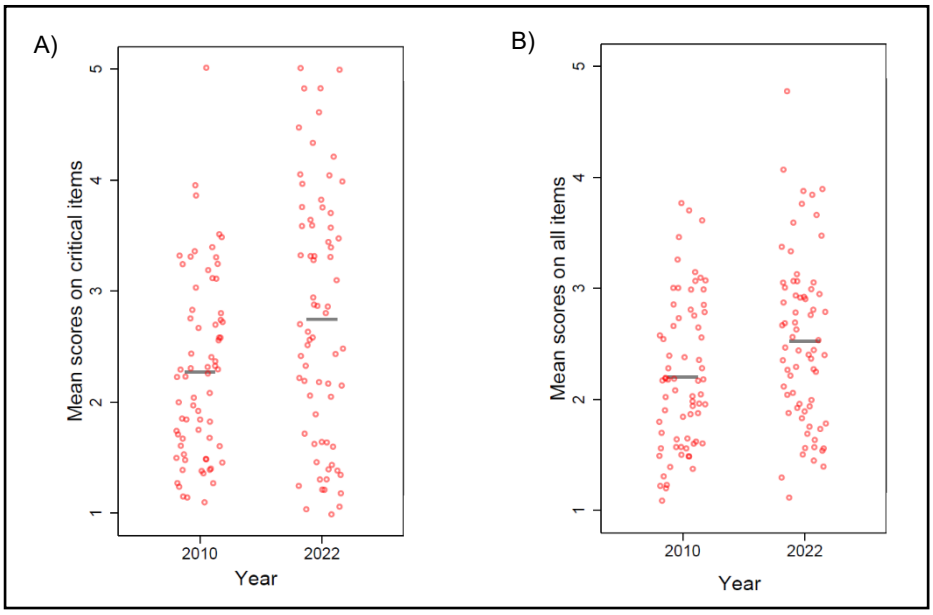

Table 1. Characteristics of included clinical practice guidelines

Characteristics	Year 2010 (n=70)	Year 2022 (n=70)
Region of origin, n (%)		
International	25 (35.7)	30 (42.9)
Europe	18 (25.7)	18 (25.7)
North America	21 (30.0)	14 (20.0)
South America	0	1 (1.4)
South-East Asia	0	1 (1.4)
Western Pacific	6 (8.6)	6 (8.6)
Target population, n (%)		
Adult	43 (61.4)	40 (57.1)
Pediatrics	6 (8.6)	6 (8.6)
Both	21 (30.0)	24 (34.3)
Developing organization, n (%)		
Professional society	49 (70.0)	51 (72.9)
Governmental agency and WHO	15 (21.4)	11 (15.7)
Other groups [a]	6 (8.6)	8 (11.4)
Funding source, n (%)		
Direct industry funding	9 (12.9)	4 (5.7)
Other sources	32 (45.7)	52 (74.3)
Not reported	29 (41.4)	14 (20.0)
Clinical condition, n (%)		
Blood diseases	1 (1.4)	0
Circulatory system diseases	8 (11.4)	8 (11.4)
Digestive system diseases	5 (7.1)	5 (7.1)
Endocrine, nutritional or metabolic diseases	2 (2.9)	3 (4.3)
Genitourinary diseases	2 (2.9)	5 (7.1)
Immune system diseases	3 (4.3)	2 (2.9)
Infectious diseases	14 (20)	7 (10.0)
Mental or neurodevelopmental diseases	1 (1.4)	2 (2.9)
Musculoskeletal diseases	4 (5.7)	6 (8.6)
Neoplasms	14 (20)	13 (18.6)
Nervous system diseases	7 (10)	7 (10.0)
Neonatal diseases	0 (0)	1 (1.4)
Pain management	2 (2.9)	2 (2.9)
Pregnancy, prenatal conditions, and childbirth	2 (2.9)	2 (2.9)
Respiratory diseases	1 (1.4)	1 (1.4)
Skin diseases	2 (2.9)	4 (5.7)
Sleep-wake diseases	2 (2.9)	1 (1.4)
Visual diseases	0	1 (1.4)

WHO: World Health Organization
[a] Other groups that developed guidelines included study groups, non-for-profit or charity organizations.

Table 2. Primary and secondary outcomes

Outcomes of interest	Year 2010 (Pre-IOM) (n=70)	Year 2022 (Post-IOM) (n=70)	Absolute difference (95%CI) [b]	p-value
Primary outcome				
Mean scores across critical items [a], mean (SD)	2.28 (0.81)	2.74 (1.14)	0.46 (0.13 to 0.79)	0.006
Secondary outcomes				
Mean scores across all items, mean (SD)	2.20 (0.66)	2.52 (0.76)	0.32 (0.08 to 0.56)	0.008
Mean score of 4 or higher across critical items [a], n (%)	2 (2.9)	13 (18.6)	15.7 (5.8 to 25.6)	0.005
Scores at item level				
Disclosure of funding sources item, mean (SD)	3.34 (1.98)	4.20 (1.61)	0.86 (0.25 to 1.46)	0.006
Disclosure and management of COI item, mean (SD)	2.59 (1.94)	3.43 (1.88)	0.84 (0.20 to 1.48)	0.010
Composition of the GDG item, mean (SD)	1.34 (1.13)	1.57 (1.41)	0.23 (-0.20 to 0.66)	0.291
Search strategy item, mean (SD)	2.69 (1.37)	3.04 (1.31)	0.36 (-0.09 to 0.81)	0.117
Study selection item, mean (SD)	1.66 (1.20)	2.14 (1.43)	0.49 (0.04 to 0.93)	0.031
Synthesis of evidence item, mean (SD)	2.24 (1.04)	2.77 (1.49)	0.53 (0.10 to 0.96)	0.016
Rating the strength of recommendations item, mean (SD)	2.61 (1.53)	2.61 (1.57)	0 (-0.52 to 0.52)	1.000
Articulation of recommendations item, mean (SD)	1.73 (1.14)	1.80 (1.41)	0.07 (-0.36 to 0.50)	0.742
External review item, mean (SD)	2.09 (1.15)	2.10 (1.14)	0.01 (-0.37 to 0.40)	0.941
Updating plan item, mean (SD)	1.74 (0.85)	1.57 (0.81)	-0.17 (-0.45 to 0.11)	0.222

CI: confidence interval; COI: conflict of interest; GDG: guideline development group; IOM: Institute of Medicine; SD: standard deviation. The range for continuous outcomes was 1 (lowest adherence) to 5 (highest adherence).

[a] Critical items included disclosure and management of COIs, study selection, synthesis of evidence, and rating the strength of recommendations.

[b] We calculated mean difference and corresponding 95% confidence intervals for continuous outcomes and difference in the crude proportions for mean score of 4 or higher across critical items.

Supplementary Appendix C2

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Supplement 1. Search Strategy

Guidelines published in 2010

May 15, 2023

MEDLINE (OVID)

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy:
---
1 guideline.pt.
2 practice guideline.pt.
3 guideline/ or practice guideline/
4 (guideline* or consensus* or recommendat* or CPG or CPGs or best practice*).ti.
5 or/1-4
6 (therap* or treatment* or intervention* or management).ti.
7 5 and 6
8 limit 7 to english language
9 limit 8 to yr="2010"

Embase (OVID)
Database: Embase <1974 to 2023 May 12>
Search Strategy:
---
1 exp practice guideline/
2 (guideline* or consensus* or recommendat* or CPG or CPGs or best practice*).ti.
3 1 or 2
4 (therap* or treatment* or intervention* or management).ti.
5 3 and 4
6 limit 5 to english language
7 limit 6 to yr="2010"

PsycInfo (OVID)
Database: APA PsycInfo <1806 to May Week 2 2023>
Search Strategy:
---
1 treatment guidelines/
2 (guideline* or consensus* or recommendat* or CPG or CPGs or best practice*).ti.
3 1 or 2
4 (therap* or treatment* or intervention* or management).ti.
5 3 and 4
6 limit 5 to english language
7 limit 6 to yr="2010"

Guidelines published in 2022

May 15, 2023

MEDLINE (OVID)

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy:
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1 guideline.pt.
2 practice guideline.pt.
3 Practice Guideline/ or Guideline/
4 (guideline* or consensus* or recommendat* or CPG or CPGs or best practice*).ti.
5 or/1-4
6 (therap* or treatment* or intervention* or management).ti.
7 5 and 6
8 limit 7 to english language
9 limit 8 to yr="2022"

Embase (OVID)
Database: Embase <1974 to 2023 May 12>
Search Strategy:
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1 exp practice guideline/
2 (guideline* or consensus* or recommendat* or CPG or CPGs or best practice*).ti.
3 1 or 2
4 (therap* or treatment* or intervention* or management).ti.
5 3 and 4
6 limit 5 to english language
7 limit 6 to yr="2022"

Database: APA PsycInfo <1806 to May Week 2 2023>
Search Strategy:
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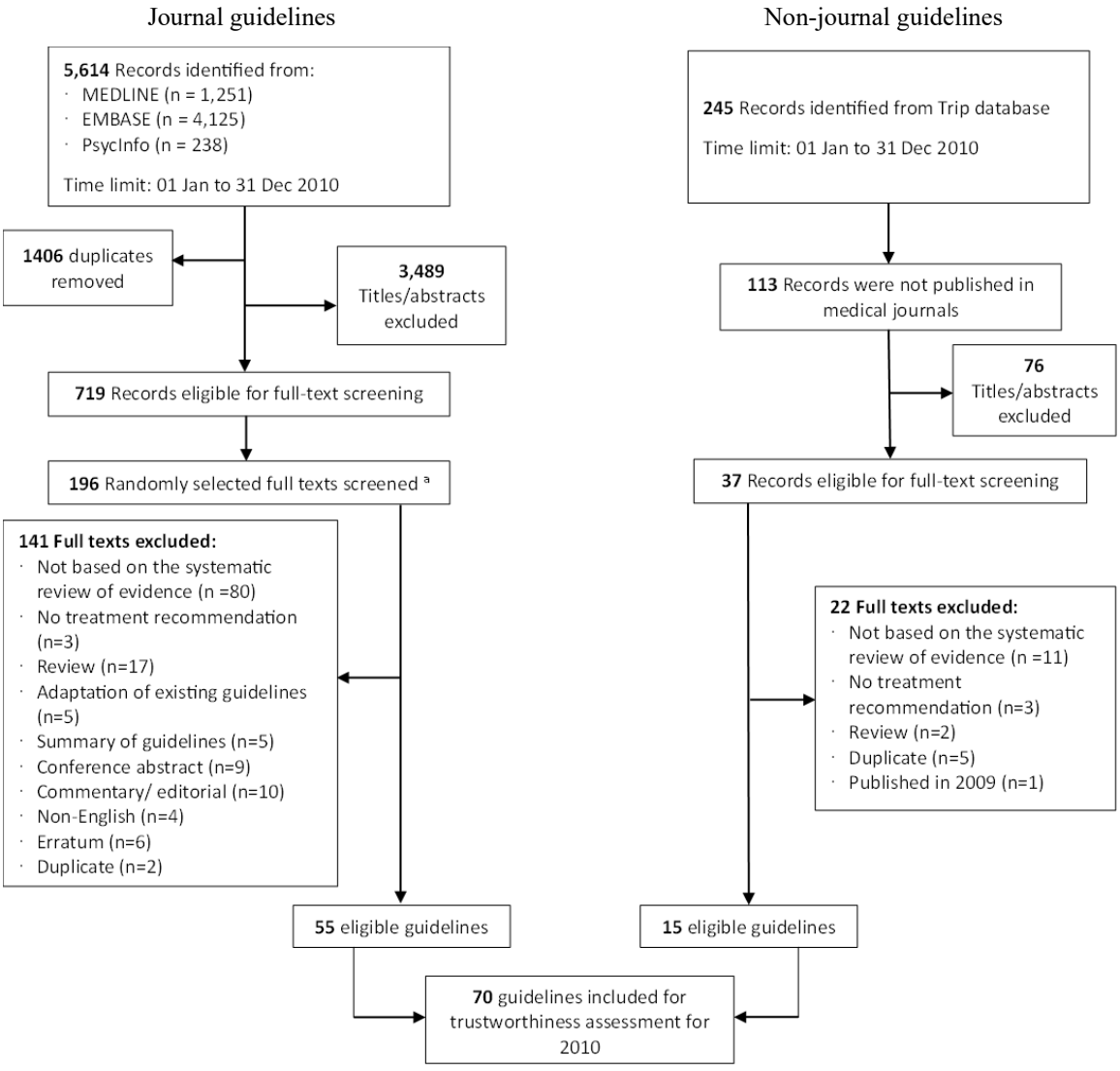
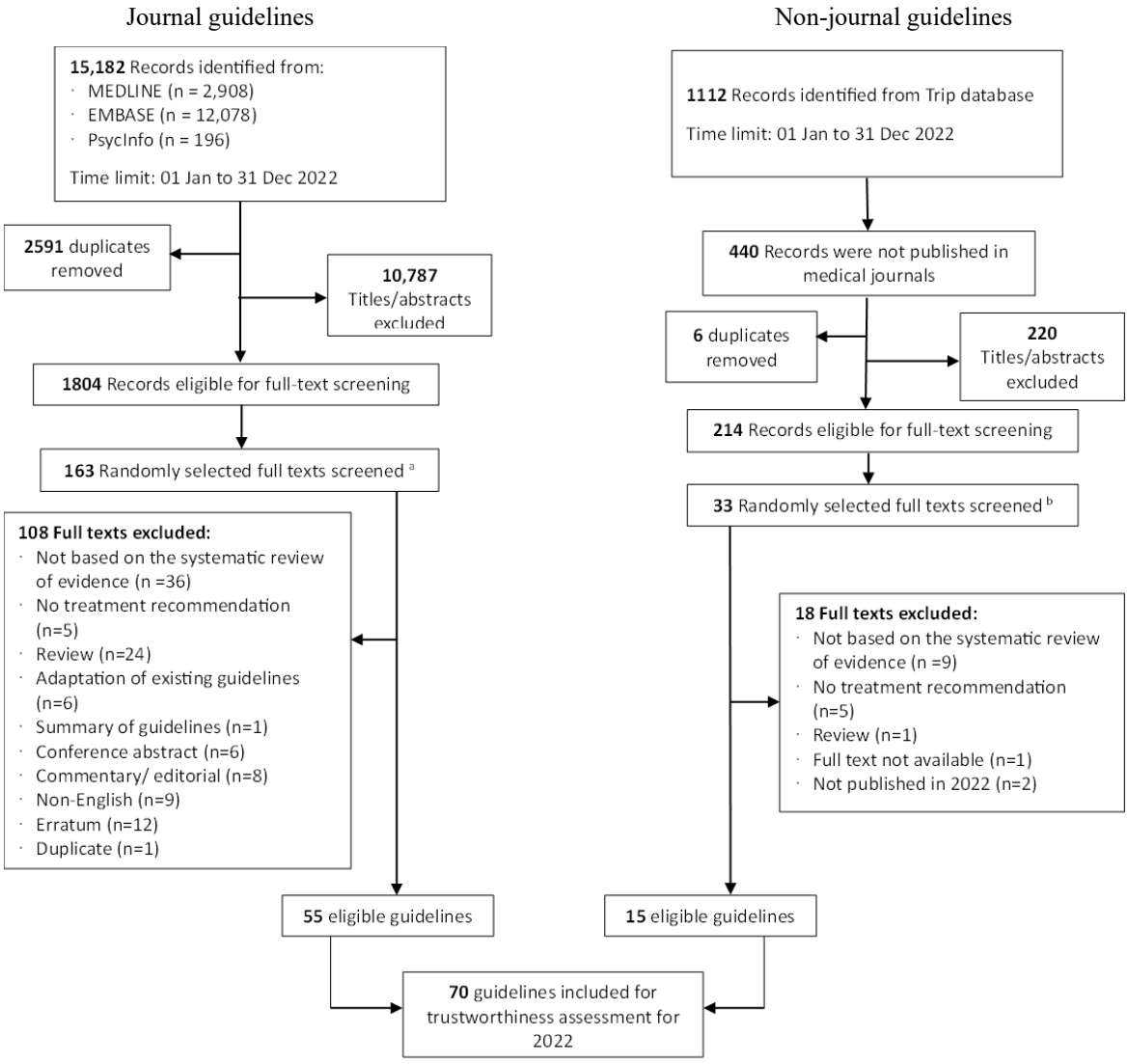
1 treatment guidelines/
2 (guideline* or consensus* or recommendat* or CPG or CPGs or best practice*).ti.
3 1 or 2
4 (therap* or treatment* or intervention* or management).ti.
5 3 and 4
6 limit 5 to english language
7 limit 6 to yr="2022"

Supplementary Figure 1. Selection of clinical practice guidelines published in 2010



Supplementary Figure 2. Selection of clinical practice guidelines published in 2022



[a] We screened full texts in random order until we reached the target sample size (55 guidelines) within this stratum.

[b] We found only 15 eligible guidelines in 2010 within the stratum of non-journal guidelines; thus, for Year 2022, we screened full texts in random order until we identified 15 eligible guidelines in this stratum.

Supplementary Table 1. Full texts excluded and reasons for exclusion from 2010

First author/ developing organization	Title	Reason for exclusion
Guidelines published in medical journals		
Schultz	New Zealand Society of Gastroenterology statement on the use of biological therapy in inflammatory bowel disease	Adaptation of existing guidelines
Grimer	UK Guidelines for the Management of Bone Sarcomas	Adaptation of existing guidelines
Rolfs	Utah clinical guidelines on prescribing opioids for treatment of pain	Adaptation of existing guidelines
Grimer	Guidelines for the management of soft tissue sarcomas	Adaptation of existing guidelines
Heymann	Brazilian consensus on the treatment of fibromyalgia	Adaptation of existing guidelines
Robbins	A practice guide for continuous opioid therapy for refractory daily headache	Commentary/ editorial
Talarico	Diagnosis and management of neuro-Behcet's disease: International consensus recommendations	Commentary/ editorial
Vlieland	Clinical guidelines: New guidelines on nondrug treatment in RA	Commentary/ editorial
Aalbers	Combination therapy in hypertension: new recommendations	Commentary/ editorial
Winslow	New DHHS guidelines for antiretroviral therapy	Commentary/ editorial
Hua	Cardiac resynchronization therapy for chronic heart failure in China: guideline and practice	Commentary/ editorial
Yasuda	Consensus session for appropriate managements of bleeding non malignant gastro-duodenal ulcers, Indication for endoscopic resection of colorectal polyps and surveillance guidelines, and Stone management of the bile duct.	Commentary/ editorial
Piacenti	Treatment recommendations for patients from the community: concerns regarding the new guidelines for treatment of intra-abdominal infection	Commentary/ editorial
File	New guidelines for the management of complicated intra-abdominal infections	Commentary/ editorial
Traynor	HIV treatment guidelines revised	Commentary/ editorial
Preston	Clinical practice guidelines for the management of women with decreased fetal movements (DFM)	Conference abstract
Ellis	A systematic review and consensus recommendations on the use of biomarkers in the treatment of non-small cell lung carcinoma (NSCLC)	Conference abstract
Hwang	Prevalence and treatment consensus for late-onset hypogonadism in Taiwan	Conference abstract
Giacobbe	CANMAT Clinical guidelines for the use of neurostimulation therapies for the management of major depressive disorder in adults	Conference abstract

Wolff	German Austrian-Swiss consensus on clinical practice in chronic GVHD: Guidance for diagnosis, immunosuppressive treatment and supportive care of chronic graft-versus-host disease	Conference abstract
Samalin	Management of acute depression in bipolar disorder. Formalized recommendations from the French Society of Biological Psychiatry: Methodology and perspectives	Conference abstract
Yamada	Evidence-based practice guidelines for treatment of premenstrual dysphoric disorder in Japan	Conference abstract
Huth-Kuehne	International recommendations on the diagnosis and treatment of patients with acquired haemophilia A	Conference abstract
Moss	Clinical practice recommendations for the pharmacological management of first-episode psychosis	Conference abstract
Charloux	Fitness for radical treatment. ERS-ESTS guidelines	No treatment recommendation
Grunberger	Statement by the American Association of Clinical Endocrinologists Consensus Panel on insulin pump management	No treatment recommendation
McNaughton	Summary of best practice recommendations for management of enterocutaneous fistulae from the Canadian association for enterostomal therapy ECF best practice recommendations panel	No treatment recommendation
Aloe	Brazilian guidelines for the treatment of narcolepsy	Non-English
Rouleau	A collaborative work: "Le guide de therapie antiretrovirale pour les professionnels du quebec". recommendations for first line therapy	Non-English
Trinidad-Ramos	Early hearing detection and intervention: 2010 CODEPEH recommendation	Non-English
Nast	Evidence-based (S3) guideline for the treatment of psoriasis vulgaris - Update: "Therapeutic options" and "Efalizumab"	Non-English
Hiratzka	2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the diagnosis and management of patients with thoracic aortic disease. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, A	Duplicate
Hazinski	2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations	Duplicate
Mermel	Erratum: Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. (Clin Infect Dis (2009) 49 (1-45))	Erratum
Visvanathan	Corrigendum to "American Society of Clinical Oncology clinical practice guideline update on the use of pharmacologic interventions including tamoxifen, raloxifene, and aromatase inhibition for breast cancer risk reduction" [Gynecol. Oncol. 115 (2009) 132-	Erratum
Solomkin	Erratum: Diagnosis and management of complicated intra-abdominal infection in adults and children: Guidelines by the Surgical Infection Society and the Infectious Diseases	Erratum

	Society of America (Clinical Infectious Diseases (2010) 50:2 (133-164))	
Pathirana	Erratum: European S3-Guidelines on the systemic treatment of psoriasis vulgaris (Journal of the European Academy of Dermatology and Venereology (2009) 23:SUPPL. 2 (1-70))	Erratum
Poldermans	Erratum: Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery: The Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European	Erratum
Mermel	Erratum: Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. (Clinical Infectious Diseases (2009) 49:(1-45))	Erratum
Engelhardt	Consensus statement from European experts on the diagnosis, management, and treatment of multiple myeloma: from standard therapy to novel approaches	Not based on the systematic review of evidence
Schmoll	Testicular seminoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Not based on the systematic review of evidence
D'Addario	Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Not based on the systematic review of evidence
Stupp	High-grade malignant glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Not based on the systematic review of evidence
Labianca	Primary colon cancer: ESMO Clinical Practice Guidelines for diagnosis, adjuvant treatment and follow-up	Not based on the systematic review of evidence
Castro	SEOM clinical guidelines for the adjuvant treatment of colorectal cancer	Not based on the systematic review of evidence
White	An evidence-based clinical guideline for initial management of behavioral emergencies	Not based on the systematic review of evidence
Cheson	Optimal use of bendamustine in chronic lymphocytic leukemia, non-Hodgkin lymphomas, and multiple myeloma: treatment recommendations from an international consensus panel	Not based on the systematic review of evidence
Kulke	NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas	Not based on the systematic review of evidence
Ansell	Diagnosis and management of Waldenstrom macroglobulinemia: Mayo stratification of macroglobulinemia and risk-adapted therapy (mSMART) guidelines	Not based on the systematic review of evidence
Roberts	Management of a malignant pleural effusion: British Thoracic Society Pleural Disease Guideline 2010	Not based on the systematic review of evidence

Cardoso	Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Not based on the systematic review of evidence
Zucca	Gastric marginal zone lymphoma of MALT type: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Not based on the systematic review of evidence
Pinto	New guidelines for diagnosis and treatment of insomnia	Not based on the systematic review of evidence
Sachdev	Consensus Statement National Consensus Workshop on Management of SAM Children through Medical Nutrition Therapy	Not based on the systematic review of evidence
Jarnagin	Surgical treatment of hepatocellular carcinoma: expert consensus statement	Not based on the systematic review of evidence
Mebazaa	Clinical review: Practical recommendations on the management of perioperative heart failure in cardiac surgery	Not based on the systematic review of evidence
MacDuff	Management of spontaneous pneumothorax: British Thoracic Society Pleural Disease Guideline 2010	Not based on the systematic review of evidence
Qiu	Chinese specialist consensus on treatment of customary pain in orthopaedics	Not based on the systematic review of evidence
Dreyling	Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Not based on the systematic review of evidence
Tamary	Consensus Paper-ICIS Expert Meeting Basel 2009 treatment milestones in immune thrombocytopenia	Not based on the systematic review of evidence
Kassouf	Canadian guidelines for treatment of non-muscle invasive bladder cancer: a focus on intravesical therapy	Not based on the systematic review of evidence
Harousseau	Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Not based on the systematic review of evidence
Schwarz	Nonoperative therapies for combined modality treatment of hepatocellular cancer: expert consensus statement	Not based on the systematic review of evidence
Crino	Early stage and locally advanced (non-metastatic) non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Not based on the systematic review of evidence
Casali	Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Not based on the systematic review of evidence
Chan	Nasopharyngeal cancer: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Not based on the systematic review of evidence
Al Jahdali	Saudi guidelines for testing and treatment of latent tuberculosis infection	Not based on the systematic review of evidence

Strosberg	The NANETS consensus guidelines for the diagnosis and management of poorly differentiated (high-grade) extrapulmonary neuroendocrine carcinomas	Not based on the systematic review of evidence
Athanasou	Bone sarcomas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up	Not based on the systematic review of evidence
Nickel	2010 Update: Guidelines for the management of benign prostatic hyperplasia	Not based on the systematic review of evidence
Baccarani	Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Not based on the systematic review of evidence
Bellmunt	Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up	Not based on the systematic review of evidence
Sheean	Botulinum toxin assessment, intervention and after-care for upper limb hypertonicity in adults: International consensus statement	Not based on the systematic review of evidence
Cascinu	Pancreatic cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Not based on the systematic review of evidence
Farabaugh	Management of physical health in patients with schizophrenia: Practical recommendations	Not based on the systematic review of evidence
Jelic	Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Not based on the systematic review of evidence
Escudier	Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Not based on the systematic review of evidence
Farabaugh	Management of chronic spine-related conditions: consensus recommendations of a multidisciplinary panel	Not based on the systematic review of evidence
Matthews	Developing combination immunotherapies for type 1 diabetes: recommendations from the ITN-JDRF Type 1 Diabetes Combination Therapy Assessment Group	Not based on the systematic review of evidence
Tilly	Diffuse large B-cell non-Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Not based on the systematic review of evidence
Braunschweig	Management of patients receiving implantable cardiac defibrillator shocks: recommendations for acute and long-term patient management	Not based on the systematic review of evidence
Silversides	Canadian Cardiovascular Society 2009 Consensus Conference on the management of adults with congenital heart disease: shunt lesions	Not based on the systematic review of evidence
Checkley	Eosinophilia in returning travellers and migrants from the tropics: UK recommendations for investigation and initial management	Not based on the systematic review of evidence
Stahl	Esophageal cancer: Clinical Practice Guidelines for diagnosis, treatment and follow-up	Not based on the systematic review of evidence

Gothefors	Swedish clinical guidelines--prevention and management of metabolic risk in patients with severe psychiatric disorders	Not based on the systematic review of evidence
Rachlis	Canadian consensus guidelines for the optimal use of maraviroc in the treatment of HIV-infected adults	Not based on the systematic review of evidence
Van Cutsem	Molecular markers and biological targeted therapies in metastatic colorectal cancer: expert opinion and recommendations derived from the 11th ESMO/World Congress on Gastrointestinal Cancer, Barcelona, 2009	Not based on the systematic review of evidence
Gilleece	British HIV Association guidelines for antiretroviral treatment of HIV-2-positive individuals 2010	Not based on the systematic review of evidence
Namiki	Management of hepatitis C; Report of the Consensus Meeting at the 45th Annual Meeting of the Japan Society of Hepatology (2009)	Not based on the systematic review of evidence
Aschner	Practical steps to improving the management of type 1 diabetes: recommendations from the Global Partnership for Effective Diabetes Management	Not based on the systematic review of evidence
Janson	Nordic Guidelines 2010 for diagnosis and treatment of gastroenteropancreatic neuroendocrine tumours	Not based on the systematic review of evidence
Chiang	2010 guidelines of the Taiwan Society of Cardiology for the management of hypertension	Not based on the systematic review of evidence
Okines	Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Not based on the systematic review of evidence
Schots	The Belgian 2010 consensus recommendations for the treatment of multiple myeloma	Not based on the systematic review of evidence
Pavel	ENETS consensus guidelines for the management of brain, cardiac and ovarian metastases from neuroendocrine tumors	Not based on the systematic review of evidence
Guinot	Consensus on 3D treatment planning in gynaecologic brachytherapy of the Radiation Oncology Spanish Society (SEOR) Brachytherapy Group	Not based on the systematic review of evidence
Kardos	Guidelines of the German Respiratory Society for diagnosis and treatment of adults suffering from acute or chronic cough	Not based on the systematic review of evidence
Hudson	Maxillary canine management in the pre-adolescent: a guideline for general practitioners	Not based on the systematic review of evidence
Taylor	Clinical practice guidelines for the management of atypical haemolytic uraemic syndrome in the United Kingdom	Not based on the systematic review of evidence
Sturdee	Recommendations for the management of postmenopausal vaginal atrophy	Not based on the systematic review of evidence
Marret	Clinical practice guidelines on menorrhagia: management of abnormal uterine bleeding before menopause	Not based on the systematic review of evidence

Ralph	The management of Peyronie's disease: evidence-based 2010 guidelines	Not based on the systematic review of evidence
Cripps	Consensus recommendations for the use of anti-egfr therapies in metastatic colorectal cancer	Not based on the systematic review of evidence
Carra	Optimising outcomes in multiple sclerosis: Consensus guidelines for the diagnosis and treatment of Multiple Sclerosis in Latin America	Not based on the systematic review of evidence
Furst	Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2009	Not based on the systematic review of evidence
Kamisawa	Japanese consensus guidelines for management of autoimmune pancreatitis: III. Treatment and prognosis of AIP	Not based on the systematic review of evidence
Asmis	Diagnosis and management of hepatocellular carcinoma: results of a consensus meeting of The Ottawa Hospital Cancer Centre	Not based on the systematic review of evidence
Tsara	Guidelines for diagnosing and treating sleep related breathing disorders in adults and children (Part 3: obstructive sleep apnea in children, diagnosis and treatment)	Not based on the systematic review of evidence
Kianmanesh	ENETS Consensus Guidelines for the management of peritoneal carcinomatosis from neuroendocrine tumors	Not based on the systematic review of evidence
Brochard	An Official ATS/ERS/ESICM/SCCM/SRLF Statement: Prevention and Management of Acute Renal Failure in the ICU Patient: an international consensus conference in intensive care medicine	Not based on the systematic review of evidence
Kishnani	Glycogen storage disease type III diagnosis and management guidelines	Not based on the systematic review of evidence
Yu	Chinese expert consensus statement on clinical diagnosis and treatment of malignant tumor bone metastasis and bone related diseases	Not based on the systematic review of evidence
Mesia Nin	SEOM clinical guidelines for the treatment of head and neck cancer	Not based on the systematic review of evidence
Vedantham	Interventional endovascular management of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis: a position statement by the Society of Interventional Radiology, endorsed by the Canadian Interventional Radiology Association	Not based on the systematic review of evidence
Gregoire	Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Not based on the systematic review of evidence
Brook	British HIV Association guidelines for the management of coinfection with HIV-1 and hepatitis B or C virus 2010	Not based on the systematic review of evidence
Horwich	Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Not based on the systematic review of evidence

Willemze	Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Not based on the systematic review of evidence
Eichhorst	Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Not based on the systematic review of evidence
Morjaria	Recommendation for optimal management of severe refractory asthma	Review
Tallman	Treatment of patients with acute promyelocytic leukemia: a consensus statement on risk-adapted approaches to therapy	Review
Hankey	Management of cholesterol to reduce the burden of stroke in Asia: consensus statement	Review
Masterson	Depression 2: Exploring management options for adults with moderate to severe symptoms	Review
Radicioni	Consensus statement on diagnosis and clinical management of Klinefelter syndrome	Review
Bushby	Diagnosis and management of Duchenne muscular dystrophy, part 1	Review
Romano	Noonan syndrome: clinical features, diagnosis, and management guidelines	Review
Giugliani	Mucopolysaccharidosis I, II, and VI: Brief review and guidelines for treatment	Review
Gridelli	Recent issues in first-line treatment of advanced non-small-cell lung cancer: Results of an international expert panel meeting of the italian association of thoracic oncology	Review
Jaroszewski	Current management of pectus excavatum: a review and update of therapy and treatment recommendations	Review
Zheng	Treatment guideline for hemangiomas and vascular malformations of the head and neck	Review
Zhang	OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009	Review
Sliwa	Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy	Review
Molassiotis	Clinical expert guidelines for the management of cough in lung cancer: report of a UK task group on cough	Review
Du	Experts' agreement on therapy for bone metastases	Review
Kumada	Guidelines for the treatment of chronic hepatitis and cirrhosis due to hepatitis B virus infection for the fiscal year 2008 in Japan	Review
Van Den Berg	Current guidelines for carotid stenosis management	Review
Armstrong	AAN recommendations on symptomatic treatment for muscle cramps	Summary of existing guidelines

Boyer	The Role of Transjugular Intrahepatic Portosystemic Shunt (TIPS) in the Management of Portal Hypertension: update 2009	Summary of existing guidelines
Greenspoon	A summary of recent recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding	Summary of existing guidelines
Huang	Guideline on antimicrobial therapy of sexually transmitted diseases in Taiwan	Summary of existing guidelines
Hoffken	Guidelines of the Paul-Ehrlich-Society of Chemotherapy, the German Respiratory Diseases Society, the German Infectious Diseases Society and of the Competence Network CAPNETZ for the Management of Lower Respiratory Tract Infections and Community-acquired P	Summary of existing guidelines
Guidelines that were not published in medical journals		
British Columbia Perinatal Health Program	BCPHP Obstetric Guideline 19 MATERNITY CARE PATHWAY	No treatment recommendation
European Association of Urology Nurses	Continent Urinary Diversion	No treatment recommendation
American Society of Breast Surgeons	Performance and Practice Guidelines for Stereotactic Breast Procedures	No treatment recommendation
Australian Resuscitation Council	Jellyfish Stings	Not based on the systematic review of evidence
National Hemophilia Foundation	MASAC Recommendations Regarding Radionuclide Synovectomy	Not based on the systematic review of evidence
Australian Society of Clinical Immunology and Allergy	Management of Latex-Allergic Individuals	Not based on the systematic review of evidence
Clinical Practice Guidelines Portal	Problem drug use - guidelines for providing mental health first aid to an Aboriginal or Torres Strait Islander person	Not based on the systematic review of evidence
Regulation and Quality Improvement Authority	Northern Ireland Guidelines for Management of Chronic Kidney Disease	Not based on the systematic review of evidence
Regulation and Quality Improvement Authority	Guidelines & Clinical Standards of Care for People with Diabetes in Care Homes	Not based on the systematic review of evidence
Regulation and Quality Improvement Authority	Hyponatraemia Guideline	Not based on the systematic review of evidence
Tasmanian Department of Health	Palliative care management guidelines emergencies in palliative care	Not based on the systematic review of evidence

Clinical Practice Guidelines Portal	Rural adult emergency clinical guidelines third edition	Not based on the systematic review of evidence
British Association for Sexual Health and HIV	Guidelines on the management of sexual problems in women : the role of androgens	Not based on the systematic review of evidence
British Association for Sexual Health and HIV	Guidelines on the management of sexual problems in men : the role of androgens	Not based on the systematic review of evidence
European Dermatology Forum	Guidelines in classification, diagnosis, and treatment of the photodermatoses 7. Endogenous: The (cutaneous) porphyrias	Duplicate
European Dermatology Forum	European Guidelines for Photodermatoses 2 Photoaggravated Disorders	Duplicate
European Dermatology Forum	European Dermatology Guideline for the photodermatoses 3. Photoprotection	Duplicate
European Dermatology Forum	Evidence-Based Guidelines for the Classification and Management of Drug Induced Phototoxicity	Duplicate
European Dermatology Forum	European Dermatology Guideline for the photodermatoses 2. Phototesting	Duplicate
World Gastroenterology Organisation	Helicobacter Pylori in Developing Countries	review
World Gastroenterology Organisation	Constipation: A Global Perspective	review
British Society for Disability and Oral Health	Clinical Holding Guidelines	Published in 2009

Supplementary Table 2. Full texts excluded and reasons for exclusion from 2022

First author/ developing organization	Title	Reason for exclusion
Guidelines published in medical journals		
Jarzab	Diagnosis and treatment of thyroid cancer in adult patients - Recommendations of Polish Scientific Societies and the National Oncological Strategy. 2022	Adaptation of existing guidelines
Omair	Recommendations for the treatment of rheumatoid arthritis in Saudi Arabia: adolopment of the 2021 American College of Rheumatology guidelines	Adaptation of existing guidelines
Commons	Australian guideline on management of diabetes-related foot infection: part of the 2021 Australian evidence-based guidelines for diabetes-related foot disease	Adaptation of existing guidelines
Kubica	Pre-hospital treatment of patients with acute coronary syndrome: Recommendations for medical emergency teams. Expert position update 2022	Adaptation of existing guidelines
Lee	2022 Consensus statement on the management of familial hypercholesterolemia in Korea	Adaptation of existing guidelines
Rawashdeh	National Consensus for the Management of Acute Gastroenteritis in Jordanian Children: Consensus Recommendations Endorsed by the Jordanian Paediatric Society	Adaptation of existing guidelines
Fallon	Correspondence on 'EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update'	Commentary/ editorial
Farrington	Palliative Care Expert Group. Therapeutic guidelines: palliative care. Version 3. Melbourne:Therapeutic Guidelines Limited; 2010	Commentary/ editorial
Gnant	Customizing early breast cancer therapies - The 2021 St. Gallen International Breast Cancer Consensus Conference	Commentary/ editorial
Han	Chinese expert consensus statement on dual antiplatelet therapy in patients with coronary artery disease	Commentary/ editorial
Kurowski	Clinical Guideline Synopsis of Evaluation and Management of Well-Appearing Febrile Infants Aged 8 to 60 Days	Commentary/ editorial
Santulli	Updated ACC/AHA/HFSA 2022 guidelines on heart failure: what is new? From epidemiology to clinical management	Commentary/ editorial
Crea	European Society of Cardiology guidance for the management of cardiovascular disease during the pandemic and a focus on long COVID	Commentary/ editorial
Crews	Systemic Therapy for Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: ASCO Guideline Update Q and A	Commentary/ editorial
Cano Garcia	RECOMMENDATIONS for NURSES on the MANAGEMENT of PATIENTS with SYSTEMIC LUPUS ERYTHEMATOUS: A DELPHI CONSENSUS	Conference abstract
Coghill	Evidence-Based Guideline for Diagnosis, Management and Treatment of Attention-Deficit Hyperactivity Disorder	Conference abstract

D'Oria	PRINciples of optimal antithrombotiC therapy and coagulation managEment during elective fenestrated and branched EndovaScular aortic repairS (PRINCE2SS): An International Expert Based Delphi Consensus Study	Conference abstract
Girardin	Swiss consensus on the management of acute diverticulitis	Conference abstract
Lazaro-Fontanet	Prevention and management of anastomotic leakage after colorectal surgery: A Swiss national consensus	Conference abstract
Lotfy	Egyptian Evidence-Based Consensus Recommendations for Diagnosis and Targeted Management of Childhood-Onset Systemic Lupus Erythematosus. An Initiative by the Egyptian College of Pediatric Rheumatology	Conference abstract
Al Rayes	Consensus-based recommendations on the diagnosis, referral and clinical management of patients with psoriatic arthritis	No treatment recommendation
Kohl	Definition, diagnosis, and clinical management of non-obstructive kidney dysplasia: a consensus statement by the ERKNet working group on Kidney Malformations	No treatment recommendation
Vasiliu	Therapeutic management of buying/shopping disorder: A systematic literature review and evidence-based recommendations	No treatment recommendation
Esposito	Italian intersociety consensus on management of long covid in children	no treatment recommendation
Lange	Consensus management recommendations for less common non-tuberculous mycobacterial pulmonary diseases	No treatment recommendation
Barboza	Clinical practice guideline: Symptomatic treatment of multiple sclerosis. Demyelinating Diseases Working Group. Argentinean Neurological Society	Non-English
Cisneros-Garza	The second Mexican consensus on hepatocellular carcinoma. Part II: Treatment	Non-English
Sebastiani	Treatment management of patients with systemic lupus erythematosus: a delphi consensus analysis	Non-English
Stander	S2k guideline: Diagnosis and treatment of chronic pruritus	Non-English
Calderaro	Update of the Brazilian Society of Cardiology's Perioperative Cardiovascular Assessment Guideline: Focus on Managing Patients with Percutaneous Coronary Intervention - 2022	Non-English
Gonzalez-Lamuno	Clinical practice recommendations for the diagnosis and treatment of X-linked hypophosphatemia: A consensus based on the ADAPTE method	Non-English
Hormaza Jaramillo	Recommendations on the intervention of patients with rheumatological diseases by telemedicine in Colombia	Non-English
Lopez-Campos	Spanish COPD Guideline (GesEPOC) Update: Comorbidities, Self-Management and Palliative Care	Non-English
Nieto-Calvache	Colombian Consensus on the Treatment of Placenta Accreta Spectrum (PAS)	Non-English
Heidenreich	2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines	Duplicate
Assmann	Corrigendum to: Guideline for the diagnosis and treatment of Faecal Incontinence-A UEG/ESCP/ESNM/ESPCG collaboration (United European Gastroenterology Journal, (2022), 10, 3, (251-286), 10.1002/ueg2.12213)	Erratum

Schneider	Erratum: Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update (J Clin Oncol (2021) DOI:10.1200/JCO.21.01440)	Erratum
Box	Correction: Hand surgery and hand therapy clinical practice guideline for epidermolysis bullosa	Erratum
Lau	Correction to: APASL clinical practice guideline on hepatitis B reactivation related to the use of immunosuppressive therapy	Erratum
Sayed	Corrigendum: The American Society of Pain and Neuroscience (ASPN) Evidence-Based Clinical Guideline of Interventional Treatments for Low Back Pain (J Pain Res. 2022;15:3729-3832)	Erratum
Anand	Erratum to 'Indian National Association for the Study of Liver Consensus Statement on Acute Liver Failure (Part-2): Management of Acute Liver Failure' [J Clin Exp Hepatol 10 (2020) 477-517]	Erratum
Anonymous,	Erratum to: Multidisciplinary collaborative consensus guidance statement on the assessment and treatment of fatigue in postacute sequelae of SARS-CoV -2 infection (PASC) patients (PM&R, (2021), 13, 9, (1027-1043), 10.1002/pmrj.12684)	Erratum
Anonymous,	Erratum: Executive Summary: Surviving Sepsis Campaign: International Guidelines for the Management of Sepsis and Septic Shock 2021 (Crit Care Med (2021) 49 (1974-1982) DOI: 10.1097/CCM.0000000000005357)	Erratum
Anonymous,	Erratum: International Practice Recommendations for the Recognition and Management of Hearing and Vision Impairment in People with Dementia (Gerontology DOI: 10.1159/000515892)	Erratum
Anonymous,	Erratum: Urological Society of Australia and New Zealand (USANZ) and Australasian Chapter of Sexual Health Medicine (AChSHM) for the Royal Australasian College of Physicians (RACP) clinical guidelines on the management of erectile dysfunction (Med J Aust	Erratum
Yates	Erratum: EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis (Ann Rheum Dis (2016) 75 (1583-1594) DOI: 10.1136/annrheumdis-2016-209133)	Erratum
Zucca	Corrigendum to "Marginal zone lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up": [Annals of Oncology 31 (2020) 17-29	Erratum
Ampudia-Blasco	Spanish Consensus on the Use of isCGM in the Management of Patients With Insulin Therapy: The MONITOR Project	Not based on the systematic review of evidence
Brajcich	Management of colorectal cancer during the COVID-19 pandemic: Recommendations from a statewide multidisciplinary cancer collaborative	Not based on the systematic review of evidence
Casali	Gastrointestinal stromal tumours: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up	Not based on the systematic review of evidence

Cettler	Guidelines for treatment of acute pain in children - the consensus statement of the Section of Paediatric Anaesthesiology and Intensive Therapy of the Polish Society of Anaesthesiology and Intensive Therapy	Not based on the systematic review of evidence
Dominguez-Gil	Prevention and Management of Donor-transmitted Cancer After Liver Transplantation: Guidelines From the ILTS-SETH Consensus Conference	Not based on the systematic review of evidence
Fraguas	Aripiprazole for the treatment of schizophrenia: Recommendations of a panel of Spanish experts on its use in clinical practice	Not based on the systematic review of evidence
Grover	ISP good clinical practice recommendations for the management of dentin hypersensitivity	Not based on the systematic review of evidence
Kodjikian	Recommendations for the management of diabetic macular oedema with intravitreal dexamethasone implant: A national Delphi consensus study	Not based on the systematic review of evidence
LeBlanc	Management of Myeloma Manifestations and Complications: The Cornerstone of Supportive Care: Recommendation of the Canadian Myeloma Research Group (formerly Myeloma Canada Research Network) Consensus Guideline Consortium	Not based on the systematic review of evidence
Lin	Expert consensus statement on therapeutic drug monitoring and individualization of linezolid	Not based on the systematic review of evidence
Madry	Treatment recommendations of Polish Adult Leukemia Group (PALG) for management of myelodysplastic syndromes (MDS) and other MDS-related conditions in Poland	Not based on the systematic review of evidence
Mariano	A multisociety organizational consensus process to define guiding principles for acute perioperative pain management	Not based on the systematic review of evidence
McGlothlin	ISHLT consensus statement: Perioperative management of patients with pulmonary hypertension and right heart failure undergoing surgery	Not based on the systematic review of evidence
Nielsen	Acupuncture Intervention for Acute Pain in the Emergency Department (ACUITY): a Consensus Process	Not based on the systematic review of evidence
Obermannova	Oesophageal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up	Not based on the systematic review of evidence
Ode	ISPAD Clinical Practice Consensus Guidelines 2022: Management of cystic fibrosis-related diabetes in children and adolescents	Not based on the systematic review of evidence
Sgarbura	Consensus statement for treatment protocols in pressurized intraperitoneal aerosol chemotherapy (PIPAC)	Not based on the systematic review of evidence
Wang	Chinese expert consensus on the multidisciplinary management of pneumonitis associated with immune checkpoint inhibitor	Not based on the systematic review of evidence
Weber	Oncoplastic breast consortium recommendations for mastectomy and whole breast reconstruction in the setting of post-mastectomy radiation therapy	Not based on the systematic review of evidence

Yang	Consensus on Treatment of Acne Scars in China (2021)	Not based on the systematic review of evidence
Anonymous,	Chinese Clinical Practice Guideline for the Management of "CKD-PeriDialysis"-the Periods Prior to and in the Early-Stage of Initial Dialysis	Not based on the systematic review of evidence
Barbato	The Italian consensus conference on psychological therapies for anxiety and depressive disorders: findings and recommendations	Not based on the systematic review of evidence
Chang	Society of Skeletal Radiology- white paper. Guidelines for the diagnostic management of incidental solitary bone lesions on CT and MRI in adults: bone reporting and data system (Bone-RADS)	Not based on the systematic review of evidence
Chen	2021 Chinese consensus on the diagnosis and management of primary immune thrombocytopenia in pregnancy	Not based on the systematic review of evidence
de Graaf	Systemic treatment of children and adolescents with atopic dermatitis aged >=2 years: a Delphi consensus project mapping expert opinion in Northern Europe	Not based on the systematic review of evidence
Deng	Molecular diagnosis and treatment of meningiomas: an expert consensus (2022)	Not based on the systematic review of evidence
Diaz	Joint recommendations on the management of patients with osteoporosis and/or fragility fractures during and after the pandemic due to COVID-19 of SEIOMM, SEFRAOS, SER, SEMI, SEGG, SEMG, SEMERGEN and SEEN	Not based on the systematic review of evidence
Dru	SFE-AFCE-SFMN 2022 Consensus on the management of thyroid nodules: Thyroid nodules and pregnancy	Not based on the systematic review of evidence
Freitas-Junior	Management of early-stage triple-negative breast cancer: recommendations of a panel of experts from the Brazilian Society of Mastology	Not based on the systematic review of evidence
Khoury	The Detection, Evaluation, and Management of Dyslipidemia in Children and Adolescents: A Canadian Cardiovascular Society/ Pediatric Cardiology Association Clinical Practice Update	Not based on the systematic review of evidence
Marczynska	Updated principles of prevention, diagnosis and treatment of COVID-19 in children in Poland - recommendations for paediatricians and family medicine doctors	Not based on the systematic review of evidence
Martinez-Garcia	SEOM-GEINO clinical guideline of systemic therapy and management of brain central nervous system metastases (2021)	Not based on the systematic review of evidence
Phillips	Topical Treatment of Recurrent Vulvovaginal Candidiasis: An Expert Consensus	Not based on the systematic review of evidence
Pludowski	Clinical Practice in the Prevention, Diagnosis and Treatment of Vitamin D Deficiency: A Central and Eastern European Expert Consensus Statement	Not based on the systematic review of evidence
Seshadri	Management of Decompensated Cirrhosis in the Surgical ICU: an American Association for the Surgery of Trauma Critical Care Committee Clinical Consensus Document	Not based on the systematic review of evidence

Ananthakrishnan	Lifestyle, behaviour, and environmental modification for the management of patients with inflammatory bowel diseases: an International Organization for Study of Inflammatory Bowel Diseases consensus	Not based on the systematic review of evidence
Bhavsa	Portal cavernoma cholangiopathy: Update and recommendations on diagnosis and management	Review
Cegla	National Institute for Health and Care Excellence guidelines for lipid management	Review
Gilbert	Treatment of advanced Parkinson's disease	Review
Janas-Kozik	Polish Psychiatric Association diagnostic and therapeutic management guidelines for patients with early-onset schizophrenia	Review
Lau	Recurrent aphthous stomatitis: A comprehensive review and recommendations on therapeutic options	Review
Lu	Risk Management for Radiation-Induced Cardiovascular Disease (RICVD): The 2022 Consensus Statement of the Taiwan Society for Therapeutic Radiology and Oncology (TASTRO) and Taiwan Society of Cardiology (TSOC)	Review
Rouadi	WAO-ARIA consensus on chronic cough - Part III: Management strategies in primary and cough-specialty care. Updates in COVID-19	Review
Awada	Belgian expert consensus for tumor-agnostic treatment of NTRK gene fusion-driven solid tumors with larotrectinib	Review
Cadena	Spontaneous subarachnoid hemorrhage: a best-practice approach to identification and management in the ED	Review
Cleere	Contemporary management of paragangliomas of the head and neck	Review
Ebell	Updated American College of Chest Physicians Guideline on Antithrombotic Therapy for Venous Thromboembolism	Review
Fargeot	French recommendations for the management of adult & pediatric chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	Review
Flisiak	Management of SARS-CoV-2 infection: recommendations of the Polish Association of Epidemiologists and Infectiologists as of February 23, 2022	Review
Ma	Clinical Practice Guidelines for the Management of Behavioral and Psychological Symptoms of Dementia: A Systematic Review with AGREE II	Review
Rana	Aortic Valve Stenosis: Diagnostic Approaches and Recommendations of the 2021 ESC/EACTS Guidelines for the Management of Valvular Heart Disease -A Review of the Literature	Review
Santoro	Improving assessment and management of pain in hemophilia: an Italian Delphi consensus statement	Review
Dobrowolski	Metabolic syndrome - a new definition and management guidelines: A joint position paper by the Polish Society of Hypertension, Polish Society for the Treatment of Obesity, Polish Lipid Association, Polish Association for Study of Liver, Polish Society of	Review
Carrascosa	Practical Update of the Guidelines Published by the Psoriasis Group of the Spanish Academy of Dermatology and Venereology (GPs) on the Treatment of Psoriasis with	Review

	Biologic Agents: Part 2 - Management of Special Populations, Patients With Comorbid Conditio	
Criss	APTA Geriatrics' Guiding Principles for Best Practices in Geriatric Physical Therapy: An Executive Summary	Review
Paraskevas	Optimal Management of Asymptomatic Carotid Stenosis in 2021: The Jury is Still Out. An International, Multispecialty, Expert Review and Position Statement	Review
Prendergast	The 2021 ESC/EACTS guidelines for the management of valvular heart disease: A new template for Heart Teams and their patients	Review
Valencia	Update on the management of local anesthetic systemic toxicity	Review
Caravaca-Fontan	The management of membranous nephropathy-an update	Review
Stemler	Antifungal Prophylaxis in Acute Myeloid Leukemia: New Drugs, New Challenges: Summary of the EHA Guideline on Antifungal Prophylaxis in Adult Patients With Acute Myeloid Leukemia Treated With Novel-targeted Therapies	Review
Freedman	Adjuvant Abemaciclib Plus Endocrine Therapy in the Treatment of High-Risk Early Breast Cancer: ASCO Guideline Rapid Recommendation Update Q and A.	Summary of existing guidelines
Guidelines that were not published in medical journals		
Australian and New Zealand Society for Geriatric Medicine	Perioperative Care of Older People	No treatment recommendation
Faculty of Sexual & Reproductive Healthcare	FSRH Service Standards for Clinical Risk Management in SRH	No treatment recommendation
BC Centre for Excellence in HIV/AIDS	Primary Care Guidelines for the management of adults living with HIV/AIDS in British Columbia	No (updated) treatment recommendation
Clinical Practice Guidelines and Protocols in British Columbia	Part 2: Follow-up of Colorectal Cancer and Precancerous Lesions (Polyps)	No treatment recommendation
Cancer Care Ontario	Optimal Treatment Strategies for Localized Ewing's Sarcoma of Bone after Neoadjuvant Chemotherapy	No (updated) treatment recommendation
Children's Acute Transport Service	Poisoning	Not based on the systematic review of evidence
Carelon Medical	Proton Beam Therapy	Not based on the systematic review of evidence
Children's Acute Transport Service	Intra Osseous (IO) Line Insertio	Not based on the systematic review of evidence
Carelon Medical	Percutaneous coronary intervention	Not based on the systematic review of evidence

National Hemophilia Foundation	Recommendation on Administration of Inhibitor Bypassing Agents in the Home for Patients with Hemophilia and Inhibitors	Not based on the systematic review of evidence
SickKids Supportive Care Guidelines	Therapeutic Plasma Exchange for the ABO Incompatible Liver Transplant Patient	Not based on the systematic review of evidence
Children's Acute Transport Service	Supraventricular Tachycardia	Not based on the systematic review of evidence
Agency for Clinical Innovation	NSW Burn transfer guidelines	Not based on the systematic review of evidence
Children's Acute Transport Service	Neonatal Collapse	Not based on the systematic review of evidence
Royal College of Ophthalmologists	Designing Glaucoma Care Pathways using GLAUC-STRAT-FAST	Review
National Osteoporosis Guideline Group	Clinical guideline for the prevention and treatment of osteoporosis: Management of symptomatic osteoporotic vertebral fractures	Published in 2021
National Osteoporosis Guideline Group	Clinical guideline for the prevention and treatment of osteoporosis: Intervention thresholds and strategy	Published in 2021
Ontario Science Advisory Table Drugs and Biologics Clinical Practice Guidelines Working Group	Therapeutic management of residents of long-term care homes with COVID-19	Full guideline not available

Supplementary Table 3. Assessment of trustworthiness for the included clinical practice guidelines from 2010

First Author	Disclosure of guideline funding source	Disclosure and management of financial COIs	GDG composition	Search Strategy	Study selection	Synthesis of Evidence	Grading the strength of recommendations	Articulation of recommendations	External review	Updating plan
Guidelines published in medical journals										
AAGL [1]	No	1	Unknown	3	1	2	3	1	1	1
Ammirati [2]	Yes	1	No	4	1	2	5	4	3	2
Ansaloni [3]	Yes	5	No	4	1	2	3	4	1	1
Arlotti [4]	Yes	5	Unknown	4	3	2	5	1	1	1
Aurora [5]	No	5	No	2	1	2	5	1	1	2
Aurora [6]	No	5	Unknown	2	1	2	5	1	3	2
Barkun [7]	Yes	1	No	1	1	2	5	1	1	2
Bergh [8]	No	1	Unknown	4	1	2	2	1	1	1
Bhasin [9]	Yes	1	No	4	4	2	3	1	3	1
Body [10]	No	1	No	1	3	2	1	1	1	1
Boyce [11]	Yes	5	No	5	5	2	1	3	2	1
Burstein [12]	No	4	Unknown	4	1	2	1	1	3	2
Camm [13]	Yes	1	No	1	1	2	3	4	2	1
Chadban [14]	Yes	5	Unknown	3	1	3	1	2	1	1
Chadban [15]	Yes	5	Unknown	3	1	2	1	3	1	1
Chiodo [16]	No	1	No	1	1	2	5	1	3	2
Dasgupta [17]	Yes	5	Yes	1	1	1	2	1	2	3
Dickstein [18]	No	1	Unknown	1	1	2	2	1	1	1
Einhaupl [19]	No	1	No	4	1	2	5	1	1	1
Boumis [20]	Yes	1	No	2	2	2	1	2	1	1

Farge [21]	No	5	No	2	1	2	3	1	3	1
Farraye [22]	No	1	No	2	1	1	2	4	1	1
Fehlings [23]	Yes	5	No	2	1	2	1	1	1	1
Garbe [24]	No	5	No	1	1	1	1	1	1	3
Hazinski [25]	No	5	No	1	1	1	1	2	2	2
Hiratzka [26]	Yes	5	No	2	1	3	3	1	3	3
Horlocker [27]	No	1	Unknown	1	1	2	3	1	1	2
Kalkanis [28]	Yes	1	No	4	4	2	2	1	3	1
Lin [29]	No	1	No	1	1	1	2	1	2	1
Linskey [30]	Yes	1	No	4	1	2	2	4	3	2
Love [31]	Yes	1	No	2	1	2	3	1	1	1
Malthaner [32]	No	1	Unknown	3	4	2	1	1	3	2
Marsden [33]	No	5	Unknown	2	1	2	2	4	3	1
Mehta [34]	Yes	1	No	4	4	2	5	1	2	1
Meierkord [35]	No	1	Unknown	4	1	2	2	1	1	1
Milburn [36]	No	1	Unknown	2	1	2	2	1	1	3
Mygland [37]	No	1	Unknown	3	1	2	2	4	1	1
Neill [38]	No	5	No	1	1	2	5	1	3	2
AISF/SIMIT/SIMAST Expert Opinion Meeting [39]	No	5	No	1	1	2	5	1	3	1
Novak [40]	Yes	5	No	2	1	2	5	1	3	1
Perfect [41]	Yes	1	No	2	1	2	3	1	2	3
Pernod [42]	Yes	1	Unknown	1	1	2	2	1	2	1
Perry [43]	No	1	No	4	1	2	3	1	1	1
Peters [44]	Yes	1	No	4	1	2	2	1	2	3
Provan [45]	Yes	1	No	2	1	2	1	1	1	1
Rosenquist [46]	No	1	No	1	1	2	1	1	3	1
Ryken [47]	Yes	1	No	4	5	1	2	4	3	2

Schulman [48]	Yes	1	No	2	1	2	1	3	1	1
Shehata [49]	Yes	1	No	5	1	3	2	1	3	1
Soffietti [50]	No	1	No	1	1	1	2	1	1	1
Solomkin [51]	Yes	5	No	5	1	2	5	1	3	3
Stefanidis [52]	No	2	No	2	1	2	2	2	1	1
Steiner [53]	No	1	No	2	1	1	5	1	1	2
Thompson [54]	Yes	1	Unknown	2	1	2	2	4	1	1
Wong [55]	Yes	1	No	1	1	2	1	1	3	2
Guidelines that were not published in medical journals										
Blumberg [56]	No	1	No	4	1	5	3	1	1	3
Cavalcante [57]	Yes	5	Yes	3	4	2	5	1	3	3
Chapple [58]	Yes	1	Yes	5	3	5	1	3	5	3
Evans [59]	Yes	4	No	4	3	5	1	1	5	4
Fowell [60]	Yes	5	No	4	3	2	1	1	3	3
French [61]	Yes	1	Yes	1	1	4	5	4	2	2
Gordon [62]	Yes	5	No	4	3	2	1	3	3	4
Graham [63]	Yes	5	No	4	5	5	5	1	2	3
Hawk [64]	No	1	No	1	1	1	2	1	1	1
Lindley [65]	Yes	1	No	5	1	1	3	1	3	2
McIntyre [66]	Yes	5	Yes	1	3	5	3	3	3	3
Rennie [67]	Yes	5	No	4	3	2	1	3	5	1
Rudolf [68]	Yes	1	No	4	3	5	5	2	1	1
Walkinshaw [69]	Yes	5	No	4	1	2	1	3	1	3
Young [70]	Yes	5	Yes	4	3	5	1	1	5	2

COI: conflict of interest; GDG: guideline development group

Supplementary Table 4. Assessment of trustworthiness for the included clinical practice guidelines from 2022

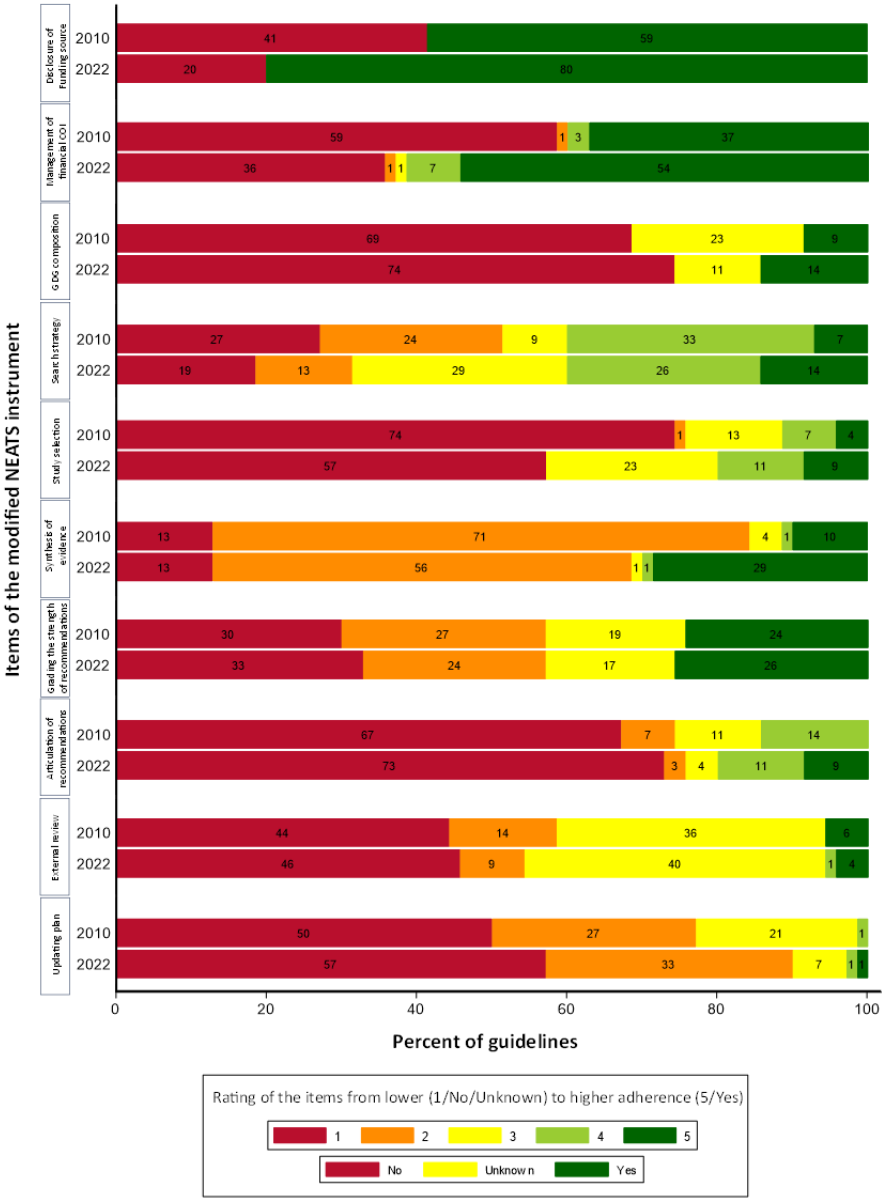
First Author	Disclosure of guideline funding source	Disclosure and management of financial COIs	GDG composition	Search Strategy	Study selection	Synthesis of Evidence	Grading the strength of recommendations	Articulation of recommendations	External review	Updating plan
Guidelines published in medical journals										
AbuRahma [71]	No	1	No	5	1	2	2	4	3	1
Ahn [72]	Yes	1	No	2	1	2	1	1	1	1
Apfelbaum [73]	Yes	2	No	5	1	3	1	1	1	3
Bagou [74]	No	4	No	1	1	2	1	1	1	1
Bartoletti [75]	Yes	5	No	5	5	5	1	1	1	1
Bernhardt [76]	Yes	1	No	2	1	2	1	1	1	1
Boland [77]	No	5	No	3	1	2	2	5	1	1
Box [78]	Yes	5	No	3	3	2	3	1	3	2
Brieva [79]	Yes	1	No	2	1	1	1	1	1	1
Capone [80]	Yes	5	No	2	1	1	1	1	3	2
Choi [81]	Yes	5	No	4	3	5	5	4	1	1
Compher [82]	Yes	1	No	4	4	5	5	1	1	2
Corniola [83]	Yes	5	No	4	3	2	1	1	1	1
Cuker [84]	Yes	5	Yes	5	4	5	5	5	3	5
de Sá [85]	Yes	1	No	2	1	2	2	1	1	1
Dhar [86]	Yes	1	No	1	1	2	3	1	3	2
Dijkermana [87]	No	1	Unknown	3	1	1	1	1	1	1
Douketis [88]	Yes	5	No	1	3	2	5	5	1	2
Drosos [89]	Yes	2	Yes	3	4	2	2	1	2	1
Duan [90]	Yes	1	No	2	1	2	1	2	1	1
Fernández-Vigo [91]	Yes	1	No	3	1	1	1	1	1	1
Germano [92]	Yes	5	No	3	5	4	2	1	3	1
Gisbert [93]	Yes	1	No	3	1	2	2	1	1	1

Glikson [94]	Yes	5	No	1	1	2	5	1	3	2
Goodman [95]	Yes	5	Yes	4	4	2	5	4	3	1
Guerrero [96]	No	5	Unknown	4	5	2	1	2	1	1
Gupta [97]	Yes	5	No	1	1	2	3	1	1	1
Halvorsen [98]	Yes	1	No	1	1	2	3	4	3	2
Heidenreich [99]	Yes	5	No	5	1	2	2	1	3	1
Hogan [100]	Yes	5	No	4	3	5	5	1	1	1
Hwang [101]	Yes	5	No	4	5	5	5	5	3	2
Isselbacher [102]	Yes	4	No	3	1	2	3	1	3	2
Jones [103]	No	5	Unknown	4	1	2	1	1	1	1
Koepsel [104]	No	5	No	2	1	2	2	1	1	2
Kremer [105]	Yes	5	No	1	4	5	2	5	2	1
Leal [106]	No	1	No	3	1	2	1	1	1	1
Lee [107]	No	5	No	4	1	5	3	1	4	1
Ligibel [108]	Yes	5	Yes	4	3	2	5	1	5	2
Marchetti [109]	Yes	1	No	2	3	2	3	1	1	2
McDonagh [110]	Yes	1	Yes	1	1	2	3	1	3	2
McQuaid [111]	Yes	5	No	5	3	2	5	1	3	1
El Miedany [112]	Yes	5	No	1	1	1	2	1	1	1
Nakamura [113]	Yes	5	No	3	1	2	5	1	3	2
Papworth [114]	Yes	1	No	3	5	1	1	1	1	1
Pei [115]	Yes	5	No	3	1	2	2	1	1	1
Pratt [116]	Yes	5	Unknown	4	1	2	3	1	3	3
Ramantani [117]	No	4	No	3	1	4	5	1	1	1
Santoro [118]	Yes	1	No	3	1	1	1	1	1	1
Sawhney [119]	No	5	Unknown	4	4	5	2	4	1	1
Sieswerda [120]	Yes	1	No	1	1	2	2	1	3	1
Tiseo [121]	Yes	1	No	2	1	2	2	1	1	1
Tom [122]	No	1	No	3	1	1	2	1	1	1
Turc [123]	Yes	1	No	4	3	5	3	4	2	1
Wyckoff [124]	No	3	Unknown	1	3	5	5	1	2	3
Yiu [125]	Yes	4	Yes	4	5	5	5	1	2	2
Guidelines that were not published in medical journals										

Affandi [126]	Yes	5	No	4	1	2	1	1	3	2
Becker [127]	Yes	1	Yes	5	1	5	3	1	3	3
Castleman [128]	Yes	5	No	4	4	5	5	3	5	2
Gibbs [129]	Yes	5	Yes	3	1	2	5	1	3	1
Dockrell [130]	Yes	1	Unknown	3	1	2	2	1	3	1
Falkson [131]	Yes	4	No	4	3	5	1	3	3	1
López-Vélez [132]	Yes	5	No	3	5	5	5	5	3	2
Heer [133]	Yes	5	No	4	3	5	1	1	3	2
Marshall [134]	Yes	5	Yes	3	3	2	1	1	3	2
Owen [135]	Yes	1	No	1	1	1	1	1	1	4
Roberts [136]	Yes	1	No	3	1	2	5	4	3	2
Soe [137]	Yes	5	No	5	3	5	1	3	5	2
Ward [138]	No	5	No	5	3	5	1	1	3	1
Wiebe [139]	Yes	5	Unknown	1	1	2	2	4	3	3
Wollenberg [140]	Yes	5	Yes	5	4	5	3	1	2	2

COI: conflict of interest; GDG: guideline development group

Supplementary Figure 3. Summary of ratings of the included guidelines across the items of the modified NEATS instrument



COI: conflict of interest; GDG: guideline development group; NEATS: National Guideline Clearinghouse Extent of Adherence to Trustworthy Standards.

[1] We rated the "disclosure of funding source" item using two response options (yes/no) and the "composition of the GDG" item using three response options (yes/no/unknown). Other items were scored on the 5-point Likert scale.

Supplementary Table 5. Limitations of the included guidelines in adherence to each item of the modified NEATS instrument

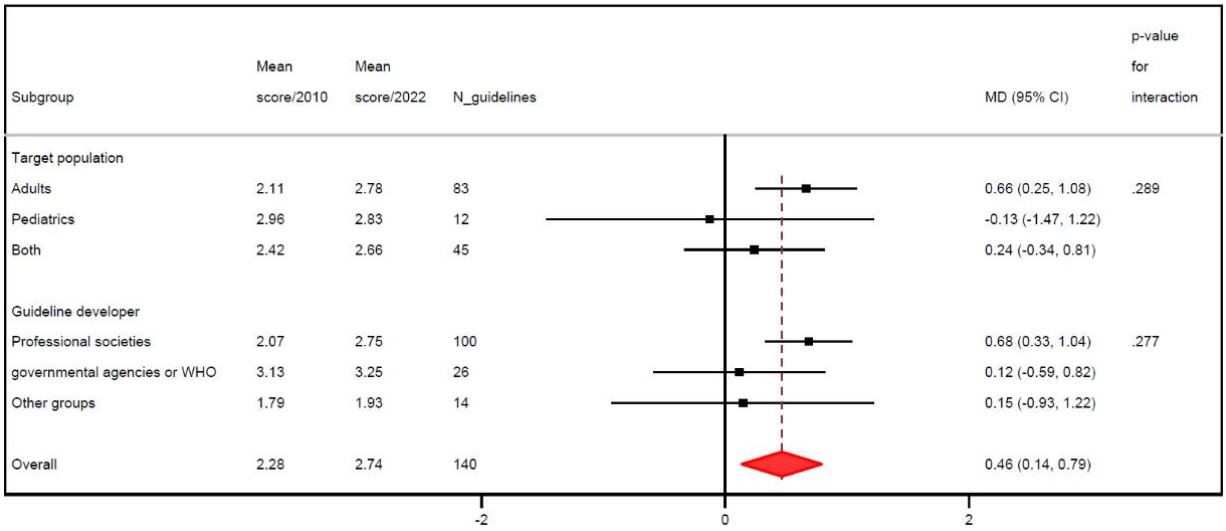
Domains of trustworthiness (The modified NEATS instrument item)	Limitations [a]	Number of guidelines with the limitation (%)		
		2010 (n=70)	2022 (n=70)	Total (n=140)
Disclosure of funding sources (item 1)	Lack of information on the funding sources for the development of the guideline	29 (41.4)	14 (20)	43 (30.7)
Disclosure and management of COIs (item 2)	Failing to explicitly identify chair when GDG members declared financial COIs	33 (47.1)	18 (25.7)	51 (36.4)
	Failing to appoint at least one chair without financial COIs	5 (7.1)	10 (14.3)	15 (10.7)
	Convening the GDG in which more than one-third of the members had financial COIs	1 (1.4)	1 (1.4)	2 (1.4)
	Not clear whether direct industry funding supported the development of the guideline	0	1 (1.4)	1 (0.7)
GDG composition (item 3)	Failing to include a patient representative	41 (58.6)	43 (61.4)	84 (60)
	Failing to include a methodologist	29 (41.4)	38 (54.3)	67 (47.8)
	Insufficient identification of GDG members (i.e., it is unclear whether the GDG included a methodologist or a patient representative)	16 (22.8)	8 (11.4)	24 (17.1)
Systematic review of evidence				
Search strategy (Item 4a)	Failing to describe search terms	19 (27.1)	13 (18.6)	32 (22.9)
	Outdated search (i.e., time of the last search to publication of the guideline was longer than 12 months for conditions with rapid evidence accrual or longer than 18 months for other conditions)	6 (8.6)	20 (28.6)	26 (18.6)
	Searched only one database	12 (17.1)	10 (14.3)	22 (15.7)
	Lack of information on which databases were searched	3 (4.3)	1 (1.4)	4 (2.8)
Study selection (Item 4b)	Failing to describe eligibility criteria	25 (35.7)	22 (31.4)	47 (33.6)
	Inadequate or ambiguous defining of eligibility criteria	24 (34.3)	21(30)	45 (32.1)
	Failing to report the method for screening retrieved studies	7 (10)	7 (10)	14 (10)
	Lack of duplicate screening of retrieved studies	2 (2.8)	9 (12.8)	11 (7.8)
	At least one component of the eligibility criteria did not match the relevant recommendation question	1 (1.4)	0	1 (0.7)
Synthesis of evidence (Item 4c)	Failing to appropriately rate the certainty of evidence (i.e., either did	50 (71.4)	39 (55.7)	89 (63.6)

	not rate the certainty of evidence for each prioritized outcome or did not present reasons for rating down/up the certainty of evidence)			
	Failing to present a quantitative or qualitative synthesis of included studies	9 (12.9)	9 (12.9)	18 (12.9)
	Incorporating only study design in rating the certainty of evidence	3 (4.3)	1 (1.4)	4 (2.9)
Rating the strength of recommendations (item 5)	Lack of rating the strength of recommendations	21 (30)	23 (32.9)	44 (31.4)
	Failing to provide explicit judgment on the balance of benefits and harms that informed the strength of recommendations	19 (27.1)	17 (24.3)	36 (25.7)
	Inappropriately formulating strong recommendations based on low or very low certainty of evidence	13 (18.6)	12 (17.1)	25 (17.9)
Articulation of recommendations (item 6)	Failing to explicitly identify the population and comparator in recommendations	47 (67.1)	51 (72.9)	98 (70)
	Failing to provide the strength of recommendation in proximity to recommendations	8 (11.4)	3 (4.3)	11 (7.9)
	Unclear direction of recommendations	5 (7.1)	2 (2.9)	7 (5)
External review (item 7)	Lack of conducting external review	31 (44.3)	32 (45.7)	63 (45)
	Insufficient identification of members of the external review team (i.e., it is unclear whether the external review team included a methodologist)	23 (32.8)	15 (21.4)	38 (27.1)
	Insufficient identification of members of the external review team (i.e., it is unclear whether the external review team included relevant clinicians)	10 (14.3)	6 (8.6)	16 (22.8)
	Failing to include a methodologist in the external review team	9 (12.8)	7 (10)	15 (21.4)
Updating plan (item 8)	Lack of plans for updating	35 (50)	40 (57.1)	75 (53.6)
	Planning timeframe longer than 3 years for reviewing evidence for potential updating	19 (27.1)	23 (32.9)	42 (30)
	Failing to present conditions that determine when partial or full guideline update is required	15 (21.4)	5 (7.1)	20 (14.3)

COI: conflict of interest; GDG: guideline development group; NEATS: National Guideline Clearinghouse Extent of Adherence to Trustworthy Standards.

[a] We rated the "disclosure of funding sources" item using two response options (yes/no) and the "composition of the GDG" item using three response options (yes/no/unknown). All other items were scored on the 5-point Likert scale (1= lowest adherence and 5= highest adherence to the item). The limitations in adherence to the items represent issues that led to a rating of "No" or "Unknown" for items with categorical response options and a score of "1", "2", or "3" for other items

Supplementary Figure 4. Results of the subgroup analyses of change in mean scores across critical items of the modified NEATS instrument comparing guidelines published in 2022 versus 2010



MD: mean difference; CI: confidence interval; N: number; NEATS: National Guideline Clearinghouse Extent of Adherence to Trustworthy Standards; WHO: World Health Organization.

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Chapter 3: Modifications to the NEATS instrument for more appropriate and reproducible assessment of guidelines trustworthiness

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BRIEF REPORT

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Modifications to the NEATS instrument for more appropriate and reproducible assessment of guidelines trustworthiness

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Abstract

Rational: The National Guideline Clearinghouse Extent of Adherence to Trustworthy Standards (NEATS) instrument measures the adherence of clinical practice guidelines to the trustworthiness standards proposed by the Institute of Medicine. However, rather than trustworthiness or methodological quality, the NEATS instrument evaluates the quality of reporting in addressing the management of conflict of interest of guideline development group members, systematic review process and assessment of the certainty of the evidence, rating the strength of recommendations, and updating plans. Furthermore, the NEATS instrument instructions on rating items are sufficiently limited that they may compromise the reproducibility of the instrument.

Methods (Modifications to the NEATS Instrument): In the context of a specific methodological research project, we developed modifications to the NEATS instrument that include modifying the wording of items to capture trustworthiness rather than reporting quality and creating an algorithm for all items that maps responses to a series of prompting questions and guides the user in arriving at a rating from 1 to 5 or yes, no, or unknown, as applicable.

Implications: Modifications to the NEATS instrument present a structured and practical framework to assess the degree to which clinical practice guidelines are trustworthy, and they ensure that items evaluate trustworthiness and improve the reproducibility of assessments across a range of raters' level of expertise in guideline methodology.

KEYWORDS

assessment of trustworthiness, clinical practice guidelines, IOM standards, methodological quality, modifications, NEATS instrument, reproducibility

1 | RATIONALE

Clinical practice guidelines are documents developed by a panel of individuals who, through systematic reviews of evidence, evaluate the benefits and harms of alternative care options to make recommendations,[1] that are fundamental to clinical, public health, and policy decision-making. It is, therefore, crucial to determine the extent to which users can have confidence in recommendations from guidelines. Multiple instruments are available to assess the trustworthiness of guidelines. The Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument is the widely accepted one that has a comprehensive scope and intends to evaluate the rigour of methods, quality of reporting, and applicability of guidelines.[2] The AGREE II, however, does not

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address important details about the process for conducting systematic reviews of evidence to inform the guidelines. The National Guideline Clearinghouse (NGC) Extent of Adherence to Trustworthy Standards (NEATS) instrument[3] overcomes this limitation by translating the eight trustworthiness standards proposed by the Institute of Medicine (IOM)[1] into 15 items with the aim to measure the methodological quality of guidelines—from which three are specific to the systematic review process. Box 1 presents the IOM standards for developing trustworthy clinical practice guidelines.

When conducting a research project with the aim of addressing the trustworthiness of guidelines and to what extent trustworthiness has changed since the introduction of the IOM standards, we used the NEATS instrument to assess trustworthiness. In doing so, we faced two challenges. First, for some domains, the NEATS instrument evaluates the quality of reporting rather than the risk of bias or methodological quality, the latter being both the apparent intent of the instrument and a construct more relevant to guideline trustworthiness. For example, in addressing the search strategy from the systematic review supporting the guideline, the NEATS instrument asks whether the guideline or a companion document reports a list of databases, search terms, and time of the search. This question addresses reporting and not trustworthiness: authors may, for instance, report that they used only a single database, inadequate search terms, and the search may be outdated. They would satisfy the item in terms of reporting but not in terms of trustworthiness. Second, the instructions provided for using the instrument have limitations. For several items rated on a 5-point Likert scale, for instance, users must determine how to assign ratings of 'poor', 'fair', 'good', 'very good', or 'excellent' without details about what makes adherence to an item fit into each of these categories. This threatens the reproducibility of the assessments and may lead to inconsistent judgements.

Key points

- National Guideline Clearinghouse Extent of Adherence to Trustworthy Standards (NEATS) instrument measures the adherence of guidelines to the trustworthiness standards proposed by the Institute of Medicine.
- NEATS instrument, for some domains, evaluates the quality of reporting rather than trustworthiness or methodological quality and lacks sufficient instructions on rating items.
- We developed modifications to the NEATS instrument to address these limitations. We modified the wording of items to capture trustworthiness rather than reporting quality and created an algorithm for all items that guides the user on arriving at a specific rating.
- Our modifications ensure items evaluate the appropriateness of the guideline development process and improve the reproducibility of assessments across a range of raters' level of expertise in guideline methodology.

2 | MODIFICATIONS TO THE NEATS INSTRUMENT

To optimize our ongoing research project, over multiple discussions, we reached a consensus on how to modify the instrument with two goals: (1) specifically addressing the appropriateness of the guideline development process and (2) improving the reproducibility of assessments across a range of raters' level of expertise in guideline methodology.

To achieve these goals, we first modified the wording of some items to capture trustworthiness rather than reporting quality. This includes items addressing whether the guideline panel appropriately managed the conflict of interests (COI) of members (item 2)[4–6]; whether the systematic search of available evidence was relevant, up to date, and included an adequate selection of databases and additional methods to identify relevant studies (item 5a)[7–9]; whether eligibility criteria of systematic review match recommendation questions and the study selection process was at low risk of bias (item 5b)[7–9]; whether assessment of the certainty of the evidence underlying recommendations was appropriate (item 6)[7]; whether the strength of recommendations matches balance of benefits and harms, values and preferences of patients, and certainty of underlying evidence (item 9)[10]; and whether the updating plan of the guideline is appropriate (item 12) (Table 1).

Second, we created an algorithm for all items that maps the responses to a series of prompting questions and guides the user on arriving at a rating from 1 to 5 or yes, no, or unknown, as applicable. Figure 1 presents an example of the algorithm. Where applicable, we provide additional details, including examples, to interpret the prompting questions. The prompting questions were answered 'Yes', 'No' or 'No information/unclear' and were agreed on for less subjectivity in the interpretation. All algorithms start with a key question where the answer 'No' or 'No information/unclear' means the lowest adherence to the given item.

Additionally, we grouped items from the NEATS instrument addressing the same aspect of the guideline development into a single item. For example, we grouped together three items (items 3a, 3b and 4, addressing the inclusion of clinical experts, methodologists, and patients'

representatives) related to the 'composition of guideline development group'. Another example is the item on 'rating the certainty of the evidence' (item 6) which we considered as a relevant aspect of the 'synthesis of evidence' item (item 5c). We also grouped together items 7–9 to address the appropriateness of the rating of strength of recommendations.

The Supporting Information S1 provides the modified instrument manual. Our modified tool includes 10 items covering all eight domains addressed in the NEATS instrument. Two of the 10 items are measured using two or three response options (one item [yes/no] and one item [yes/no/unknown]), and 8 items are rated on the 5-point Likert scale. The response 'Yes' on categorical items or a score of 5 on the other items represents the highest adherence to the given item, and a score of 4 represents acceptable adherence. We agreed on the following items as critical in addressing the trustworthiness of clinical practice guidelines: disclosure and management of COIs (item 2), study selection and synthesis of evidence from the systematic review process (items 4b and 4c), and grading the strength of recommendations (item 5).

3 | IMPLICATIONS

Our modification of the NEATS instrument presents a structured framework to evaluate the degree to which practice guidelines are trustworthy. Because we developed this modification to address a specific need that arose in the context of a research project, this modification has not undergone formal instrument development or validation. In addition, to ensure feasibility, we decided to simplify the assessment of some of the items (e.g., we focused on financial COIs, usually classified as high levels of COI, and did not include intellectual COIs that are considered moderate[11]). Nevertheless, this modification raises awareness regarding the limitations of the NEATS instrument and provides a promising practical solution to addressing those limitations. Researchers who want to study the trustworthiness of guidelines, journal editors who want to evaluate the trustworthiness of guidelines for publication, and clinicians who want to recognize a trustworthy guideline for use in their practice may benefit from our modification to the NEATS instrument that facilitates much more explicit and appropriate judgements.

BOX 1 Institute of Medicine standards for developing trustworthy clinical practice guidelines.

1. The processes by which a guideline is funded should be detailed explicitly and publicly accessible.
2. The guideline development group members should declare all current and planned financial and nonfinancial activities pertinent to the potential scope of the guideline.
   a) The chair or cochairs should not have a conflict of interest.
   b) Members with a conflict of interest should represent not more than a minority of the guideline development group.
   c) Members of the guideline development group should divest themselves of financial activities they or their family members have in entities whose interests could be affected by guideline recommendations.
   d) Funders should have no role in guideline development.
3. The guideline development group should be multidisciplinary and balanced, comprising a variety of methodological experts, clinicians, and populations expected to be affected by the guideline.
4. Guideline developers should use systematic reviews that meet standards set by the Institute of Medicine's Committee on Standards for Systematic Reviews of Comparative Effectiveness Research.
5. For each recommendation, guidelines should provide a rating of the strength of the recommendation based on consideration of (a) balance of benefits and harms; (b) certainty of the evidence underpinning the recommendation; and (c) value and preferences of patients.
6. Recommendations should be articulated in a standardized form detailing precisely what the recommended action is, and under what circumstances it should be performed.
7. External reviewers should comprise a full spectrum of relevant stakeholders, including scientific and clinical experts, relevant organizations, and patient representatives and a draft of the guideline at the external review stage or immediately following it should be made available to the public for comment.
8. The proposed date for future update should be documented in the guideline.
   a) Literature should be monitored regularly following the publication to identify the emergence of new, potentially relevant evidence and to evaluate the continued validity of the guideline.
   b) Guidelines should be updated when new evidence suggests the need for modification of recommendations.

TABLE 1 Comparison of the wording of the National Guideline Clearinghouse Extent of Adherence to Trustworthy Standards (NEATS) items and modified items.

NEATS items	Modified items
Item 2: Financial conflicts of interest of guideline development group members have been disclosed and managed.	**Item 2:** Financial conflicts of interest of guideline development group members have been disclosed and appropriately managed.
Item 5a: The guideline or a related companion document describes a search strategy that includes a listing of database(s) searched, a summary of search terms used, and the specific time period covered by the literature search.	**Item 4a:** The guideline or related companion documents describe a search strategy that matches the relevant recommendation questions, includes an adequate selection of databases and additional methods to identify relevant studies, and is up to date.
Item 5b: The guideline or a related companion document describes the study selection that includes the number of studies identified, the number of studies included, and a summary of inclusion and exclusion criteria.	**Item 4b:** The guideline or related companion documents describe the study selection process that includes unambiguous eligibility criteria that match the relevant recommendation questions, number of studies retrieved from the search, duplicate screening of identified studies, number of studies retrieved from the search number of studies included, and reasons for excluding studies.
Item 6: The guideline provides a grading or rating of the level of confidence in or certainty regarding the quality or strength of the evidence for each recommendation.	**Item 4c:** The guideline or related companion documents provide a synthesis of evidence from the included studies and an appropriately assessed the certainty of evidence for each recommendation.
Item 9: The guideline gives a rating of the strength of the recommendation for each recommendation that takes into account benefits and harms, available evidence, and confidence in the underlying evidence.	**Item 5:** The guideline gives a rating of the strength of the recommendation for each recommendation that was appropriately informed by the balance of benefits and harms of alternative care options, value and preferences of patients, and certainty of the underlying evidence.
Item 12: The guideline describes a procedure to update the guideline.	**Item 8:** The guideline or supporting documents provide an adequate time frame for review of evidence for potential updating and describe adequate criteria that warrant updating the recommendation.

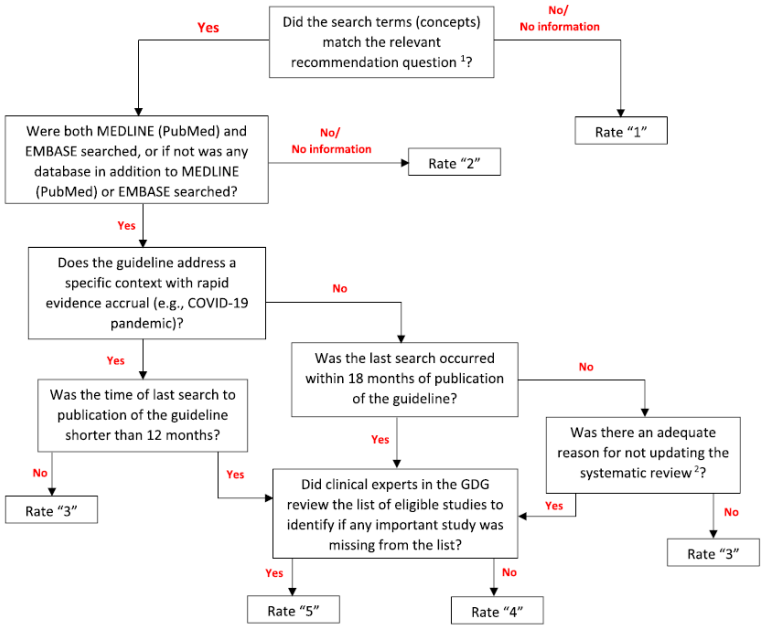

FIGURE 1 The algorithm for the assessment of the search strategy of the systematic review of evidence informing the guidelines (item 4a).

AUTHOR CONTRIBUTIONS

Maryam Ghadimi: Conceptualization; methodology; investigation; project administration; validation; visualization; writing—original draft preparation; writing—review and editing. **Gordon Guyatt**: Conceptualization; methodology; validation; writing—review and editing. **Romina Brignardello-Petersen**: Conceptualization; methodology; supervision; validation; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

ETHICS STATEMENT

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Supplementary Appendix C3

A guideline trustworthiness assessment tool based on the NEATS Instrument – Instruction Manual

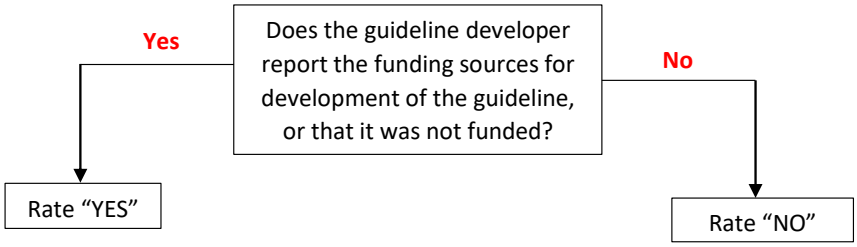
Please read carefully:

- This tool includes 10 items, of which 2 items are measured using categorical response options (one item (yes / no) and one item (yes/ no/ unknown)) and 8 items are rated on the 5-point Likert scale.
- Each item should be judged using the provided algorithm. Please read the footnotes (if provided) for more information about the prompting questions in the algorithm.
- For each item, you will find information on "where to look" to find relevant data for your judgment.
- The assessment of trustworthiness can be performed at the guideline level (i.e., assessing all recommendations in a guideline) or at the recommendation level (i.e., assessing a single or a group of recommendation(s) of interest in a guideline). Therefore, the user should prespecify the assessment level and apply the tool accordingly.

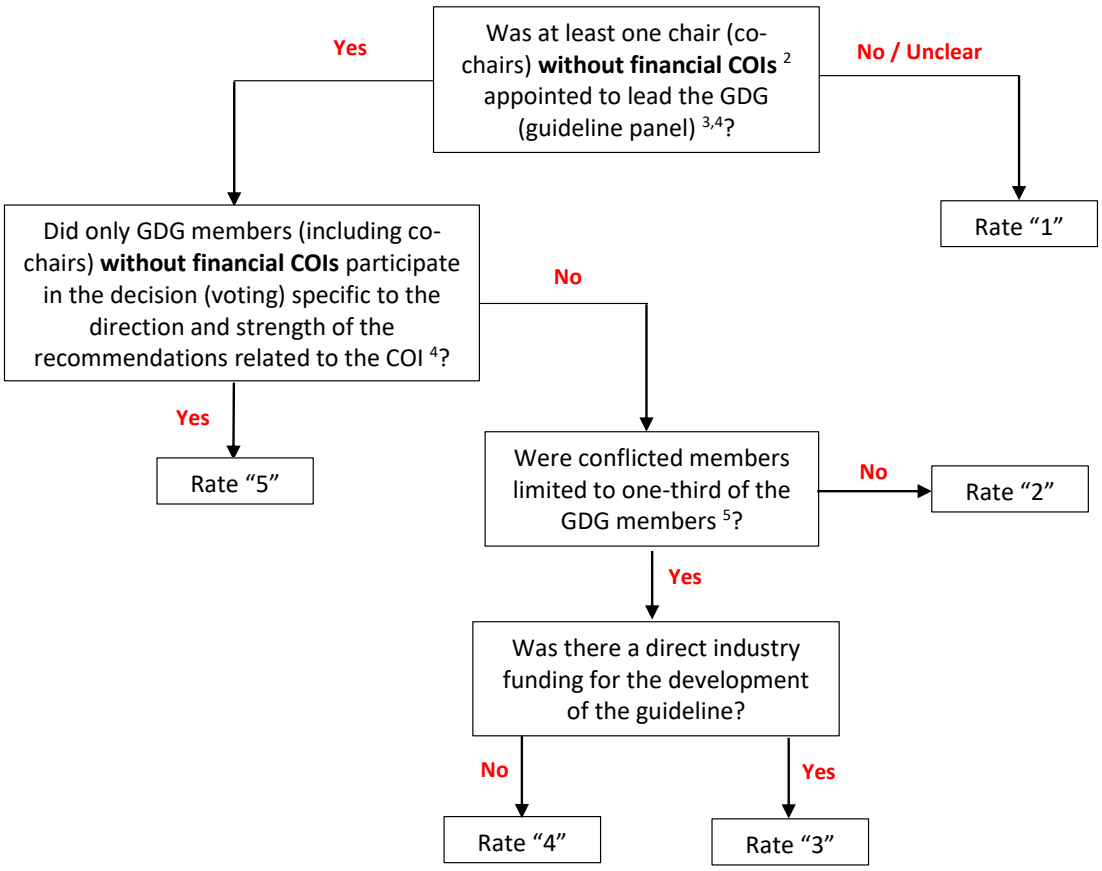
The definitions you should be familiar with before starting your assessment:

- Clinical practice guideline (CPG): Documents that were developed by a formal panel of individuals who evaluate systematic reviews of evidence and benefits and harms of alternative care options to make recommendations.
- Recommendation: An actionable statement that describes a course of action recommended or suggested by the guideline based on clinical questions, evidence retrieval, and consideration of other information in an analytic framework.
- Guideline development group (GDG) (may also be labelled as writing committee, task force, or guideline panel): A group of individuals who decides on topics to be covered within the guideline, formulates questions, develops, and agrees on the recommendations in the guideline using evidence summaries prepared by a working group, and endorses the final guideline document for approval by the oversight committee.
- The certainty of evidence (may also be labelled as quality of evidence or level of evidence): The level of confidence in the estimates of the effect of an intervention versus a comparator for a specific outcome. There are a variety of systems for evaluating the certainty of evidence which consider different characteristics of the evidence and use different categories of certainty.
- Strength of recommendation (may also be labelled as class/level of recommendation): The degree to which the GDG is confident in the balance between the desirable and undesirable consequences of implementing the recommendation. There are different frameworks for grading the strength of recommendation. These frameworks consider different criteria in determining the strength of recommendation and label the level of strength differently.
- Values and preferences of patients: The relative importance patients place on the health outcomes. This implicitly relates to other aspects that are relevant to a decision (e.g., equity, feasibility, or acceptability considerations).

1. Disclosure of Guideline Funding Source
The clinical practice guideline discloses and states explicitly its funding source(s).
Where to Look: Examine the methods for guideline development or guideline development process section, acknowledgement section, appendices, or link to any publication platform (like MAGICapp, GRADEpro, or any website, etc.) for "funding source(s)".



1. Disclosure and management of conflict of interests (COIs)
Financial COI of guideline development group members have been disclosed and appropriately managed [1].
Where to Look: Examine the methods for guideline development or guideline development process section, authorship section, appendices, or link to any publication platform (like MAGICapp, GRADEpro, or any website, etc.) for "conflict of interest" or "competing interests" or "disclosure" or "declaration of interest".



[1] This algorithm only addresses high level of COIs (financial COIs) according to the classification proposed by the American College of Physicians Clinical Guidelines Committee (DOI: https://doi.org/10.7326/M18-3279). Users can also assess intellectual COIs refers to "academic activities that create the potential for an attachment to a specific point of view that could unduly affect an individual's judgment about a specific recommendation". Users can use the same algorithm to assess guidelines concerning intellectual COIs.

[2] Financial COIs includes any financial benefit (e.g., any income from employment, consulting, speaking engagements, advising, and other management activities; equity ownership in public and privately traded companies; honoraria; loans; royalties, patents, contracts, and grants; and expert testimony) received from **for-profit-organizations** (e.g., pharmaceutical companies) related to the topic discussed or products recommended in the guideline. When the relevance of pharmaceutical companies to the products

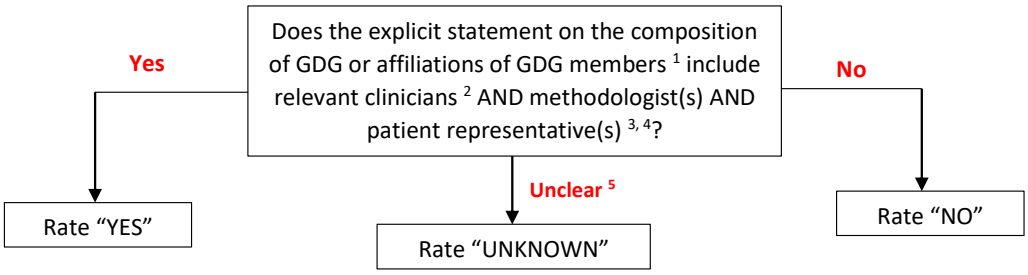
recommended in the guideline is not clarified, please assume that the financial COI is not relevant. Please note, funding received from governmental organizations (e.g., CIHR, NIH) should not be considered financial COI.

[3] If no information about COI is provided in the guidelines, choose "Unclear" and rate "1".

[4] Guidelines, in the conflict-of-interest section, may explicitly state that "no member has financial COIs" or "declared financial interests of the member perceived not in conflict with guideline topics or perceived nonsignificant that requires no action" or "members with financial COIs were excluded from participation in the voting of relevant recommendations", in any of these cases, choose "YES". If none applied, please review the COI declarations of each member.

[5] Guidelines may list GDG members for each recommendation rather than at the guideline level.

1. Guideline Development Group (GDG) Composition: Multidisciplinary
The GDG includes relevant clinical experts, methodologist(s), and patient representative(s).
Where to Look: Examine the opening paragraphs, methods for guideline development or guideline development process section, authorship section, acknowledgement section, contribution section, appendices, or link to any publication platform (like MAGICapp, GRADEpro, or any website, etc.) for the "composition of GDG".



[1] Please note that the GDG may be identified as "writing committee", "task force", or "guideline panel". If the guideline did not identify the GDG, writing committee, task force, or guideline panel (which is rare), please consider the authors of the guideline as members of the GDG. Please note that you do not need to check the affiliations of all members; when you identified all 3 groups (clinicians, methodologist(s), patient representative(s)), you can stop reviewing the affiliations of remaining members and choose "YES" for this question.

[2] Relevant clinicians are individuals with clinical specialties relevant to the topic of the guideline.

[3] Patient representatives include current and former patients, carers who provide non-reimbursed care and support to patients including family members, members of the public as potential patients and as funders of healthcare through taxation, or advocates from patient/consumer organizations. The inclusion of one of these categories in the GDG is adequate to ensure that the perspective of patients was included in the guideline development.

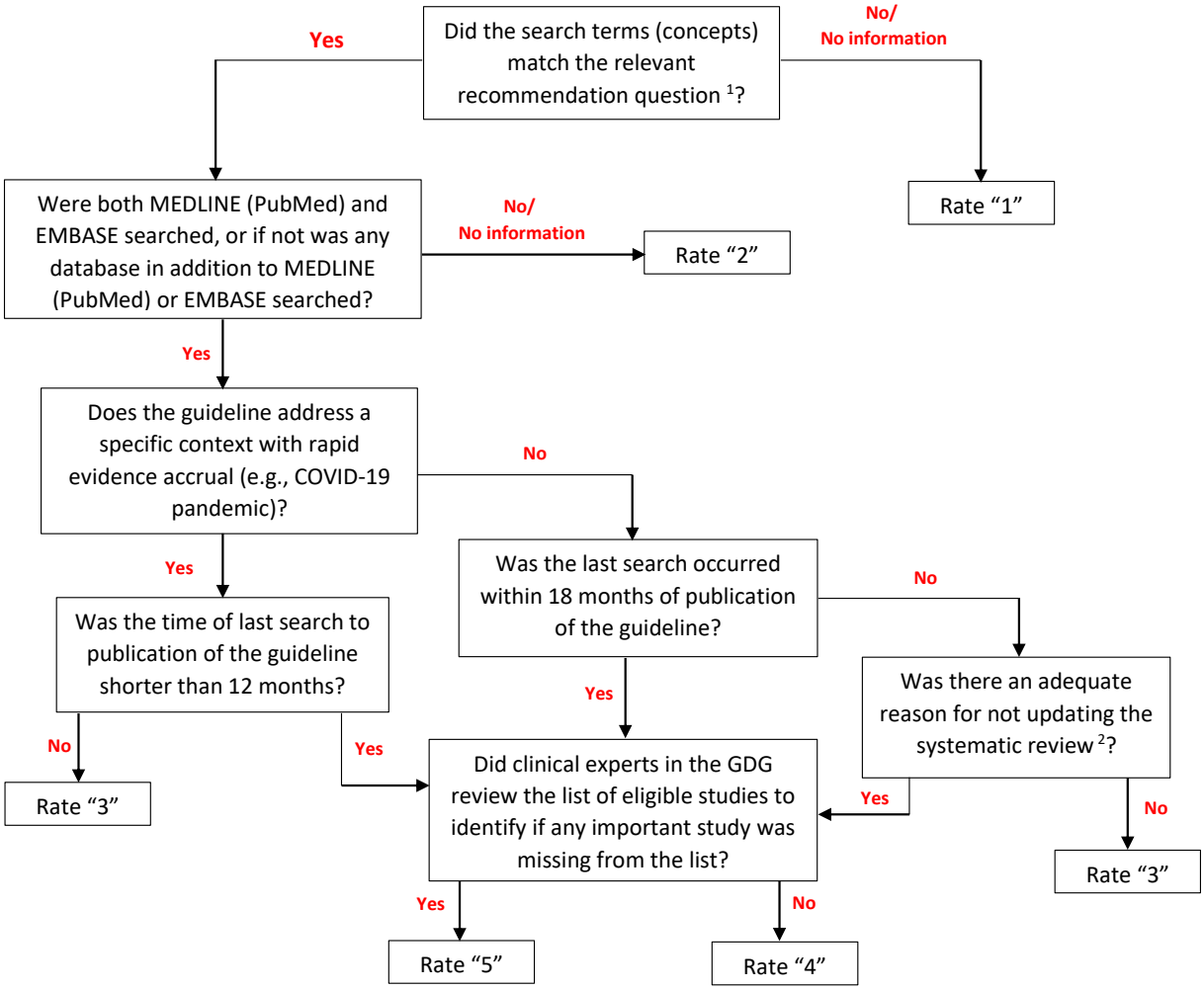
[4] Guidelines may list GDG members for each recommendation rather than at the guideline level.

[5] Affiliations are not sufficiently specified that prevent from confirming whether the GDG included all 3 disciplines, for example, you reviewed affiliations of all members and confirmed that clinicians (e.g., affiliations: Department of Medicine, McMaster University, Hamilton, Ontario, Canada; Division of General Internal Medicine, University Hospitals of Geneva, Geneva, Switzerland; St. George's University Hospital, UK; Hospital Universitario Valle Hebron, Spain) and patient representative (e.g, World Hepatitis Alliance, United Kingdom) were included but the affiliations of other member are too broad (University of Sao Paulo, Brazil; University of North Carolina, USA) to be able to confirm if they were methodologists or belong to any other groups.

4a. Use of a Systematic Review of Evidence– Search strategy

The guideline or related companion documents describe a search strategy that matches the relevant recommendation questions, includes an adequate selection of databases and additional methods to identify relevant studies, and is up to date.

Where to Look: Examine methods for guideline development or guideline development process section, appendices or any publication platform (like MAGICapp, GRADEpro, or any website, etc.) for information on the "methods of literature search". In the methods for guideline development or guideline development process section, guidelines may refer to existing systematic review(s) that informed the guideline. In this case, you need to find the full text of the linked systematic review(s) and examine the search strategy presented in the systematic review publication. Sometimes guidelines may explicitly refer to a method guidance for the development of guidelines or conducting systematic reviews of evidence in the guideline development section and provide no information on the search strategy in the guideline and supporting documents. In this case, you should find the full text of the guidance and check the search strategy to see if relevant information is provided.



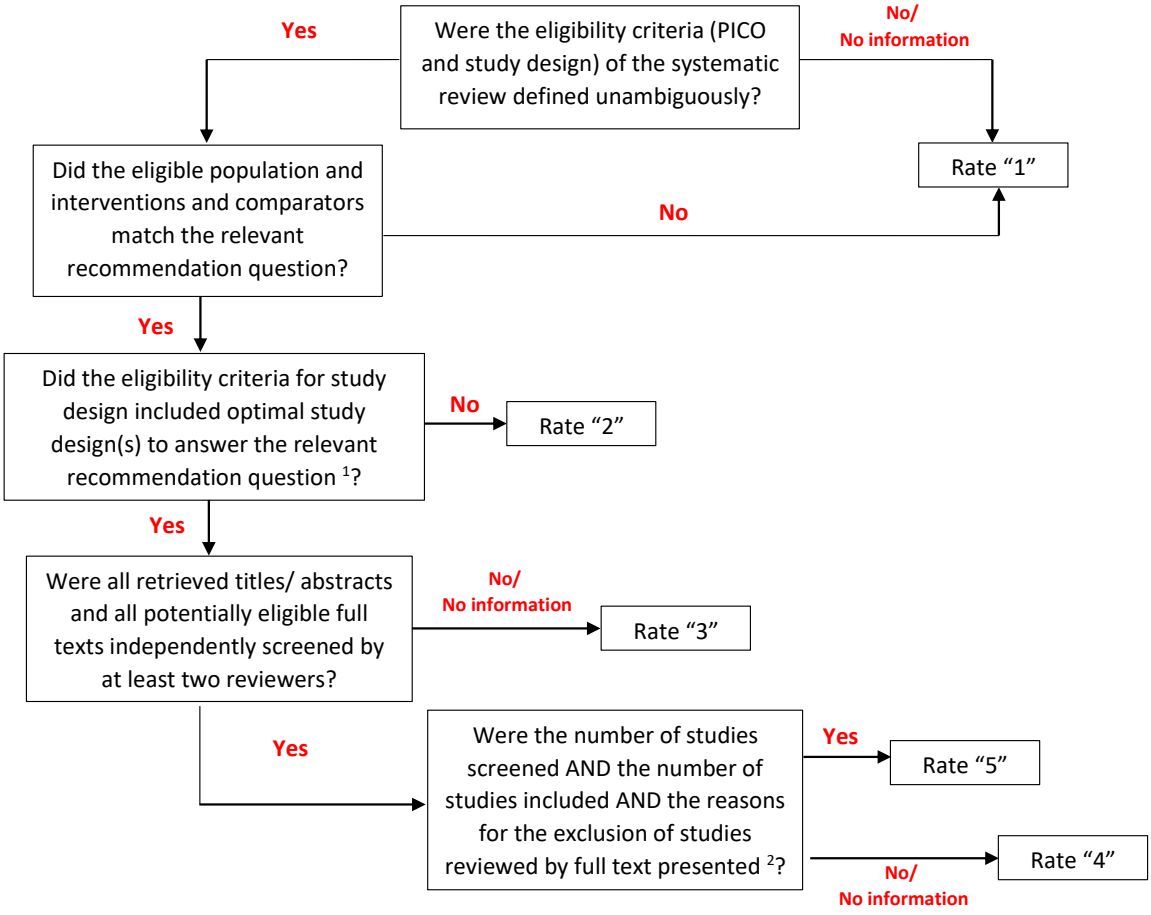
[1] This question does not ask if the search strategy included all PICO components, rather it aims to evaluate whether any search term (concept) that was included in the search strategy matches the related component in the research question.

[2] An adequate reason may relate to the activity in the clinical topic, availability of new evidence, influence of new evidence on the conclusion of the systematic review, etc.

4b. Use of a Systematic Review of Evidence – Study selection

The guideline or related companion documents describe the study selection process that includes unambiguous eligibility criteria that match the relevant recommendation questions, number of studies retrieved from the search, duplicate screening of identified studies, number of studies included, and reasons for exclusion of studies.

Where to Look: Examine methods for guideline development or guideline development process section, appendices or any publication platform (like MAGICapp, GRADEpro, or any website, etc.) for information on "eligibility criteria and study selection process". In the methods for guideline development or guideline development process section, guidelines may refer to existing systematic review(s) that informed the guideline. In this case, you need to find the full text of the linked systematic review(s) and examine the eligibility criteria and study selection process presented in the systematic review publication. Sometimes guidelines may explicitly refer to a method guidance for the development of guidelines or conducting systematic reviews of evidence in the guideline development section and provide no information on the search strategy in the guideline and supporting documents. In this case, you should find the full text of the guidance and check the study selection process to see if relevant information is provided.



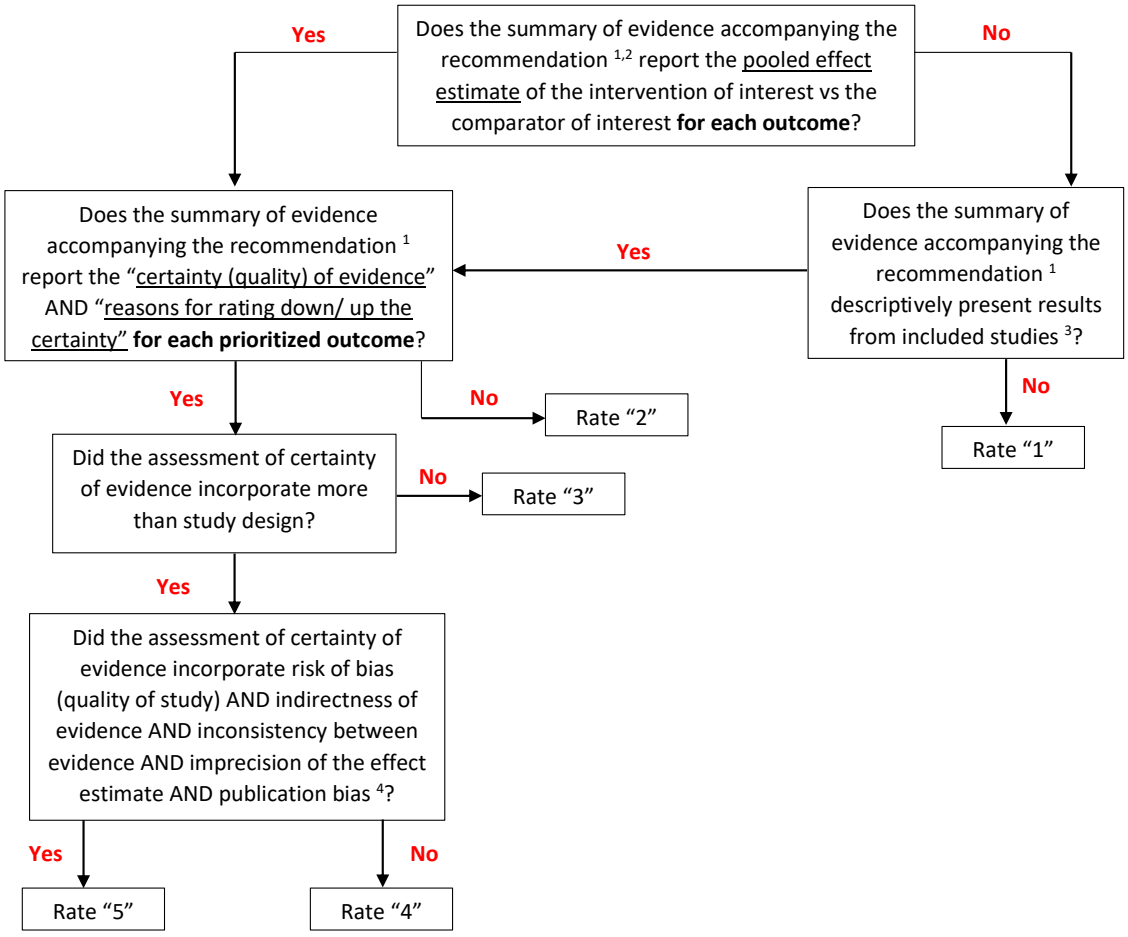
[1] Please note this question asks about the eligibility criteria, not the study designs that were finally included in the systematic review.

[2] Reasons for exclusion of studies could be presented as 1) a table in which each of the excluded studies and the reason for exclusion are listed; 2) cumulative reasons of exclusion with references to all of the studies excluded for each specific reason.

4c. Use of a Systematic Review of Evidence – Synthesis of evidence

The guideline or related companion documents provide a synthesis of evidence from the included studies and an appropriately assessed certainty of evidence for each recommendation.

Where to Look: First, please examine recommendations in the guideline main document, appendices, and any platform (like MAGICapp, GRADEpro, or any website, etc.) to address relevant questions from the algorithm (the first 3 boxes), then you should examine methods for guideline development or guideline development process section, any methods guidance that referred to, or the linked existing systematic review that you picked for item 4b (if relevant) to check the appropriateness of assessment of the certainty of evidence (the last 2 boxes).



[1] Please note sometimes guidelines provide detailed evidence summary in the evidence summary table (in the supporting document or publication platforms) and evidence summary text linked to the recommendation in the main guideline documents lacks the required information. Therefore, you need to check all the sections mentioned in the "where to look" before finalizing your answer to this question.

[2] Please note each recommendation must be linked to a specific summary of evidence, so if you see that the guideline presents a group of recommendations followed by the summary of evidence without a clear linkage between each recommendation with a specific part of the summary of evidence, please rate "1".

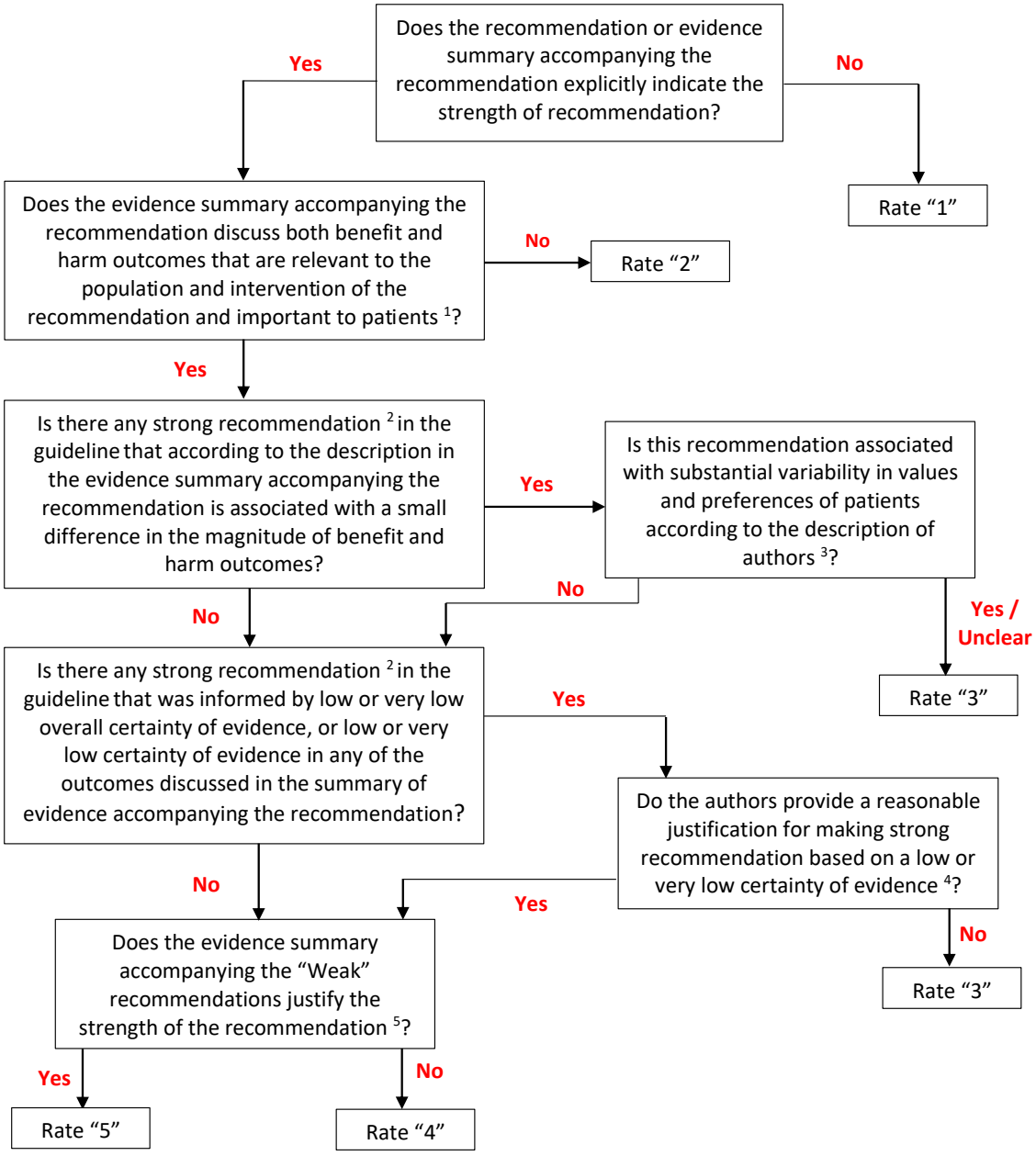
[3] The descriptive presentation of findings from included studies can be reported either for each study (usually in tables in supplementary file) or across studies per outcome (e.g., most studies showed a trivial reduction in mortality or no effect.).

[4] Please note domains of certainty assessment might be labelled differently in different frameworks. The following explanation of each domain would help you to identify if it is incorporated in the assessment of the certainty of evidence. **Risk of bias** refers to the extent to which flaws in the design and execution of studies (e.g., sequence generation, allocation concealment, blinding, incomplete data, selective reporting of outcomes, confounding, etc.) could bias the estimate of effect for each outcome; **indirectness** refers to when population, intervention, or outcomes in included studies differ from those in which we are interested; **inconsistency (heterogeneity)** refers to the degree of variability in effect size of an intervention on a specific outcome between included studies; **imprecision** refers to the degree of variability around effect estimate for specific outcome; **publication bias (reporting bias)** refers to inclusion of unrepresentative sample of studies due to the absence of results from studies that should have been included in the synthesis (whether the studies not included are published or not).

5. Grading the strength of recommendation

The guideline gives a rating of the strength of the recommendation for each recommendation that was appropriately informed by the balance of benefits and harms of alternative care options, value and preferences of patients, and certainty of the underlying evidence.

Where to Look: Examine recommendations and accompanying summary of evidence as described in each box.



[1] If the guideline acknowledged the lack of evidence on a patient-important outcome and instead used a surrogate outcome to formulate the recommendation, it is acceptable.

[2] Please note, there are different systems for grading the strength of recommendations that label the strength of recommendations differently. For example, a strong recommendation may be labelled as Class A and Class B in the USPSTF system, or Class I (strong) and Class IIa (moderate) in the AHA/ACC system.

[3] Please look for statements on the values and preferences of patients in the evidence summary accompanying the recommendations to answer this question. If there is no description of the values and preferences of patients, please choose "Unclear".

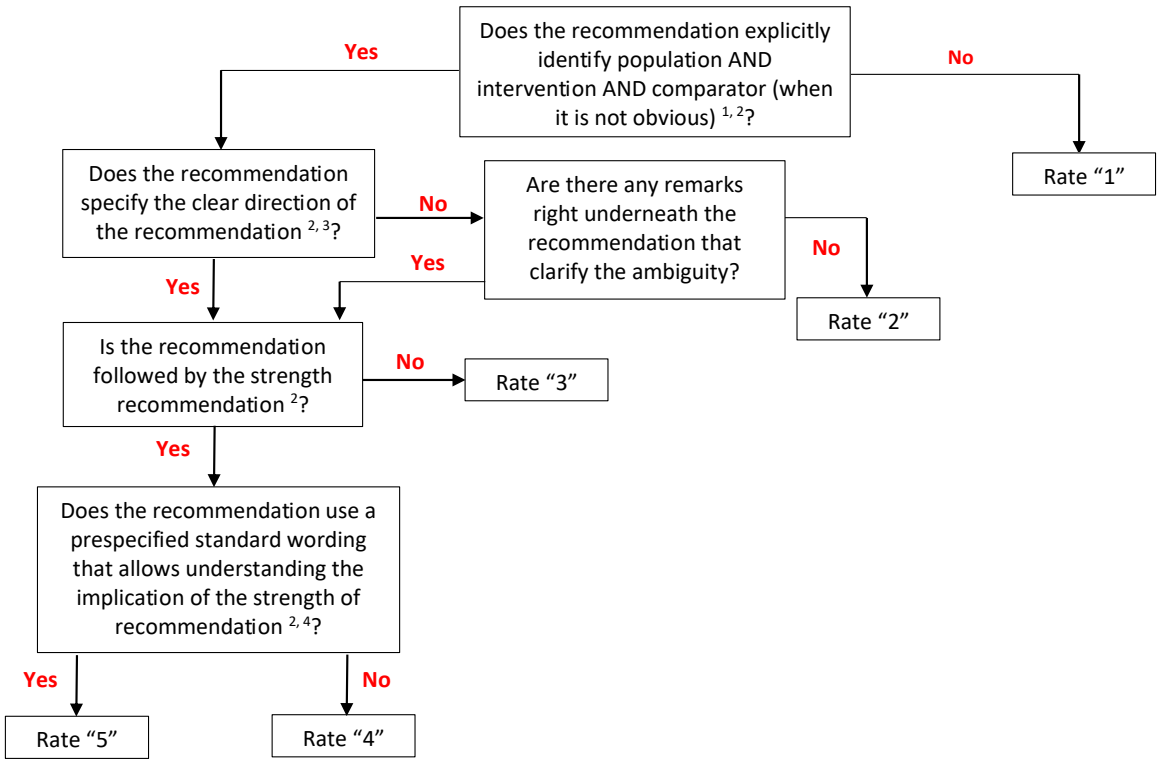
[4] A reasonable justification may include life-threatening situations or catastrophic harms or uncertain benefits and certain risk of harms.

[5] If the guideline does not have any strong recommendations, skip the boxes related to the strong recommendations. i.e., you should answer box 1 & 2 & last box. If you reach the last box but the guideline does not have any weak recommendation to assess, rate "5".

6. Specific and Unambiguous Articulation of Recommendations

The recommendations are specific and unambiguous, stating what action should or should not be taken in what situations and for what population groups. Where the recommendations are intentionally vague or underspecified, the guideline clearly describes the rationale behind those recommendations.

Where to Look: Examine recommendations, any infographics or tables that summarized recommendations, and methods for guideline development.



[1] If the comparator is obvious (e.g., we recommend vaccination against COVID-19 in Children 6 months to under 5 years of age who are at high risk for severe illness due to COVID-19; It is obvious that the comparator is no vaccination), it is not obligatory that the recommendation explicitly identifies the comparator.

[2] Please note if recommendations are summarized in any infographics or tables, this criterion needs to be evaluated in these structures as well. To choose "YES" for this question, the criterion must be met in both the recommendation and any associated summarizing structure.

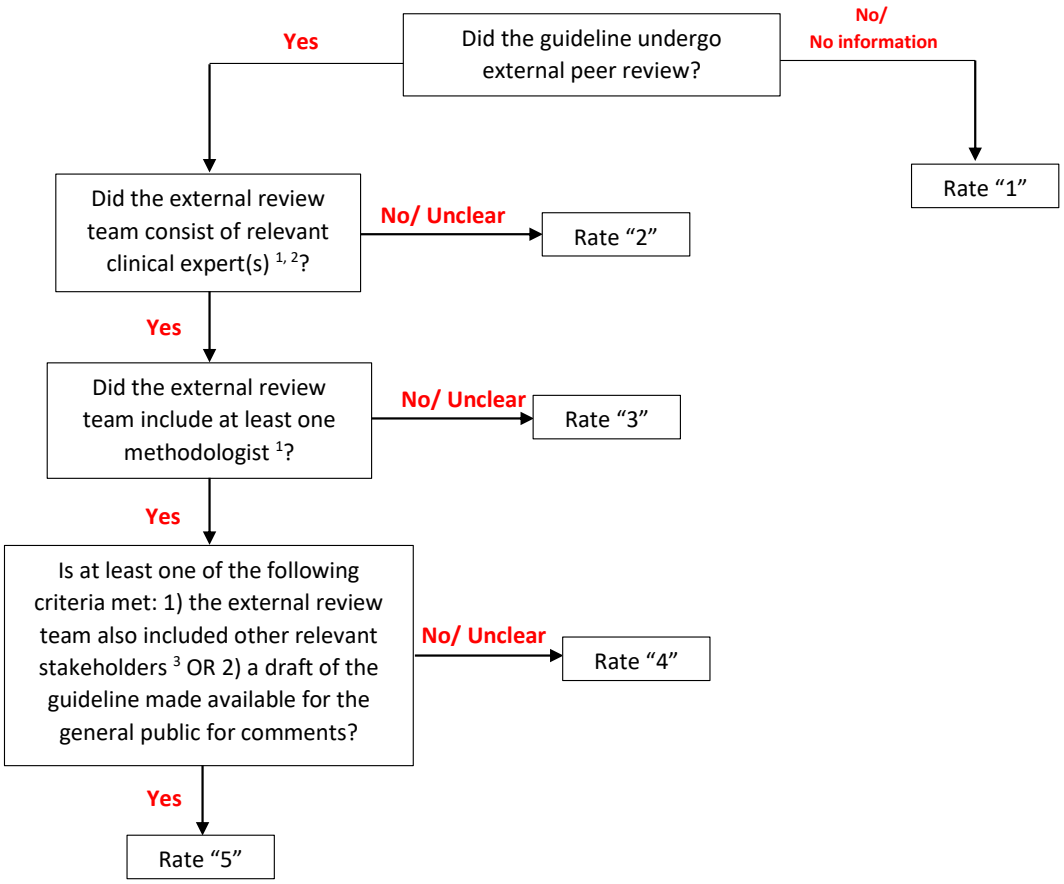
[3] The direction of recommendation clearly presents whether an intervention is recommended (suggested) or not recommended (not suggested) over other intervention(s) like "In patients who have had a stroke, we suggest clopidogrel alone vs. adding aspirin to clopidogrel." Rather than using a vague statement like "In patients who have had a stroke, clinicians should offer clopidogrel alone vs. adding aspirin to clopidogrel, if clinically appropriate."

[4] Standard wording refers to the semantic separation of strength of recommendations in the wording to convey the implication of the recommendation, for example: for strong recommendation "we recommend…, clinicians should…, clinician should not; and for weak recommendation "we suggest…, we conditionally recommend…, clinicians might…". To choose "YES" for this question: 1) the guideline explicitly specified the standard wording in the methods AND 2) followed the standard wording in the first recommendation as specified in the method. So, if any of the 2 criteria are not met, please choose "NO".

7. External review

The guideline has been reviewed by relevant stakeholders, including scientific and clinical experts, organizations, agencies, and patients.

Where to Look: Examine methods for guideline development or guideline development process section, acknowledgement section, contributions section, appendices or any publication platform (like MAGICapp, GRADEpro, or any website, etc.) for information on "Peer review" or "External reviewers".



[1] Guidelines may not explicitly list the composition of the external review team. In this case, you must review the affiliations of external reviewers to verify if the discipline was included. If external review team members were not identified or affiliations were not sufficiently specified to confirm the included disciplines, please choose "Unclear".

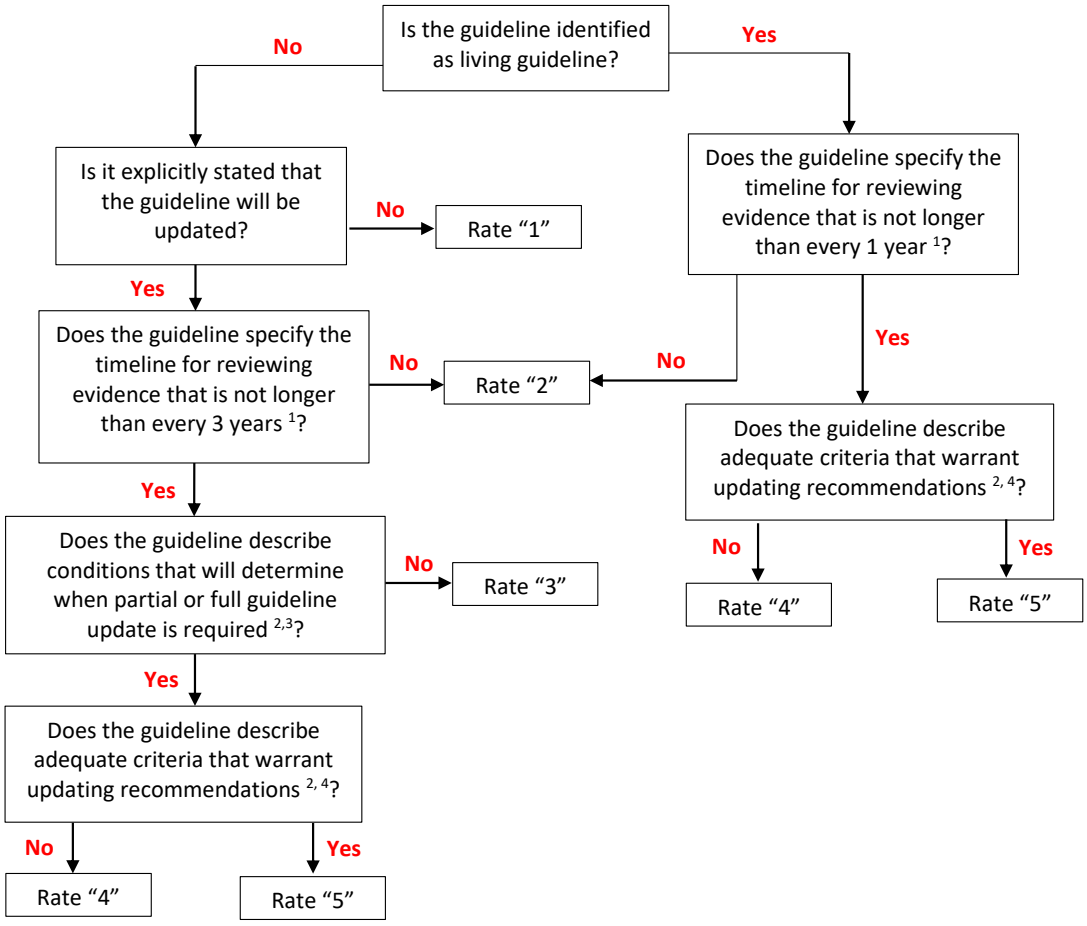
[2] If a guideline explicitly stated that we included "content experts" in the external review team. You can assume that relevant clinician reviewer(s) were included.

[3] Other relevant stakeholders include patient representatives, representatives from federal agencies, relevant professional organizations or specialty societies, advocacy organizations, public health organizations, health plans, or pharmaceutical or device companies.

8. Updating

The guideline or supporting documents provide an adequate timeframe for the review of evidence for potential updating and describe adequate criteria that warrant updating the recommendation.

Where to Look: Examine methods for guideline development or guideline development process section, appendices, and any publication platform (like MAGICapp, GRADEpro, or any website, etc.) for information on "(future) updates".



[1] If the guideline states that evidence will be "regularly" monitored without specifying an explicit timeline, please choose "NO" for this question.

[2] Please note that guidelines may not provide detailed information on updating. If the guideline refers to or cites a method guidance for the development of guidelines in the guideline development section, please find the full text of the guidance and make sure to review the updating section to see if additional information is provided to help you judge this item. However, the **explicit statement on updating** and the **timeline for updating** must be assessed in the guideline or supplementary documents, not the methods guidance.

[3] For example, a full revision of the guideline is required when at least two previous focused updates and/or new evidence suggests that a significant number of recommendations require revision.

[4] For example, a guideline should be updated if new evidence shows that a recommended intervention causes previously unknown substantial harm; that a new intervention is significantly superior to a previously recommended intervention from an efficacy or harms perspective; or that a recommendation can be applied to new populations.

Chapter 4: Empiric antibiotic regimens in adults with non-ventilator-associated hospital-acquired pneumonia: a systematic review and network meta-analysis of randomized controlled trials

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Systematic review

Empiric antibiotic regimens in adults with non-ventilator-associated hospital-acquired pneumonia: a systematic review and network meta-analysis of randomized controlled trials

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ABSTRACT

Background: The optimal empiric antibiotic regimen for non–ventilator-associated hospital-acquired pneumonia (HAP) is uncertain.
Objectives: To compare the effectiveness and safety of alternative empiric antibiotic regimens in HAP using a network meta-analysis.
Data sources: Medline, EMBASE, Cochrane CENTRAL, Web of Science, and CINAHL from database inception to July 06, 2023.
Study eligibility criteria: RCTs.
Participants: Adults with clinical suspicion of HAP.
Interventions: Any empiric antibiotic regimen vs. another, placebo, or no treatment.
Assessment of risk of bias: Paired reviewers independently assessed risk of bias using a modified Cochrane tool for assessing risk of bias in randomized trials.
Methods of data synthesis: Paired reviewers independently extracted data on trial and patient characteristics, antibiotic regimens, and outcomes of interest. We conducted frequentist random-effects network meta-analyses for treatment failure and all-cause mortality and assessed the certainty of the evidence using the *Grading of Recommendations Assessment, Development and Evaluation* approach.
Results: Thirty-nine RCTs proved eligible. Thirty RCTs involving 4807 participants found low certainty evidence that piperacillin-tazobactam (RR compared to all cephalosporins: 0.65; 95% CI: 0.42, 1.01) and carbapenems (RR compared to all cephalosporins: 0.77; 95% CI: 0.53, 1.11) might be among the most effective in reducing treatment failure. The findings were robust to the secondary analysis comparing

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piperacillin-tazobactam vs. antipseudomonal cephalosporins or antipseudomonal carbapenems vs. antipseudomonal cephalosporins. Eleven RCTs involving 2531 participants found low certainty evidence that ceftazidime and linezolid combination may not be convincingly different from cephalosporin alone in reducing all-cause mortality. Evidence on other antibiotic regimens is very uncertain. Data on other patient-important outcomes including adverse events was sparse, and we did not perform network or pairwise meta-analysis.

Conclusions: For empiric antibiotic therapy of adults with HAP, piperacillin-tazobactam might be among the most effective in reducing treatment failure. Empiric methicillin-resistant *Staphylococcus aureus* coverage may not exert additional benefit in reducing mortality.

Registration: PROSPERO (CRD 42022297224). **Maryam Ghadimi, Clin Microbiol Infect 2024;30:1351**

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Introduction

Non-ventilator-associated hospital-acquired pneumonia (HAP), defined as occurring at least 48 hours after hospital admission, is the most common healthcare-associated infection [1]. As microbiological results do not become available within 24 to 72 hours after diagnosis, and even then are often inconclusive, initial antibiotic therapy for HAP is empiric (i.e. selected based on the most common infecting organisms and patient's risk factors for mortality or acquiring multi-drug resistant (MDR) pathogens) [2,3]. Inadequate empiric antibiotic therapy for HAP is associated with increased mortality and use of healthcare resources [4,5].

The optimal empiric antibiotic regimen for HAP is uncertain. Guideline recommendations for antibiotic therapy for HAP vary and do not prioritize one regimen over another. For example, the 2016 Infectious Diseases Society of America/American Thoracic Society guidelines recommend piperacillin-tazobactam, an antipseudomonal cephalosporin, a fluoroquinolone, or a carbapenem (imipenem or meropenem) for patients at low risk of mortality with no risk factor for resistant pathogens [2]. The 2017 European Respiratory Society/European Society of Intensive Care Medicine/European Society of Clinical Microbiology and Infectious Diseases/Latin American Thoracic Association guidelines suggest considering narrower spectrum antibiotics targeting *Streptococcus pneumoniae* and methicillin-susceptible *Staphylococcus aureus* [3].

An important reason for these variations is the limited head-to-head comparisons of empiric antibiotics for HAP. Current recommendations for HAP are informed by the prevalence of pathogens causing HAP and indirect evidence from ventilator-associated pneumonia. Existing systematic reviews of randomized trials address the relative effects of only two alternative antibiotic classes, group HAP and ventilator-associated pneumonia together, include trials that target patients with gram-negative pathogens (i.e. antibiotic therapy is not empiric), or do not include all relevant evidence [6–9]. To address current limitations, we conducted a network meta-analysis (NMA) to present the comparative effects of all alternative regimens in empiric therapy of HAP.

Methods

We registered this systematic review and NMA on PROSPERO (CRD 42022297224) and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards for reporting systematic reviews and the PRISMA guidance extension for NMA [10,11].

Eligibility criteria

Eligible studies randomly assigned patients aged 18 years or older with a clinical HAP to any empiric antibiotic or antibiotic combination compared to any alternative empiric antibiotic regimen, placebo, or no treatment. We included RCTs regardless of language, year of publication, and publication status as long as at least 80% of participants were aged >18 years, suspected of having HAP, were not immunocompromised, and received empiric therapy, or investigators reported outcomes separately for clearly eligible patients.

Data sources and searches

We searched Medline, EMBASE, Cochrane CENTRAL, Web of Science, and CINAHL from the database inception to July 06, 2023. An experienced health sciences librarian refined our search strategy for each database (Supplementary Appendix). Our search also included a review of the reference lists from all included RCTs and relevant systematic reviews. Finally, to ensure completeness, clinical experts in our group reviewed the list of eligible RCTs.

Study selection

Using the Covidence platform (https://covidence.org), pairs of trained reviewers independently screened titles and abstracts and, for those potentially eligible, the associated full texts. Reviewers resolved disagreements by discussion and when necessary, with a third reviewer (M.G.).

Data extractions

Pairs of reviewers independently extracted data from each eligible RCT using a pre-specified, pilot-tested extraction form. We collected information on trial characteristics, patient characteristics (age, sex, severity of pneumonia, and comorbidities), and outcomes of interest. Reviewers resolved discrepancies by discussion and, when necessary, through adjudication by a third reviewer (M.G.). We judged the following outcomes as critical: treatment failure as defined by each study and all-cause mortality, closest to 30 days after the end of the antibiotic therapy, and the following outcomes as important: need for mechanical ventilation, closest to 30 days after the end of the antibiotic therapy, length of hospital stay, adverse events leading to discontinuation of treatment, and most common adverse events including diarrhoea, nausea and/or vomiting, allergic reactions, and acute kidney injury as defined by authors of the trials at the longest available follow-up. We extracted outcome data (number of participants who experienced an event for dichotomous outcomes and means/medians and measures of variability for continuous outcomes) from the intention-to-treat (ITT) population, and if not reported, in preferred order: modified-ITT, per-protocol, and as-treated population.

Risk of bias assessment

For each eligible trial, reviewers following training and calibration exercises, independently and in duplicate assessed the risk of bias using a modified Cochrane tool for assessing the risk of bias in randomized trials [12], rating outcomes as either 'low risk of bias', 'probably low risk of bias', 'probably high risk of bias', or 'high risk of bias'. We considered bias arising in the randomization process, bias due to inadequate allocation concealment, bias owing to unblinding of patients, healthcare providers and outcome assessors, and bias from missing outcome data. The Supplementary Appendix provides details of guidance on the assessment of risk of bias. A third reviewer (M.G.) adjudicated on discrepancies.

Data synthesis and analysis

For dichotomous outcomes, we calculated relative risks and associated 95% CIs. To obtain absolute effect estimates (risk difference and 95% CIs), we applied the relative effect measure to the baseline risk derived from the median of the risk of event across the reference intervention arms, which for each network was the most connected intervention to others (cephalosporins). For length of hospital stay, we used mean difference and corresponding 95% CI.

We performed frequentist random-effects NMA assuming a common heterogeneity across all comparisons under the multivariate meta-analysis models using the restricted maximum likelihood estimator [13]. To obtain direct estimates, we performed pairwise meta-analyses using the DerSimonian–Laird random-effects model [14]. We used design-by-treatment models [15] to assess global incoherence and node-splitting models [16] to assess local incoherence and to obtain indirect estimates. We grouped individual antibiotics within the same class into a single treatment node. We then conducted a secondary analysis separating antibiotics within the same class based on the activity against *Pseudomonas aeruginosa* (e.g. antipseudomonal cephalosporins and cephalosporins without coverage on *P. aeruginosa* divided into two separate treatment nodes) and an additional secondary analysis using individual antibiotics as separate nodes. We did not separate nodes based on the dose and duration of therapy.

We hypothesized that the effects of antibiotics may vary based on the severity of pneumonia (proportion of patients with severe pneumonia), time of the outcome measurement (day since the last day of therapy), prevalence of *P. aeruginosa* or methicillin-resistant *S. aureus* (MRSA) at baseline (i.e. number of participants with *P. aeruginosa* or MRSA respiratory culture per number of participants randomized), and co-intervention with coverage against *P. aeruginosa* or MRSA (presence or absence). Thus, we conducted multivariate random-effects network meta-regression assuming common heterogeneity for these variables [17]. We also hypothesized that treatment effects might be greater in studies with a high risk of bias and analysed subgroups using network meta-regression by high vs. low risk of bias based on sequence generation, allocation concealment, blinding, and missing outcome data domains. We assessed the credibility of any identified subgroup effects using the ICEMAN tool [18]. We implemented all analyses in Stata 17.0 (StataCorp., College Station, TX, USA).

Assessment of the certainty of the evidence

We assessed the certainty of the evidence using the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) approach for NMA, rating certainty in a nonzero effect (i.e. antibiotic A has a nonzero effect compared to antibiotic B) [19–21]. However, if the point estimate was near the null, suggesting that there was no difference between A and B, we instead rated our certainty that the truth was little or no difference between the treatments [21]. To make this certainty rating, we developed a consensus among the team members, choosing thresholds of small important difference of 2.5% for treatment failure (i.e. reduction or increase in treatment failure by 25 in 1000 patients) and 1% for all-cause mortality (i.e. reduction or increase in all-cause mortality by 10 in 1000 patients). We rated the certainty of the evidence as 'high', 'moderate', 'low', or 'very low' considering the risk of bias [22], inconsistency [23,24], indirectness [25], publication bias [26], intransitivity [27], incoherence [28], and imprecision [29]. Further description of the methods of assessing the certainty of the evidence is provided in the supplementary appendix. One methodologist (M.G.) rated each domain for each comparison per outcome, discussing uncertainties with an expert in the GRADE methodology (G.G.).

Interpretation of results

In interpreting the results, we used a modification of a previously suggested GRADE approach [30]. We chose as a reference intervention, the antibiotic regimen most connected in the network, cephalosporins, and for each outcome, we categorized antibiotics as 'among the most effective', 'intermediate effective', or 'among the least effective'. We, then, divided interventions based on the certainty of the evidence. We did not classify any of the antibiotics for which there was very low certainty evidence when compared to the reference.

We classified antibiotics as among the most effective if the point estimates comparing the antibiotic to the reference and at least two other alternatives represented an important benefit (using the thresholds of a small important difference specified above). We classified antibiotics as among the least effective if the point estimate comparing it to the reference and at least two other alternatives represented an important decrement in benefit. We classified antibiotics as intermediate effectiveness if the point estimate compared to the reference proved an unimportant benefit or decrement in benefit.

Results

Of 38 066 citations identified and 1121 full texts screened, 39 RCTs proved eligible (Fig. 1). Many trials proved ineligible because they enrolled hospitalized patients without clarification of whether participants had HAP or had been hospitalized for community-acquired pneumonia.

Study characteristics

Table 1 [31–69] presents the characteristics of eligible studies. Trials were most commonly multinational or conducted in the United States, published in English between 1984 and 2014, and funded by the pharmaceutical industry. The number of randomized participants ranged from 18 to 945 with a median of study mean ages of 59.8 years (IQR: 56.0–66.5 years). The median proportion of participants with severe pneumonia across 21 studies that explicitly reported the severity of pneumonia or reported the Acute Physiology and Chronic Health Evaluation II (APACHE II) score (we used a threshold of $\geq$15 as severe pneumonia) was 35.6 % (IQR: 25.3–92.5 %) (Table 2). Included trials evaluated 13 alternative antibiotic regimens and the median of the mean duration of therapy across trials was 9.0 days (IQR: 8.6–10.0 days) (Table S1).

Risk of bias

Of the 39 eligible trials, 27 had at least one domain at high risk of bias, most often with respect to blinding or allocation concealment.

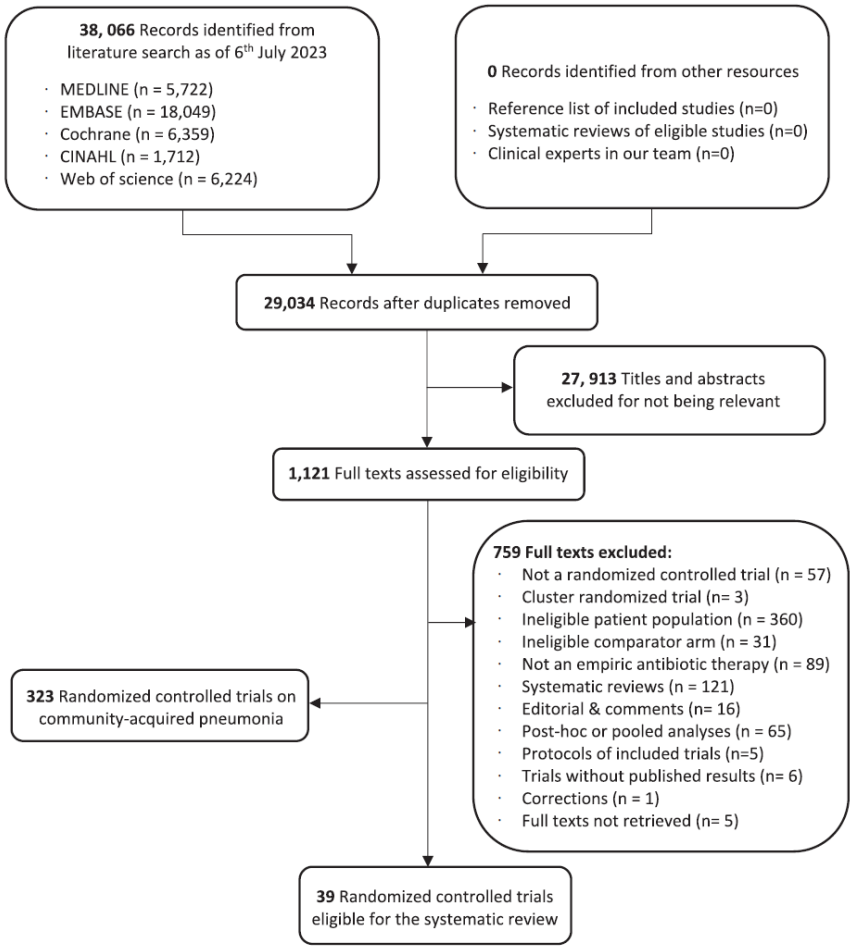

Fig. 1. PRISMA flow diagram of study selection.

The majority of trials excluded patients from the analysis of treatment failure if a pathogen resistant to either study antibiotic was isolated from the respiratory culture and were therefore assessed at high risk of bias due to missing outcome data. Tables S3–S10 present the risk of bias assessments of the eligible studies for each outcome.

Network meta-analysis

We could not include nine trials [32,38–40,42,45,49,50,65] in the treatment failure NMA and three trials [39,42,49] in the all-cause mortality NMA because they compared antibiotics within the same class. Figs. 2 and 3 present network plots and Table S2 provides outcome data for treatment failure and all-cause mortality. We found serious inconsistency in comparing the combination of a cephalosporin and an aminoglycoside vs. cephalosporin alone for treatment failure (Fig. S7). We had no concern for other direct comparisons and all-cause mortality network (Figs S1–S6, S8–S25).

Table 3 presents the categorization of antibiotics for treatment failure and all-cause mortality. Tables S11 and S12 report relative and absolute direct, indirect, and network estimates and certainty of the evidence for all comparisons. We did not identify any evidence of global or comparison-specific incoherence in any networks. Because none of the analysed pre-specified effect modifiers proved important or credible, we had no concerns regarding intransitivity. As most included trials showed trivial to no difference comparing alternative antibiotic regimens, publication bias was never strongly suspected.

Treatment failure

The treatment failure NMA included 30 trials involving 4807 participants and 13 antibiotic regimens. Treatment failure was almost always defined as a lack of clinical response that necessitated the administration of nonstudy antibiotics or death due to pneumonia. Piperacillin-tazobactam (vs. all cephalosporins, RR:

Table 1
Characteristics of included studies

First author, year	Country	Public trial registration	Number of randomized participants	Comparison	Mean age (years)	Male (%)	Mean APACHE II; APACHE II score ≥15 (%)	Baseline mechanically ventilated (%)	Proportion with severe pneumonia[a] (%)	Outcomes, and time of the assessment (days after the EOT)
Awad, 2014 [31]	Multinational	NCT00210964; NCT00229008	571	ceftobiprole vs. ceftazidime + linezolid	NR	65.2	35.9 %	14.9	35.9	Treatment failure (7 to 14 d), all-cause mortality (30 d)
Bassetti, 1991 [32]	Italy	NR	61	ceftazidime vs. ceftriaxone	59.2	NR	NR	0	NR	Treatment failure, adverse events leading to discontinuation of antibiotic EOT
Chaudhary, 2008 [33]	India	NR	200	cefepime + amikacin vs. cefepime	NR	56.0	NR	NR	NR	Treatment failure EOT
Cometta, 1994 [34]	Switzerland	NR	313	imipenem + netilmicin vs. imipenem	55.8	72.1	Mean: 9.7	NR	13.8	Treatment failure EOT
Fekete, 1994 [35]	United States	NR	66	aztreonam + cefazolin vs. ceftazidime	64.2	72.9	NR	50	NR	Treatment failure, all-cause mortality, adverse events leading to discontinuation of antibiotic EOT
Fink, 1994 [36]	United States	NR	405	ciprofloxacin vs. imipenem	59.8	70.2	Mean: 17.7	NR	100	Treatment failure 7 d
Freire, 2010 [37]	Multinational	NR	945	tigecycline vs. imipenem	58.4	68.7	24.4 %	NR	24.4	Treatment failure, all-cause mortality 10 to 21 d
Gao et al. [38], 1999	China	NR	42	cefepime vs. ceftazidime	74.2	85.7	NR	33.3	NR	Treatment failure, adverse events leading to discontinuation of antibiotic, diarrhoea EOT
Garau et al. [39], 1997	Spain	NR	151	meropenem vs. imipenem	16.9	75.9	Mean: 16.5	84	100	Treatment failure (EOT), all-cause mortality (30 d)
Garber et al. [40], 1992	Canada	NR	74	cefotaxime vs. ceftriaxone	66.5	59.5	NR	NR	NR	Treatment failure, diarrhoea 14 d
Giamarellou, 1990 [41]	Greece	NR	71	pefloxacin vs. imipenem	55.8	59.2	NR	NR	100	Treatment failure, all-cause mortality 7 d
Heinrich et al. [42], 1991	Germany	NR	94	ceftazidime vs. cefotaxime	77.5	50.0	NR	0	92.5	Treatment failure, all-cause mortality, adverse events leading to discontinuation of antibiotic EOT
Höffken, 2007 [43]	Multinational	NR	161	moxifloxacin vs. ceftriaxone/cefuroxime	65.9	53.5	20.8 %	NR	0	Treatment failure, all-cause mortality, adverse events leading to discontinuation of antibiotic, any/all GI events, diarrhoea 21 to 31 d

(*continued on next page*)

Table 1 (*continued*)

First author, year	Country	Public trial registration	Number of randomized participants	Comparison	Mean age (years)	Male (%)	Mean APACHE II; APACHE II score ≥15 (%)	Baseline mechanically ventilated (%)	Proportion with severe pneumonia[a] (%)	Outcomes, and time of the assessment (days after the EOT)
Jaccard, 1998 [44]	Switzerland	NR	154	piperacillin-tazobactam vs. imipenem	58.2	71.4	Mean: 14.8	48.7	48.8	Treatment failure, all-cause mortality EOT
Jin et al. [45], 2005	China	NR	63	meropenem vs. imipenem	48.5	65.1	NR	NR	NR	Treatment failure, any/all GI events, diarrhoea, allergic reactions EOT
Joshi, 2006 [46]	United States, Canada	NR	437	piperacillin-tazobactam vs. imipenem	53.0	71.2	Mean: 13.5	NR	NR	Treatment failure 7 to 28 d
Joshi, 1999 [47]	United States, Canada	NR	300	piperacillin-tazobactam vs. ceftazidime	56.4	75.3	Mean:12.7	NR	20.3	Treatment failure EOT
Koehler, 1990 [48]	Germany	NR	144	piperacillin + tobramycin vs. ceftazidime	66.5	72.2	NR	NR	91.0	Treatment failure, adverse events leading to discontinuation of antibiotic EOT
Mangi et al. [49], 1992	United States	NR	154	cefoperazone vs. ceftriaxone	75.5	50.0	NR	NR	NR	Treatment failure, all-cause mortality, adverse events leading to discontinuation of antibiotic
Mangi et al. [50], 1988	United States	NR	133	cefoperazone vs. ceftazidime	75.5	56.0	NR	NR	NR	Treatment failure, adverse events leading to discontinuation of antibiotic EOT
Mouton, 1995 [51]	Multinational	NR	237	meropenem vs. ceftazidime + amikacin	61.0	70.5	NR	NR	NR	Treatment failure EOT
Mouton, 1988 [52]	France	NR	212	ceftazidime + pefloxacin vs. ceftazidime + amikacin	58.1	73.6	NR	87.6	NR	Treatment failure
Norrby, 1993 [53]	Multinational	NR	393	ceftazidime vs. imipenem	58.0	63.9	Mean:14	NR	7.1	Treatment failure EOT
Raad, 2001 [54]	United States	NR	52	piperacillin-tazobactam vs. clindamycin + aztreonam	61.3	NR	NR	32.7	32.7	Treatment failure, all-cause mortality, length of hospital stay, diarrhoea, allergic reactions 14 d
Ramirez, 2013 [55]	Multinational	NCT00707239	108	tigecycline vs. imipenem	62.2	67.6	30.5 %	NR	30.5	Treatment failure 10 to 21 d
Ramirez, 1999 [56]	Mexico	NR	60	ceftazidime vs. penicillin G + amikacin	68.6	48.3	NR	0	NR	Treatment failure (10 d), all-cause mortality, length of hospital stay (22 d)
Rapp, 1984 [57]	United States	NR	35	ceftazidime vs. ticarcillin + tobramycin	41.2	NR	NR	NR	NR	Treatment failure EOT
Rapp, 1991 [58]	United States	NR	46	ciprofloxacin vs. ceftazidime	44.0	75.0	NR	68.8	NR	Treatment failure EOT
Rea-Neto, 2008 [59]	Multinational	NCT00211003	448	doripenem vs. piperacillin-tazobactam	58.3	68.0	25.3 %	NR	25.3	Treatment failure 6 to 20 d

Reith, 2006 [60]	Germany	NR	18	levofloxacin vs. ceftriaxone + clindamycin	63.0	83.0	NR	NR	NR	Treatment failure EOT
Rubinstein, 1995 [61]	Multinational	NR	580	ceftazidime vs. ceftriaxone + tobramycin	56.0	59.5	NR	NR	NR	Treatment failure EOT
Saginur, 1997 [62]	Canada	NR	149	ciprofloxacin vs. ceftazidime	61.6	35.5	NR	NR	NR	Treatment failure EOT
Schmitt, 2006 [63]	Multinational	NR	221	piperacillin-tazobactam vs. imipenem	67.1	63.8	Mean: 13.4	23.5	35.6	Treatment failure, all-cause mortality, adverse events leading to discontinuation of antibiotic, diarrhoea, nausea/vomiting 14 d
Seiger, 1997 [64]	Multinational	NR	211	meropenem vs. ceftazidime + tobramycin	54.5	76.0	NR	0	27.0	Treatment failure EOT
Shah, 1995 [65]	Germany	NR	118	ceftriaxone vs. cefotaxime	70.5	64.4	NR	0	NR	Treatment failure, diarrhoea EOT
Torres, 1989 [66]	Spain	NR	33	aztreonam + cefotaxime vs. amikacin + cefotaxime	58.5	92.9	NR	NR	96.4	Treatment failure EOT
Torres, 2000 [67]	Spain	NR	152	ciprofloxacin vs. imipenem	61.0	73.8	Mean: 14.3	100	100	Treatment failure, all-cause mortality 7 d
West, 2003 [68]	United States, Canada	NR	438	levofloxacin vs. imipenem	55.7	71.9	Mean: 14.9	10.9	49.6	Treatment failure (15 d), all-cause mortality, adverse events leading to discontinuation of antibiotic, diarrhoea, vomiting, allergic reactions (32 d)
Yakovlev, 2006 [69]	Multinational	NR	303	cefepime vs. ertapenem	67.1	48.5	29.0 %	0	29.0	Treatment failure 7 to 14 d

APACHE II: Acute Physiology and Chronic Health Evaluation II; EOT: end of therapy; GI: gastrointestinal, NR: not reported.
[a] In case of a lack of data on the proportion of patients with severe pneumonia, we estimated the proportion by considering APACHE II $\geq$ 15 as the threshold for severity.

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Table 2
Summary of characteristics of included studies

Characteristics	Measure
Number of eligible studies	39
Number of randomized patients; median (IQR)	152 (66, 303)
Mean age (y); median (IQR)	59.8 (56.0, 66.5)
Male (%); median (IQR)	68.4 (59.3, 79.3)
Prevalence of *Pseudomonas aeruginosa* respiratory culture (%); median (IQR)	11.1 (4.3,18.1)
Prevalence of Methicillin-resistant *Staphylococcus aureus* respiratory culture (%); median (IQR)	9.5 (4.6, 9.8)
Severe pneumonia (%); median (IQR)	35.6 (25.3, 92.5)
Number of studies by severity of pneumonia (%)	
Severe	5 (12.8)
Non-severe	1 (2.6)
Mixed	16 (41.0)
Not determined	17 (43.6)
Mechanically ventilated patient at baseline (%); median (IQR)	23.5 (0, 48.7)
Mean follow-up for treatment failure (days after the end of treatment); median (IQR)	1 (1, 14)
Mean follow-up for all-cause mortality (days after the end of treatment); median (IQR)	14 (4, 26)

0.65; 95% CI: 0.42–1.01; risk difference: 51 fewer per 1000 patients; 95% CI: 84 fewer to one more per 1000 patients, low certainty) and carbapenems (vs. all cephalosporins, RR: 0.77; 95% CI: 0.53–1.11; risk difference: 33 fewer per 1000 patients; 95% CI: 68 fewer to 16 more per 1000 patients, low certainty) might be among the most effective antibiotics in reducing treatment failure (Table 3). The findings were robust to the secondary analysis separating antibiotics within the same class based on the activity against *P. aeruginosa* (Fig. S26 and Table S13) and showed, with low certainty evidence, the possible superior efficacy of piperacillin-tazobactam (RR compared to antipseudomonal cephalosporins: 0.61; 95% CI: 0.41–0.93), antipseudomonal carbapenems (RR compared to antipseudomonal cephalosporins: 0.71; 95% CI: 0.48–1.05), and antipseudomonal fluoroquinolones (RR compared to antipseudomonal cephalosporins: 0.71; 95% CI: 0.45–1.13). Low certainty evidence suggests an aminoglycoside in combination with a cephalosporin without coverage on *P. aeruginosa* may be inferior to an antipseudomonal cephalosporin (RR: 1.51; 95% CI: 0.87–2.61). Evidence regarding the effect of other antibiotic regimens on treatment failure remains very uncertain.

All-cause mortality

The all-cause mortality NMA included 11 trials involving 2531 participants and nine alternative antibiotic regimens. Low certainty evidence suggests the combination of ceftazidime and linezolid may not be convincingly different from cephalosporin alone. The effect of other antibiotic regimens on all-cause mortality proved very uncertain (Table 3). The secondary analysis separating antibiotics within the same class based on the activity against *P. aeruginosa* (Fig. S27 and Table S14) showed no difference compared to the primary analysis.

Other outcomes

Data on length of hospital stay and adverse events proved sparse, and we did not perform network or pairwise meta-analysis for these outcomes. Table S20 presents effect estimates for these outcomes for each study. No trials were reported on the need for mechanical ventilation. Acute kidney injury was not explicitly identified in any trials that compared alternative antibiotic classes,

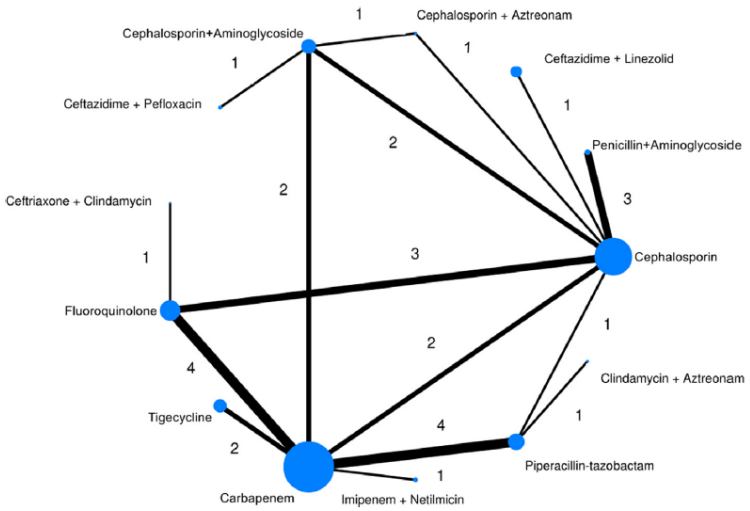

Fig. 2. Network plot for treatment failure. The size of the nodes is proportional to the number of participants randomized to each antibiotic regimen and the lines link nodes are weighted according to the number of trials informed by specific direct comparison.

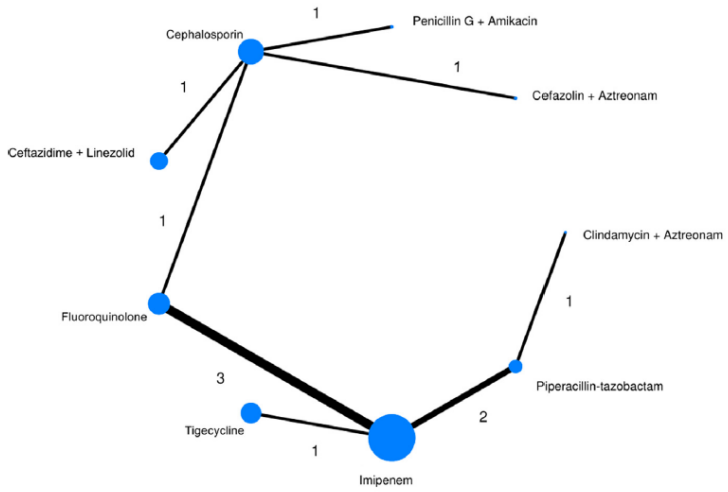

Fig. 3. Network plot for all-cause mortality. The size of the nodes is proportional to the number of participants randomized to each antibiotic regimen and the lines link nodes are weighted according to the number of trials informed by specific direct comparison.

rather, trials reported increased serum creatinine or abnormal renal function without a clear definition of the events.

Additional analyses

There were insufficient data available from included studies to explore effect modification by severity of pneumonia and prevalence of *P. aeruginosa* on treatment failure. We found no evidence of effect modification by other variables for any of the outcomes. The secondary analysis separating individual antibiotics into single nodes revealed very uncertain evidence of whether there is a difference in the effects of antibiotics within the same class on treatment failure (Fig. S28 and Tables S15–S19). We did not explore the effects of individual antibiotics on all-cause mortality because 6 trials that evaluated 10 alternative antibiotics were disconnected from the network.

Discussion

This systematic review and NMA provides a comprehensive and up-to-date overview of the evidence for empiric antibiotic therapy for HAP. Comparing alternative antibiotic regimens, piperacillin-tazobactam and carbapenems might be among the most effective empiric antibiotics in reducing treatment failure. Antipseudomonal fluoroquinolones, with low certainty, might be superior to antipseudomonal cephalosporins in reducing treatment failure. However, carbapenems and fluoroquinolones are less attractive choices as first-line empiric antibiotics due to the risk of the emergence of resistant gram-negatives [70] and adverse effects [71]. In terms of implications for clinical practice, our findings of possible superior efficacy in reducing treatment failure with piperacillin-tazobactam, based on the evidence from RCTs rather than solely data on the prevalence of pathogens or outcomes associated with failure to cover specific pathogens, provides a higher certainty evidence for the existing recommendations on prescribing antibiotics with activity against *P. aeruginosa* and other gram-negatives in the empiric treatment of HAP and informs recommendations on preferred empiric antibiotics. Consistent with current recommendations, we also found low certainty evidence that empiric coverage against *P. aeruginosa* only through aminoglycosides may be inferior in reducing treatment failure compared to other alternatives.

Current guidelines on HAP empiric treatment based on the very low certainty evidence suggest the empiric combination therapy with two antipseudomonal antibiotics rather than monotherapy for patients with risk factors for resistant *P. aeruginosa* and the addition of an antibiotic active against MRSA for patients with an MRSA risk factor [2,3]. Evidence comparing an antipseudomonal double coverage to monotherapy proved very uncertain in our NMA (Table S13). We also found low certainty evidence that empiric MRSA coverage may not exert additional benefit in reducing mortality. However, limited data did not allow investigation of the effects by risk factors. Thus, our findings may not be applicable to patients at risk of acquiring resistant pathogens.

This is the first systematic review to evaluate the comparative effects of all alternative antibiotics for the empiric therapy of HAP. Our broad eligibility criteria had few restrictions and included all languages, and our search was exhaustive and up-to-date. To minimize bias, the screening process, data abstraction, and risk of bias assessment were conducted in duplicate. We used standardized criteria to assess the risk of bias and assessed the certainty of the evidence and interpreted results using the GRADE methodology including a modification that allowed worthwhile inferences despite limitations in the evidence. We further compared the effect of antibiotics within the same class based on the activity spectrum. Our review benefited from multidisciplinary guidance from clinical experts and methodologists.

Limitations of this review reflect those of the available evidence. First, the evidence for all interventions was low or very low certainty primarily due to a limited number of trials and many available trials having few events and secondarily due to concerns with risk of bias. Second, no studies addressed need for mechanical ventilation and few studies addressed length of hospital stay. Studies reported very limited information regarding adverse events, thus precluding NMA. Third, most trials excluded patients with resistant pathogens to either study antibiotic from the analysis of treatment failure, while the presence of resistant pathogens is

Table 3
Summary of relative and absolute effects and classification of antibiotic regimens compared with the reference (all cephalosporins)

	Treatment failure					All-cause mortality				
Baseline risk [a]	145 per 1000					150 per 1000				
Small important difference [b]	25 per 1000					10 per 1000				
Intervention vs. cephalosporins	RR (95% CI)	RD (95% CI)	Certainty of evidence	Classification	Narrative summary	RR (95% CI)	RD (95% CI)	Certainty of evidence	Classification	Narrative summary
Penicillin + Aminoglycoside	2.78 (1.38, 5.60)	258 (55, 667)	Low	Among the least effective	May be inferior to cephalosporins and some alternatives	1.5 (0.47, 4.78)	75 (−80, 567)	Very low	NA [c]	NA
Piperacillin–tazobactam	0.65 (0.42, 1.01)	−51 (−84, 1)	Low	Among the most effective	May be superior to cephalosporins and some alternatives	0.95 (0.31, 2.88)	−8 (−104, 282)	Very low	NA [c]	NA
Imipenem + Netilmicin	0.71 (0.29, 1.75)	−42 (−103, 109)	Very low	NA [c]	NA	—	—	—	—	—
Carbapenems	0.77 (0.53, 1.11)	−33 (−68, 16)	Low	Among the most effective	May be superior to cephalosporins and some alternatives	0.65 (0.26, 1.68)	−53 (−111, 102)	Very low	NA [c]	NA
Cephalosporin + Aminoglycoside	0.97 (0.62, 1.53)	−4 (−55, 77)	Very low	NA [c]	NA	—	—	—	—	—
Ceftazidime + Pefloxacin	1.89 (0.76, 4.66)	129 (−35, 531)	Very low	NA [c]	NA	—	—	—	—	—
Ceftriaxone + Clindamycin	0.18 (0.02, 1.55)	−119 (−142, 80)	Very low	NA [c]	NA	—	—	—	—	—
Ceftazidime + Linezolid	1.02 (0.6, 1.74)	3 (−58, 107)	Very low	NA [c]	NA	1.07 (0.75, 1.54)	11 (−38, 81)	Low	Intermediate effectiveness	May not be convincingly different than cephalosporins
Fluoroquinolones	0.85 (0.56, 1.28)	−22 (−64, 41)	Very low	NA [c]	NA	0.77 (0.33, 1.82)	−35 (−101, 123)	Very low	NA [c]	NA
Aztreonam + Clindamycin	0.53 (0.12, 2.33)	−68 (−128, 193)	Very low	NA [c]	NA	0.32 (0.03, 3.54)	−102 (−146, 381)	Very low	NA [c]	NA
Cephalosporin + Aztreonam	0.64 (0.2, 2.1)	−52 (−116, 160)	Very low	NA [c]	NA	1.6 (0.62, 4.1)	90 (−57, 465)	Very low	NA [c]	NA
Tigecycline	0.81 (0.42, 1.55)	−28 (−84, 80)	Very low	NA [c]	NA	0.64 (0.23, 1.79)	−54 (−116, 119)	Very low	NA [c]	NA

NA, not applicable; RD, risk difference.
[a] The baseline risks was derived from the median of risk of event across the arms that randomized patients to cephalosporins.
[b] We chose ± 2.5% (±25 events per 1000 participants) and ± 1% (±10 events per 1000 participants) as small important difference thresholds for treatment failure and all-cause mortality, respectively. We decided on these thresholds based on a consensus among the team members.
[c] Not applicable; antibiotics for which there was very low certainty evidence when compared to cephalosporins, were not classified.

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one of the main risk factors for treatment failure in empiric therapy. Fourth, there was insufficient data available to explore the effect modification by severity of pneumonia or prevalence of *P. aeruginosa* on treatment failure. Fifth, most available RCTs were published in the 1990s; no trial has been conducted on empiric antibiotic therapy for HAP since 2014. Indeed, emerging evidence on HAP in recent years has focused on new antibiotics for definitive therapy of patients with MDR gram-negatives. Data from the SENTRY Antimicrobial Surveillance study in patients hospitalized with pneumonia between 1997 and 2016 from North America, Asia-Pacific region, Europe, and Latin America showed an improvement in susceptibility of *P. aeruginosa* isolates including piperacillin-tazobactam susceptibility in the later years of the study [72,73] and a decreasing trend in MRSA rates across the regions [73]. However, because antimicrobial resistance patterns vary geographically and over time, this may raise issues regarding the potential applicability of our results to the sites with high rates of resistant pathogens.

In terms of implications for research, our findings highlight the need for new RCTs on empiric antibiotics for HAP. Available RCTs are relatively old; some addressed antibiotic regimens that are no longer in the practice of HAP treatment. Considering the limitations in available evidence, future RCTs should address all relevant patient-important outcomes including adverse events and rigorously collect and report data on factors that may modify the effect of antibiotics. Future studies should classify patients according to the severity of HAP and report outcomes by severity. In addressing concerns about the methodological quality of available evidence, future RCTs should implement proper measures to conceal the allocation of antibiotics with adequate blinding of healthcare providers and outcome assessors, complete follow-up, and appropriate analysis of randomized patients (i.e. ITT).

Conclusions

Piperacillin-tazobactam might be among the most effective antibiotics in reducing treatment failure in the empiric management of HAP. Empiric MRSA coverage may not exert additional benefit in reducing mortality in HAP patients. However, whether the addition of MRSA coverage or double coverage for *P. aeruginosa* may improve outcomes in patients at risk of acquiring resistant pathogens remains uncertain.

Author contributions

Conceptualization: M.G., G.G., and R.A.C.S.; Methodology: M.G., G.G., R.A.C.S., M.L., B.S.R., and R.B.P.; Resource: M.G. and R.C.; Investigation: M.G., A.A.H., D.A., H.G., Y.W., L.Y., A.A., J.B., A.G., W.S.H.K., G.A.G., V.L., J.P.L., and S.M.; Data curation: M.G.; Writing-original draft: M.G.; Writing-review and editing: all authors; Visualization: M.G.; Project administration: M.G.; Supervision: G.G., R.A.C.S., M.L., B.S.R., and R.B.P.

Transparency declaration

M.L. has received Honoria for participation on advisory and data safety and monitoring boards for influenza and COVID-19 vaccines, is on an antibiotic working group for the WHO Essential Medicines List, and participated in advisory boards for Paladin Labs, AVIR pharma, Xediton Pharmaceuticals. B.S.R. is a member of the GRADE Working Group and has received research funding from the Canadian Institute for Health Research (CIHR), Institute for Pain Research and Care (IPRC), Chronic Pain Centre of Excellence for Canadian Veterans, and PIPRA A.G. for research in different areas of pain, delirium, and perioperative care. A.G. is a board member of the GBS/CIDP Foundation of Canada. This study did not receive any funding.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2024.05.017.

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Supplementary Appendix C4

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Search strategy

OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

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50 Animal experiment/ not (human experiment/ or human/)
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Cochrane Library

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#2 MeSH descriptor: [Respiratory Tract Infections] this term only
#3 MeSH descriptor: [Pneumococcal Infections] explode all trees
#4 MeSH descriptor: [Pleuropneumonia] explode all trees
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#6 MeSH descriptor: [Respiratory Distress Syndrome] explode all trees
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#8 (respiratory near/2 (infection*))
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#13 #9 and #12

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S62 S44 OR S61

S61 S40 AND S60

S60 S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59

S59 (MH "Randomized Controlled Trials")

S58 (MH "Double-Blind Studies")

S57 (MH "Single-Blind Studies")

S56 (MH "Random Assignment")

S55 (MH "Pretest-Posttest Design")
S54 (MH "Cluster Sample")
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S52 AB (random*)
S51 TI (trial)
S50 MH (sample size) AND AB (assigned OR allocated OR control)
S49 MH (placebos)
S48 PT (randomized controlled trial)
S47 AB (CONTROL W5 GROUP)
S46 MH (CROSSOVER DESIGN) OR MH (COMPARATIVE STUDIES)
S45 AB (CLUSTER W3 RCT)
S44 S40 AND S43
S43 S41 OR S42
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S41 (MH "Systematic Review") OR "systematic review"
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S35 TX Sulfamethizole or Sulfathiazole or Sulfapyridine or Prontosil or Sulfanilamide or Sulfadiazine or Sulfalene or Sulfamethoxazole or Sulfamerazine or Sulfametrole or Trimethoprim-sulfamethoxazole or septra or cotrimoxazole or Sulfisoxazole or Sulfamethazine or Iclaprim or Brodimoprim
S34 TX Clindamycin or Solithromycin or Telithromycin or Cethromycin or Lincomycin or Roxithromycin or Spiramycin or Troleandomycin
S33 TX Doxycycline or Tigecycline or Chlortetracycline or Demeclocycline or Lymecycline or Meclocycline or Metacycline or Minocycline or Penimepicycline or Rolitetracycline or Eravacycline
S32 TX Azithromycin or Clarithromycin or Erythromycin or Nafithromycin or Dirithromycin or Flurithromycin or Josamycin orMidecamycin or Miocamycin or Rokitamycin
S31 TX Vancomycin or Linezolid or Telavancin or Oritavancin or Teicoplanin or Dalbavancin or Daptomycin or Posizolid or Radezolid or Tedizolid or Ranbezolid
S30 TX Gentamicin or Amikacin or Tobramycin or Plazomicin or Streptomycin or Dihydrostreptomycin or Ribostamycin or Kanamycin or Arbekacin or Netilmicin or Sisomicin or Isepamicin or Verdamicin or Eperezolid or Bekanamycin or Dibekacin or Micronomicin
S29 TX levofloxacin or Ciprofloxacin or Moxifloxacin or Omadacycline or Lascufloxacin or Zabofloxacin or Gatifloxacin or Grepafloxacin or Trovafloxacin or Enoxacin or Fleroxacin or Lomefloxacin or Nadifloxacin or Ofloxacin or Norfloxacin or Pefloxacin or Rufloxacin or Balofloxacin or Pazufloxacin or Sparfloxacin or Temafloxacin or Tosufloxacin or Clinafloxacin or Garenoxacin or Sitafloxacin or Prulifloxacin or Nemonoxacin or Alatrofloxacin
S28 TX Imipenem or Meropenem or Ertapenem or Imipenem-relebactam or Meropenem-vaborbactam or Doripenem or Biapenem or Ertapenem or Panipenem
S27 TX Cefepime or Ceftazidime or Cefotaxime or Ceftriaxone or Cefpodoxime or Cefuroxime or Ceftaroline or Ceftolozane-tazobactam or Ceftazidime-avibactam or Ceftaroline-avibactam or

cefoperazone-sulbactam or Ceftobiprole medocaril or Ceftazidime-avibactam or Cefazolin or Cefacetrile or Cefadroxil or Cefalexin or Cephaloridine or Cefalotin or Cefatrizine or Cefazedone or Cefradine or Cefroxadine or Cefaclor or Cefamandole or Cefminox or Cefonicid or Ceforanide or Cefotiam or Cefprozil or Cefbuperazone or Cefuzonam or cephamycin or Cefoxitin or Cefotetan or Cefmetazole or Loracarbef or Cefixime or Cefoperazone or Cefcapene or Cefdinir or Cefditoren or Cefetamet or Cefmenoxime or Cefodizime or Cefpimizole or Cefpiramide or Cefpodoxime or Cefsulodin or Cefteram or Ceftibuten or Ceftizoxime or oxacephem or Flomoxef or Latamoxef or Moxalactam or Cefiderocol or Cefozopran or Cefpirome or Ceftobiprole or Ceftolozane or Carumonam or Nocardicin A

S26 TX Aztreonam or Aztreonam-avibactam or Lefamulin

S25 TX Piperacillin-tazobactam or Amoxicillin or Ampicillin or Ampicillin-sulbactam or Amoxicillin-clavulanate or Pivampicillin or Hetacillin or Bacampicillin or Metampicillin or Talampicillin or Epicillin or Carbenicillin or Ticarcillin or Temocillin or Ureidopenicillins or Azlocillin or Mezlocillin or Cyclacillin or Sulbenicillin or Aspoxicillin or Amdinocillin or Penicillin G Benzathine or Procaine benzylpenicillin or Azidocillin or Phenoxymethylpenicillin or Cloxacillin or Dicloxacillin or Flucloxacilli or Oxacillin or Meticillin or Nafcillin or Ampicillin-flucloxacillin or Sultamicillin or Ticarcillin-clavulanate

S24 (MH "Antiinfective Agents, Fluoroquinolone") OR "Fluoroquinolone*"

S23 (MH "Sulfonamides") OR "sulfonamide*"

S22 (MH "Folic Acid Antagonists+")

S21 "Antifolate*"

S20 "Monobactam*"

S19 (MH "Cephalosporins") OR "Cephalosporin*"

S18 "Carbapenem*" OR (MH "Carbapenems+")

S17 (MH "Penicillins+") OR "Penicillin*"

S16 (MH "Antibiotics, Lactam+") OR "Beta-lactam*"

S15 "Glycopeptide*"

S14 "Oxazolidinone*"

S13 (MH "Aminoglycosides+") OR "Aminoglycoside*"

S12 "ketolide*"

S11 (MH "Antibiotics, Macrolide+") OR "macrolide*"

S10 "lincosamide*"

S9 (MH "Tetracycline") OR "tetracycline*"

S8 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7

S7 TX (respiratory N2 (infection* or distress))

S6 "ARDS"

S5 (MH "Respiratory Distress Syndrome")

S4 TX pneumon* or bronchopneumon* or pleuropneumon*

S3 (MH "Pneumococcal Infections+")

S2 (MH "Respiratory Tract Infections")

S1 (MH "Pneumonia+")

Web of Science

16 #14 not #15

15 TOPIC: (TOPIC: (Rat OR rats OR mouse OR mice OR rodent OR murine OR canine OR porcine OR pig OR hog OR dog OR rabbit*))

14 #13 AND #7

13 #12 OR #11 OR #10 OR #9 OR #8

12 TOPIC: ((random: OR placebo: OR double-blind:))
11 TOPIC: (((treatment OR control) NEAR/3 group*))
10 TOPIC: (((clinical OR control*) NEAR/3 trial))
9 TOPIC: ((allocat* NEAR/5 group*))
8 TOPIC: ((("systematic review" or meta-analysis)))
7 #6 AND #3
6 #5 OR #4
5 TOPIC: (((Piperacillin-tazobactam or Amoxicillin or Ampicillin or Ampicillin-sulbactam or Amoxicillin-clavulanate or Pivampicillin or Hetacillin or Bacampicillin or Metampicillin or Talampicillin or Epicillin or Carbenicillin or Ticarcillin or Temocillin or Ureidopenicillins or Azlocillin or Mezlocillin or Cyclacillin or Sulbenicillin or Aspoxicillin or Amdinocillin or Penicillin G Benzathine or Procaine benzylpenicillin or Azidocillin or Phenoxymethylpenicillin or Cloxacillin or Dicloxacillin or Flucloxacilli or Oxacillin or Meticillin or Nafcillin or Ampicillin-flucloxacillin or Sultamicillin or Ticarcillin-clavulanate or Aztreonam or Aztreonam-avibactam or Lefamulin or Cefepime or Ceftazidime or Cefotaxime or Ceftriaxone or Cefpodoxime or Cefuroxime or Ceftaroline or Ceftolozane-tazobactam or Ceftazidime-avibactam or Ceftaroline-avibactam or cefoperazone-sulbactam or Ceftobiprole medocaril or Ceftazidime-avibactam or Cefazolin or Cefacetrile or Cefadroxil or Cefalexin or Cephaloridine or Cefalotin or Cefatrizine or Cefazedone or Cefradine or Cefroxadine or Cefaclor or Cefamandole or Cefminox or Cefonicid or Ceforanide or Cefotiam or Cefprozil or Cefbuperazone or Cefuzonam or cephamycin or Cefoxitin or Cefotetan or Cefmetazole or Loracarbef or Cefixime or Cefoperazone or Cefcapene or Cefdinir or Cefditoren or Cefetamet or Cefmenoxime or Cefodizime or Cefpimizole or Cefpiramide or Cefpodoxime or Cefsulodin or Cefteram or Ceftibuten or Ceftizoxime or oxacephem or Flomoxef or Latamoxef or Moxalactam or Cefiderocol or Cefozopran or Cefpirome or Ceftobiprole or Ceftolozane or Carumonam or Nocardicin A or Imipenem or Meropenem or Ertapenem or Imipenem-relebactam or Meropenem-vaborbactam or Doripenem or Biapenem or Ertapenem or Panipenem or levofloxacin or Ciprofloxacin or Moxifloxacin or Omadacycline or Lascufloxacin or Zabofloxacin or Gatifloxacin or Grepafloxacin or Trovafloxacin or Enoxacin or Fleroxacin or Lomefloxacin or Nadifloxacin or Ofloxacin or Norfloxacin or Pefloxacin or Rufloxacin or Balofloxacin or Pazufloxacin or Sparfloxacin or Temafloxacin or Tosufloxacin or Clinafloxacin or Garenoxacin or Sitafloxacin or Prulifloxacin or Nemonoxacin or Alatrofloxacin or Gentamicin or Amikacin or Tobramycin or Plazomicin or Streptomycin or Dihydrostreptomycin or Ribostamycin or Kanamycin or Arbekacin or Netilmicin or Sisomicin or Isepamicin or Verdamicin or Eperezolid or Bekanamycin or Dibekacin or Micronomicin or Vancomycin or Linezolid or Telavancin or Oritavancin or Teicoplanin or Dalbavancin or Daptomycin or Posizolid or Radezolid or Tedizolid or Ranbezolid or Azithromycin or Clarithromycin or Erythromycin or Nafithromycin or Dirithromycin or Flurithromycin or Josamycin or Midecamycin or Miocamycin or Rokitamycin or Doxycycline or Tigecycline or Chlortetracycline or Demeclocycline or Lymecycline or Meclocycline or Metacycline or Minocycline or Penimepicycline or Rolitetracycline or Eravacycline or Clindamycin or Solithromycin or Telithromycin or Cethromycin or Lincomycin or Roxithromycin or Spiramycin or Troleandomycin or Sulfamethizole or Sulfathiazole or Sulfapyridine or Prontosil or Sulfanilamide or Sulfadiazine or Sulfalene or Sulfamethoxazole or Sulfamerazine or Sulfametrole or Trimethoprim-sulfamethoxazole or septra or cotrimoxazole or Sulfisoxazole or Sulfamethazine or Iclaprim or Brodimoprim or Metronidazole or Tinidazole or Ornidazole or Streptogramin or Quinupristin-dalfopristin or Chloramphenicol or Fusidic acid or Fosfomycin or Murepavidin or Rifampicin or Rifabutin or Rifapentine)))
4

TOPIC: (((tetracycline* or lincosamide* or macrolide* or ketolide* or Aminoglycoside* or Oxazolidinone* or Glycopeptide or Beta-lactam* or Penicillin* or Carbapenem* or Cephalosporin or Monobactam* or Antifolate* or sulfonamide* or Fluoroquinolone*)))
3 #2 OR #1
2 TOPIC: ((respiratory near/2 infection*))
1 TOPIC: (((pneumon* or bronchopneumon* or pleuropneumon*))

Assessment of certainty of evidence using GRADE approach

We assessed the certainty of evidence for each outcome for which we performed a network meta-analysis by rating the certainty of evidence for each direct comparison, starting rating at high and rating down based on the risk of bias, inconsistency, indirectness, and publication bias. We rated down the certainty of most direct estimates one level for risk bias because of serious concerns with respect to the blinding and allocation concealment of trials contributing to the respective direct evidence [1]. We also rated down one level for inconsistency based on variability in point estimates and non-overlap in confidence intervals for comparison of the combination of a cephalosporin and an aminoglycoside versus cephalosporin alone for treatment failure [2, 3]. We did not rate down certainty for indirectness [4] or publication bias [5]. Then, we rated the certainty of indirect estimates by first selecting the most dominant first-order loop - a loop that has only one common comparator between the two antibiotic regimens being compared [6, 7]. When no first order loop was available, we selected the most dominant second or higher order loop. If there proved more than one first-order loop, we selected the loop with the largest number of participants. The starting certainty of the indirect estimate was the lowest of the contributing direct estimates with further rating down for intransitivity (i.e., differences in effect modifiers between the direct comparisons that inform the indirect estimate) [6, 7]. We did not identify any evidence of intransitivity in any of the networks [8].

In the final step, we rated the certainty of the network estimate for each comparison based on the direct or indirect evidence that most contributed to the network estimate [6, 7]. When both direct and indirect evidence contributed similarly to the network estimate, we selected

the evidence with higher certainty. Subsequently, we assessed incoherence between direct and indirect estimate [9] and imprecision [10, 11] of network estimates to obtain the final certainty of evidence. We detected no case of incoherence for any of the comparisons. To assess imprecision, we rated certainty in a non-zero effect, rating down one level if the confidence interval (CI) crossed the null threshold. However, if the point estimate was near the null and the CI included the null threshold, we did not rate down for imprecision. If the CI includes both important benefit and harm, we rated down two levels for imprecision and if the CI was extremely wide, we rated down three levels for imprecision. If the CI did not cross any threshold, we calculated optimal information size and if it was not met, we rated down one or two levels for imprecision.

Table S1. Details of antibiotic regimens and co-administered antibiotics

First author, year	Arm 1	Dosing, duration, and co-interventions	Arm 2	Dosing, duration, and co-interventions
Awad [12], 2014	ceftobiprole	500 mg IV q8h for 7-14 days +/- fluoroquinolone or aminoglycoside	ceftazidime + linezolid	ceftazidime 2 g IV every q8h + linezolid 600 mg IV q12h for 7-14 days +/- fluoroquinolone or aminoglycoside
Basseti [13], 1991	ceftazidime	2 g IV q12h for a mean of 9 days	ceftriaxone	2 g IV q24h for a mean of 9 days
Chaudhary [14], 2008	cefepime + amikacin	cefepime 2 g IV q12h + amikacin 500mg q12h for 7-10 days	cefepime	2 g IV q12h for 7-10 days
Cometta [15], 1994	imipenem + netilmicin	imipenem 500mg q6h + netilmicin 150 mg q12h for a mean of 10 days	imipenem	500mg q6h for a mean of 10 days
Fekete [16], 1994	aztreonam + cefazolin	aztreonam 1 to 2g IV q8h + cefazolin 1g IV q8h for 5-14 days	ceftazidime	1 to 2g IV q8h for 5-14 days +/- vancomycin
Fink [17], 1994	ciprofloxacin	400 mg IV q8h +/- metronidazole +/- vancomycin	imipenem	1g IV q8h +/- vancomycin
Freire [18], 2010	tigecycline	100 mg IV followed by 50 mg IVq12h for 7-14 days +/- ceftazidime +/- aminoglycoside	imipenem	500 mg to 1 g IV q8h for 7-14 days +/- vancomycin +/- aminoglycoside
Gao [19], 1999	cefepime	2 g IV q12h for 8-10 days	ceftazidime	2 g IV q12h for 8-10 days
Garau [20], 1997	meropenem	1g IV q8h for a mean of 11 days	imipenem	1g IV q8h for a mean of 11 days
Garber [21], 1992	cefotaxime	1 g IV q8h for 7-10 days	ceftriaxone	1 g IV q12h for 7-10 days
Giamarellou [22], 1990	pefloxacin	400 mg IV q8h for a mean of 12 days	imipenem	1 g IV q8h for a mean of 12 days
Heinrich [23], 1991	ceftazidime	1 g IV q8h	cefotaxime	2 g IV q8h
Höffken [24], 2007	moxifloxacin	400 mg IV q24h for 7-14 days	ceftriaxone/cefuroxime	ceftriaxone 2 g IV q24h for 3 doses followed by oral cefuroxime axetil 500 mg q12h for 7-14 days
Jaccard [25], 1998	piperacillin-tazobactam	4.5 g IV q8h for a mean of 10 days	imipenem	500 mg IV q6h for a mean of 10 days
Jin [26], 2005	meropenem	500 mg IV q8h IV for 7-10 days	imipenem	1 g q8h iv for 7-10 days
Joshi [27], 2006	piperacillin-tazobactam	4.5 g IV q6h for 5-21 days + tobramycin	imipenem	500 mg IV q6h for 5-21 days + tobramycin
Joshi [28], 1999	piperacillin-tazobactam	3.375 g IV q4h for a mean of 9 days + tobramycin	ceftazidime	2 g IV q8h for a mean of 9 days + tobramycin

Koehler [29], 1990	piperacillin + Tobramycin	piperacillin 4 g IV q8h + tobramycin 80 mg q8h for 7-10 days	ceftazidime	1 g IV q8h for 7-10 days
Mangi [30], 1992	cefoperazone	2g IV q12h for a mean of 8 days	ceftriaxone	2g IV q24h for a mean of 8 days
Mangi [31], 1988	cefoperazone	2 g IV q12h for a mean of 9 days	ceftazidime	2 g IV q8h for a mean of 9 days
Mouton [32], 1995	meropenem	1 g IV q8h for a mean of 9 days	ceftazidime + amikacin	ceftazidime 2 g IV q8h + amikacin 15 mg/kg/day IV for a mean of 9 days
Mouton [33], 1988	ceftazidime + pefloxacin	ceftazidime 1 g IV q8h + pefloxacin 400 mg q12h) +/- metronidazole	ceftazidime + amikacin	ceftazidime 1 g IV q8h + amikacin 15 mg/kg/day IV +/- metronidazole
Norrby [34], 1993	ceftazidime	2 g IV q12h for a mean of 9 days	imipenem	500 mg q6h for a mean of 9 days
Raad [35], 2001	piperacillin-tazobactam	4.5 g IV q6h for a mean of 7 days + amikacin	aztreonam + clindamycin	aztreonam 2 g IV every q8h + clindamycin 900 mg q8h for a mean of 7 days + amikacin
Ramirez [36], 2013	tigecycline	150 mg IV followed by 75 mg IV q12h, or 200 mg IV followed by 100 mg q12h for 7-14 days +/- ceftazidime +/- aminoglycoside	imipenem	1 g IV q8h for 7-14 days +/- vancomycin +/- aminoglycoside for 7-14 days
Ramirez [37], 1999	ceftazidime	for 10 days	penicillin G + amikacin	for 10 days
Rapp [38], 1984	ceftazidime	2 g IV q8h for 5-14 days	ticarcillin + tobramycin	ticarcillin g3 g IV q4h + tobramycin dosed to achieve trough levels of 1.5-2 pg/ml and peak levels of 5-7 pg/ml for 5-14 days
Rapp [39], 1991	ciprofloxacin	300 mg IV q12h for a mean of 10 days	ceftazidime	2 g IV q8h for a mean of 10 days
Rea-Neto [40], 2008	doripenem	500mg IV q8h for at least 72 hours, then patients could be switched to oral levofloxacin 750 mg q24h for total duration of 7 -14 days +/- vancomycin +/- amikacin	piperacillin-tazobactam	4.5 g IV q6h for at least 72 hours, then patients could be switched to oral levofloxacin 750 mg q24h for total duration of 7 -14 days +/- vancomycin +/- amikacin
Reith [41], 2006	levofloxacin	500 mg q24h for a mean of 7 days	ceftriaxone + clindamycin	ceftriaxone 2 g q24h + clindamycin 600 mg q8h for a mean of 7 days
Rubinstein [42], 1995	ceftazidime	2 g IV q8h for a mean of 9 days +/- metronidazole	ceftriaxone + tobramycin	ceftriaxone 2g IV q24h + tobramycin 3 to 5 mg/kg IV (after a loading dose of 2 mg/kg) for a mean of 9 days +/- metronidazole

Saginur [43], 1997	ciprofloxacin	300 mg IV q12h for at least 72 hours, then patients could be switched to 750 mg oral ciprofloxacin q12h for total duration of 10-12 days +/- clindamycin	ceftazidime	2 g q8h for 10-12 days +/- clindamycin
Schmitt [44], 2006	piperacillin-tazobactam	4.5g IV q8h for 5-21 days	imipenem	1g IV q8h for 5-21 days
Seiger [45], 1997	meropenem	1 g IV q8h for a mean of 10 days	ceftazidime + tobramycin	Ceftazidime 2 g IV q8h + tobramycin 1 mg/kg IV (after a loading dose of 1.5 to 2 mg/kg) q8h for a mean of 10 days
Shah [46], 1995	ceftriaxone	2 g IV q12h for a mean of 8 days	cefotaxime	2 g IV q12h for a mean of 8 days
Torres [47], 1989	aztreonam + cefotaxime	aztreonam 1g IV q8h + cefotaxime 2g IV q6h	amikacin + cefotaxime	amikacin 500mg IV q12h + cefotaxime 2g IV q6h
Torres [48], 2000	ciprofloxacin	800-1200 mg IV q24h for a mean of 9 days	imipenem	2-4 g IV q24h for a mean of 9 days
West [49], 2003	levofloxacin	750 mg q24h IV for at least 24 hours, then patients could be switched to oral levofloxacin for total duration of 7-15 days +/- ceftazidime (or another non-carbapenem β-lactam) +/- vancomycin	imipenem	500 mg to 1 g IV q6-8h for at least 72 hours, then patients could be switched to oral ciprofloxacin for total duration of 7-15 days +/- aminoglycoside +/- vancomycin
Yakovlev [50], 2006	cefepime	2 g IV q12h for at least 72 hours, then patients could be switched to oral antimicrobial agent for total duration of 7-14 days +/- metronidazole	ertapenem	1 g IV q24h for at least 72 hours, then patients could be switched to oral antimicrobial agent for total duration of 7-14 days

Table S2. Outcome data (treatment failure and all-cause mortality) by eligible studies

First author, year	Arm 1	Arm 2	Treatment failure		All-cause mortality	
			N event 1 / N analysed 1	N event 2 / N analysed 2	N event 1 / N analysed 1	N event 2 / N analysed 2
Awad [12], 2014	ceftobiprole	ceftazidime + linezolid	116 / 287	117 / 284	48 / 287	51 / 284
Basseti [13], 1991	ceftazidime	ceftriaxone	3 / 31	3 / 28	---	---
Chaudhary [14], 2008	cefepime + amikacin	cefepime	11 / 100	29 /100	---	---
Cometta [15], 1994	imipenem + netilmicin	imipenem	14 / 86	16 / 91	---	---
Fekete [16], 1994	aztreonam + cefazolin	ceftazidime	2 /20	4 /28	8 / 30	6 / 36
Fink [17], 1994	ciprofloxacin	imipenem	47 /121	59 /130	---	---
Freire [18], 2010	tigecycline	imipenem	65 / 313	59 / 313	41 / 336	43 / 345
Gao [19], 1999	cefepime	ceftazidime	1 / 18	2 / 24	---	---
Garau [20], 1997	meropenem	imipenem	4 / 37	10 / 42	15 / 47	18 / 48
Garber [21], 1992	cefotaxime	ceftriaxone	4 /30	6 / 27	---	---
Giamarellou [22], 1990	pefloxacin	imipenem	10 / 26	4 / 28	1 / 26	3 / 28
Heinrich [23], 1991	ceftazidime	cefotaxime	0 /18	0 /18	1 / 21	0 / 19
Höffken [24], 2007	moxifloxacin	ceftriaxone/cefuroxime	21 / 77	26 / 82	8 / 77	11 / 82
Jaccard [25], 1998	piperacillin-tazobactam	imipenem	13 / 75	23 / 79	7 / 75	6 / 79
Jin [26], 2005	meropenem	imipenem	1 / 25	1 / 26	---	---
Joshi [27], 2006	piperacillin-tazobactam	imipenem	25 / 65	29 / 72	---	---
Joshi [28], 1999	piperacillin-tazobactam	ceftazidime	19 / 70	20 / 42	---	---
Koehler [29], 1990	piperacillin + Tobramycin	ceftazidime	8 / 66	4 / 60	---	---
Mangi [30], 1992	cefoperazone	ceftriaxone	7 / 28	7 / 27	7 / 28	6 / 27
Mangi [31], 1988	cefoperazone	ceftazidime	13 / 43	10 / 45	---	---
Mouton [32], 1995	meropenem	ceftazidime + amikacin	7 / 37	9 /32	---	---

Mouton [33], 1988	ceftazidime + pefloxacin	ceftazidime + amikacin	20 / 57	13 / 72	---	---
Norrby [34], 1993	ceftazidime	imipenem	23 / 125	28 / 129	---	---
Raad [35], 2001	piperacillin-tazobactam	aztreonam + clindamycin	5 / 30	3 / 22	4 / 30	1 / 22
Ramirez [36], 2013	tigecycline	Imipenem	7 / 29	4 / 15	---	---
Ramirez [37], 1999	ceftazidime	penicillin G + Amikacin	5 /30	22 / 30	4 / 30	6 / 30
Rapp [38], 1984	ceftazidime	ticarcillin + tobramycin	2 / 17	3 / 18	---	---
Rapp [39], 1991	ciprofloxacin	ceftazidime	2 / 17	2 / 15	---	---
Rea-Neto [40], 2008	doripenem	piperacillin-tazobactam	16 / 105	13 / 93	---	---
Reith [41], 2006	levofloxacin	ceftriaxone + clindamycin	3 / 7	1 / 11	---	---
Rubinstein [42], 1995	ceftazidime	ceftriaxone + tobramycin	24 / 159	32 / 138	---	---
Saginur [43], 1997	ciprofloxacin	ceftazidime	1 / 26	2 / 34	---	---
Schmitt [44], 2006	Piperacillin-tazobactam	imipenem	22 / 107	221 / 110	17 / 110	11 / 111
Seiger [45], 1997	meropenem	ceftazidime + tobramycin	1 / 17	5 / 19	---	---
Shah [46], 1995	ceftriaxone	cefotaxime	9 / 62	9 / 56	---	---
Torres [47], 1989	aztreonam + cefotaxime	amikacin + cefotaxime	2 /13	4 /16	---	---
Torres [48], 2000	ciprofloxacin	imipenem	18 / 52	17 / 57	8 / 41	4 / 34
West [49], 2003	levofloxacin	imipenem	69 / 204	63 / 206	38 / 220	32 / 218
Yakovlev [50], 2006	cefepime	ertapenem	9 / 64	7 / 79	---	---

Table S3. Risk of bias assessment of included studies for treatment failure

First author, year	Comparison	Randomization	Allocation concealment	Blinding of patients	Blinding of healthcare providers	Blinding of data collectors	Blinding of outcome assessors	Blinding of data analysts	Missing outcome data
Awad, 2014	ceftobiprole vs ceftazidime + linezolid	Low risk	Low risk	Probably low risk	Probably low risk	Probably low risk	Probably low risk	Probably high risk	High risk
Basseti, 1991	ceftazidime vs ceftriaxone	Probably low risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Low risk
Chaudhary, 2008	cefepime + amikacin vs cefepime	Probably low risk	Probably high risk	High risk	High risk	High risk	High risk	High risk	Low risk
Cometta, 1994	Imipenem + netilmicin vs imipenem	Probably low risk	Probably high risk	High risk	High risk	High risk	High risk	High risk	Probably low risk
Fekete, 1994	aztreonam + cefazolin vs ceftazidime	Probably low risk	Probably high risk	High risk	High risk	High risk	High risk	High risk	High risk
Fink, 1994	ciprofloxacin vs imipenem	Low risk	Probably low risk	Probably low risk	Probably low risk	Probably low risk	Probably low risk	Probably high risk	High risk
Freire, 2010	tigecycline vs imipenem	Probably low risk	Low risk	Probably low risk	Probably low risk	Probably low risk	Probably low risk	Probably high risk	Probably low risk
Gao, 1999	cefepime vs ceftazidime	Probably low risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Low risk
Garau, 1997	meropenem vs imipenem	Probably low risk	Probably high risk	High risk	High risk	High risk	High risk	High risk	Low risk
Garber, 1992	cefotaxime vs ceftriaxone	Probably low risk	Probably high risk	High risk	High risk	High risk	High risk	High risk	High risk
Giamarellou, 1990	pefloxacin vs imipenem	Probably low risk	Probably high risk	High risk	High risk	High risk	High risk	High risk	Low risk
Heinrich, 1991	ceftazidime vs cefotaxime	Probably low risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Low risk
Höffken, 2007	moxifloxacin vs ceftriaxone/cefuroxime	Probably low risk	Probably high risk	High risk	High risk	High risk	High risk	High risk	High risk
Jaccard, 1998	piperacillin-tazobactam vs imipenem	Probably low risk	Probably high risk	High risk	High risk	High risk	High risk	High risk	Low risk

Jin, 2005	meropenem vs imipenem	Probably low risk	Probably high risk	High risk	High risk	High risk	High risk	High risk	Low risk
Joshi, 2006	piperacillin-tazobactam vs imipenem	Low risk	Probably low risk	Probably low risk	Probably low risk	Probably low risk	Probably low risk	Probably high risk	Low risk
Joshi, 1999	piperacillin-tazobactam vs ceftazidime	Low risk	Probably high risk	High risk	High risk	High risk	High risk	High risk	Low risk
Koehler, 1990	piperacillin + tobramycin vs ceftazidime	Probably low risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably low risk
Mangi, 1992	cefoperazone vs ceftriaxone	Low risk	Probably high risk	High risk	High risk	High risk	High risk	High risk	High risk
Mangi, 1988	cefoperazone vs ceftazidime	Low risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably low risk
Mouton, 1995	meropenem vs ceftazidime + amikacin	Probably low risk	Probably high risk	High risk	High risk	High risk	High risk	High risk	Probably high risk
Mouton, 1988	ceftazidime + pefloxacin vs ceftazidime + amikacin	Low risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	High risk
Norrby, 1993	ceftazidime vs imipenem	Low risk	Probably high risk	High risk	High risk	High risk	Low risk	High risk	Low risk
Raad, 2001	piperacillin-tazobactam vs clindamycin + aztreonam	Probably low risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Low risk
Ramirez, 2013	tigecycline vs imipenem	Probably low risk	Probably low risk	Probably low risk	Probably low risk	Probably low risk	Probably low risk	Probably high risk	High risk
Ramirez, 1999	ceftazidime vs penicillin G + amikacin	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Low risk
Rapp, 1984	ceftazidime vs ticarcillin + tobramycin	Probably low risk	Probably high risk	High risk	High risk	High risk	High risk	High risk	Low risk

Rapp, 1991	ciprofloxacin vs ceftazidime	Probably low risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Low risk
Rea-Neto, 2008	doripenem vs piperacillin-tazobactam	Probably low risk	Probably high risk	High risk	High risk	High risk	Low risk	Low risk	High risk
Reith, 2006	levofloxacin vs ceftriaxone + clindamycin	Probably low risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Low risk
Rubinstein, 1995	ceftazidime vs ceftriaxone + tobramycin	Probably low risk	Probably high risk	High risk	High risk	High risk	Low risk	High risk	High risk
Saginur, 1997	ciprofloxacin vs ceftazidime	Probably low risk	Low risk	High risk	High risk	High risk	High risk	High risk	High risk
Schmitt, 2006	piperacillin-tazobactam vs imipenem	Probably low risk	Low risk	Probably high risk	Probably low risk	Probably low risk	Probably high risk	Probably high risk	High risk
Seiger, 1997	meropenem vs ceftazidime + tobramycin	Probably low risk	Probably high risk	High risk	High risk	High risk	High risk	High risk	High risk
Shah, 1995	ceftriaxone vs cefotaxime	Probably low risk	Probably high risk	High risk	High risk	High risk	High risk	High risk	Low risk
Torres, 1989	aztreonam + cefotaxime vs amikacin + cefotaxime	Probably low risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	High risk
Torres, 2000	ciprofloxacin vs imipenem	Probably low risk	Probably high risk	High risk	High risk	High risk	High risk	High risk	High risk
West, 2003	levofloxacin vs imipenem	Low risk	Low risk	High risk	High risk	High risk	High risk	High risk	Probably low risk
Yakovlev, 2006	cefepime vs ertapenem	Low risk	Probably low risk	Probably low risk	Probably low risk	Probably low risk	Probably low risk	Probably high risk	High risk

Table S4. Risk of bias assessment of included studies for all-cause mortality

First author, year	Comparison	Randomization	Allocation concealment	Blinding of patients	Blinding of healthcare providers	Blinding of data collectors	Blinding of outcome assessors	Blinding of data analysts	Missing outcome data
Awad, 2014	ceftobiprole vs ceftazidime + linezolid	Low risk	Low risk	Probably low risk	Probably low risk	Probably low risk	Low risk	Probably high risk	Low risk
Fekete, 1994	aztreonam + cefazolin vs ceftazidime	Probably low risk	Probably high risk	High risk	High risk	High risk	Low risk	High risk	Low risk
Freire, 2010	tigecycline vs imipenem	Probably low risk	Low risk	Probably low risk	Probably low risk	Probably low risk	Low risk	Probably high risk	Low risk
Garau, 1997	meropenem vs imipenem	Probably low risk	Probably high risk	High risk	High risk	High risk	Low risk	High risk	Low risk
Giamarellou, 1990	pefloxacin vs	Probably low risk	Probably high risk	High risk	High risk	High risk	Low risk	High risk	Low risk
Heinrich, 1991	ceftazidime vs cefotaxime	Probably low risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Low risk	Probably high risk	Low risk
Höffken, 2007	moxifloxacin vs ceftriaxone/cefuroxime	Probably low risk	Probably high risk	High risk	High risk	High risk	Low risk	High risk	High risk
Jaccard, 1998	piperacillin-tazobactam vs imipenem	Probably low risk	Probably high risk	High risk	High risk	High risk	Low risk	High risk	Low risk
Mangi, 1992	cefoperazone vs ceftriaxone	Low risk	Probably high risk	High risk	High risk	High risk	Low risk	High risk	High risk
Raad, 2001	piperacillin-tazobactam vs clindamycin + aztreonam	Probably low risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Low risk	Probably high risk	Low risk
Ramirez, 1999	ceftazidime vs penicillin G + amikacin	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Low risk	Probably high risk	Low risk
Schmitt, 2006	piperacillin-tazobactam vs imipenem	Probably low risk	Low risk	Probably high risk	Probably low risk	Probably low risk	Low risk	Probably high risk	High risk

Torres, 2000	ciprofloxacin vs imipenem	Probably low risk	Probably high risk	High risk	High risk	High risk	Low risk	High risk	High risk
West, 2003	levofloxacin vs imipenem	Low risk	Low risk	High risk	High risk	High risk	Low risk	High risk	Probably low risk

Table S5. Risk of bias assessment of included studies for length of hospital stay

First author, year	Comparison	Randomization	Allocation concealment	Blinding of patients	Blinding of healthcare providers	Blinding of data collectors	Blinding of outcome assessors	Blinding of data analysts	Missing outcome data	Competing effect due to death
Raad, 2001	piperacillin-tazobactam vs clindamycin + aztreonam	Probably low risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Low risk	Probably low risk
Ramirez, 1999	ceftazidime vs penicillin G + amikacin	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Low risk	Probably low risk

Table S6. Risk of bias assessment of included studies for adverse events leading to discontinuation of antibiotic regimens

First author, year	Comparison	Randomization	Allocation concealment	Blinding of patients	Blinding of healthcare providers	Blinding of data collectors	Blinding of outcome assessors	Blinding of data analysts	Missing outcome data
Basseti, 1991	ceftazidime vs ceftriaxone	Probably low risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Low risk
Fekete, 1994	aztreonam + cefazolin vs ceftazidime	Probably low risk	Probably high risk	High risk	High risk	High risk	High risk	High risk	Low risk
Gao, 1999	cefepime vs ceftazidime	Probably low risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Low risk

Heinrich, 1991	ceftazidime vs cefotaxime	Probably low risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Low risk
Höffken, 2007	moxifloxacin vs ceftriaxone/cefuroxime	Probably low risk	Probably high risk	High risk	High risk	High risk	High risk	High risk	High risk
Koehler, 1990	piperacillin + tobramycin vs ceftazidime	Probably low risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Low risk
Mangi, 1992	cefoperazone vs ceftriaxone	Low risk	Probably high risk	High risk	High risk	High risk	High risk	High risk	Low risk
Mangi, 1988	cefoperazone vs ceftazidime	Low risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably low risk
Schmitt, 2006	piperacillin-tazobactam vs imipenem	Probably low risk	Low risk	Probably high risk	Probably low risk	Probably low risk	Probably high risk	Probably high risk	High risk
West, 2003	levofloxacin vs imipenem	Low risk	Low risk	High risk	High risk	High risk	High risk	High risk	Probably low risk

Table S7. Risk of bias assessment of included studies for any/all gastrointestinal adverse events

First author, year	Comparison	Randomization	Allocation concealment	Blinding of patients	Blinding of healthcare providers	Blinding of data collectors	Blinding of outcome assessors	Blinding of data analysts	Missing outcome data
Höffken, 2007	moxifloxacin vs ceftriaxone/cefuroxime	Probably low risk	Probably high risk	High risk	High risk	High risk	High risk	High risk	High risk
Jin, 2005	meropenem vs imipenem	Probably low risk	Probably high risk	High risk	High risk	High risk	High risk	High risk	Low risk

Table S8. Risk of bias assessment of included studies for diarrhoea

First author, year	Comparison	Randomization	Allocation concealment	Blinding of patients	Blinding of healthcare providers	Blinding of data collectors	Blinding of outcome assessors	Blinding of data analysts	Missing outcome data
Gao, 1999	cefepime vs ceftazidime	Probably low risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Low risk
Garber, 1992	cefotaxime vs ceftriaxone	Probably low risk	Probably high risk	High risk	High risk	High risk	High risk	High risk	Low risk
Höffken, 2007	moxifloxacin vs ceftriaxone/cefuroxime	Probably low risk	Probably high risk	High risk	High risk	High risk	High risk	High risk	High risk
Jin, 2005	meropenem vs imipenem	Probably low risk	Probably high risk	High risk	High risk	High risk	High risk	High risk	Low risk
Raad, 2001	piperacillin-tazobactam vs clindamycin + aztreonam	Probably low risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Low risk
Schmitt, 2006	piperacillin-tazobactam vs imipenem	Probably low risk	Low risk	Probably high risk	Probably low risk	Probably low risk	Probably high risk	Probably high risk	High risk
Shah, 1995	ceftriaxone vs cefotaxime	Probably low risk	Probably high risk	High risk	High risk	High risk	High risk	High risk	Low risk
West, 2003	levofloxacin vs imipenem	Low risk	Low risk	High risk	High risk	High risk	High risk	High risk	Probably low risk

Table S9. Risk of bias assessment of included studies for Nausea and vomiting

First author, year	Comparison	Randomization	Allocation concealment	Blinding of patients	Blinding of healthcare providers	Blinding of data collectors	Blinding of outcome assessors	Blinding of data analysts	Missing outcome data
Schmitt, 2006	piperacillin-tazobactam vs imipenem	Probably low risk	Low risk	Probably high risk	Probably low risk	Probably low risk	Probably high risk	Probably high risk	High risk
West, 2003	levofloxacin vs imipenem	Low risk	Low risk	High risk	High risk	High risk	High risk	High risk	Probably low risk

Table S10. Risk of bias assessment of included studies for any/all allergic reactions

First author, year	Comparison	Randomization	Allocation concealment	Blinding of patients	Blinding of healthcare providers	Blinding of data collectors	Blinding of outcome assessors	Blinding of data analysts	Missing outcome data
Jin, 2005	meropenem vs imipenem	Probably low risk	Probably high risk	High risk	High risk	High risk	High risk	High risk	Low risk
Raad, 2001	piperacillin-tazobactam vs clindamycin + aztreonam	Probably low risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Low risk
West, 2003	levofloxacin vs imipenem	Low risk	Low risk	High risk	High risk	High risk	High risk	High risk	Probably low risk

Risk of bias assessment instruction (modified Cochrane ROB 1.0)

1. Was the allocation sequence adequately generated?

Definitely YES >>> Trial explicitly stated use of an adequate method of randomization: e.g., random number generator, random number table, coin tossing, shuffling cards or envelopes, throwing dice, drawing of lots, minimization with or without random element.

Probably YES >>> Trial is described as "randomized" without further description on the method of randomization.

Probably NO >>> Trial is described as randomized but there is substantial imbalance in baseline characteristics or key prognostic factor (severity of pneumonia) based on all randomized participants that suggest problem with randomization process, or trial described as randomized but there are substantial differences between intervention group sizes, compared with the intended allocation ratio.

Definitely NO >>> Trial used quasi-randomization: e.g., sequence generated by odd or even date of birth, date (or day) of admission or hospital or clinic record number, alteration between treatment arms.

2. Was the allocation adequately concealed?

Definitely YES >>> Trial used central allocation (including telephone, web-based), or trial is blinded and explicitly stated that drug prepared by pharmacist, or trial used sequentially numbered drug containers of identical appearance.

Probably YES >>> Trial described as double or triple blind, or trial explicitly stated that patients and healthcare providers/ investigators are blinded, or trial used sequentially numbered opaque sealed envelopes.

Probably NO >>> Trial is described as single blind or unblinded and no information or insufficient information on allocation concealment (e.g., if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque, and sealed.)

Definitely NO >>> Trial used an open random allocation schedule (e.g., a list of random numbers), assignment envelopes without appropriate safeguards (e.g., if envelopes were unsealed or non-opaque or not sequentially numbered), or trial used a quasi-randomization method.

3. Blinding: Was knowledge of the allocated interventions adequately prevented?

3.a. Were patients blinded?

Definitely YES >>> Trial explicitly stated that patients were blinded.

Probably YES >>> There is no explicit statement about blinding of patients, but trial is described as placebo-controlled trial or active control drug trial (A vs. B) and mention of "double dummy" or that medications were identical or matched, or trial is described as single-blind or double-blind or triple-blind.

Probably NO >>> There is no explicit statement about blinding of patients, but trial is described as active control drug trial (A vs. B) and no mention of "double dummy" or that medications were identical or matched.

Definitely NO >>> Trial explicitly stated that patients were not blinded, or trial is described as open-label or unblinded.

3.b. Were healthcare providers blinded?

Definitely YES >>> Trial explicitly stated that healthcare providers were blinded.

Probably YES >>> Trial explicitly stated that investigators were blinded, or there is no explicit statement about blinding of healthcare providers, but trial described as placebo-controlled trial or active control drug trial (A vs. B) and mention of "double dummy" or that medications were identical or matched, or trial is described as double-blind or triple-blind.

Probably NO >>> There is no explicit statement about blinding of healthcare providers, but trial described as active control drug trial (A vs. B) and no mention of "double dummy" or that medications were identical or matched, trial is described as single-blind.

Definitely NO >>> Trial explicitly stated that healthcare providers were not blinded, trial is described as open-label or unblinded.

3.c. Were data collectors blinded?

Definitely YES >>> Trial explicitly stated that data collectors were blinded.

Probably YES >>> Trial explicitly stated that investigators were blinded, there is no explicit statement about blinding of data collectors, but trial described as placebo-controlled trial or active control drug trial (A vs. B) and mention of "double dummy" or that medications were identical or matched, or trial is described as double-blind or triple-blind.

Probably NO >>> There is no explicit statement about blinding of data collectors, but trial described as active control drug trial (A vs. B) and no mention of "double dummy" or that medications were identical or matched, trial is described as single-blind.

Definitely NO >>> Trial explicitly stated that data collectors were not blinded, or trial is described as open-label or unblinded.

3.d. Were outcome assessors blinded?

Definitely YES >>> Trial explicitly stated that outcome assessors or adjudicators were blinded, or outcome assessors were not blinded but outcomes are objective (outcome measurement are not likely influenced by lack of blinding) [treatment failure if measured via objective criteria, mortality, need for mechanical ventilation, length of hospital stay].

Probably YES >>> There is no explicit statement about blinding of outcome assessors or adjudicators, but trial described as placebo-controlled trial or active control drug trial (A vs. B) and mention of "double dummy" or that medications were identical or matched, or trial is described as double-blind or triple-blind.

Probably NO >>> There is no explicit statement about blinding of outcome assessors or adjudicators, but trial described as active control drug trial (A vs. B) and no mention of "double dummy" or that medications were identical or matched, or trial described as single-blind.

Definitely NO >>> Trial explicitly stated that outcome assessors were not blinded, or trial is described as open-label or unblinded.

3.e. Were data analysts blinded?

Definitely YES >>> Trial explicitly stated that data analysts were blinded.

Probably NO >>> There is no explicit statement about blinding status of data analysts, or trial is described as single-blind or double-blind or triple-blind.

Definitely NO >>> Trial explicitly stated that data analysts were not blinded, or trial is described as open-label or unblinded.

4. Was loss to follow-up (missing outcome data) infrequent?

Definitely YES >>> no missing outcome data (outcome measured in all randomized participants) or loss to follow-up < 5% (including outcome data that has been imputed)

Probably YES >>> loss to follow-up 5 – 10 % (including outcome data that has been imputed) and there is no compelling reason to think that missing outcome data is related to the true outcome and there is no substantial imbalance in numbers of or reasons for missing data across intervention groups and authors provide explicit information regarding reasons for missing outcome data across groups.

Probably NO >>> loss to follow-up 5-10 % (including outcome data that has been imputed) and there is compelling reason to think that missing outcome data is related to the true outcome or there are substantial imbalances in numbers of or reasons for missing data across intervention groups or authors fail to provide explicit information regarding reasons for missing outcome data across groups.

Definitely NO >>> loss to follow-up ≥ 10 % (including outcome data that has been imputed) or authors do not specify and there are reasons to think the loss to follow-up was substantial.

5. Is the continuous outcome free of competing effect due to death?

Definitely YES >>> Results are very unlikely to have been affected by competing risk due to death. For example, the intervention arm increased the risk of death, but the duration of hospitalization is shorter in the control arm.

Probably YES >>> Results are unlikely to have been affected by competing risk due to death. For example, the intervention arm increased the risk of death, but the duration of

hospitalization is slightly shorter in the control arm or there is no appreciable difference between arms.

Probably NO >>> Results are likely to have been affected by competing risk due to death. For example, the intervention arm increased the risk of death, and the duration of hospitalization is appreciably lower in the intervention arm.

Definitely NO >>> Results are very likely to have been affected by competing risk due to death. For example, the intervention arm increased the risk of death, and the duration of hospitalization is much lower in the intervention arm.

Table S11. Direct, indirect, and network estimates and certainty of evidence for treatment failure (closest to 30 days after the end of antibiotic therapy); primary analysis

Comparison	Direct estimate	Indirect estimate	Network estimate						
	RR (95% CI)	RR (95%CI)	RR (95%CI)	RD (95%CI) [1]	Starting evidence	Starting certainty	Incoherence	Imprecision	Certainty of evidence
Penicillin + Aminoglycoside vs Cephalosporin	2.79 (1.4, 5.56)	NA	2.78 (1.38, 5.6)	258 (55, 667)	Direct	Moderate †	Not serious	Serious	Low
Piperacillin-tazobactam vs Cephalosporin	0.57 (0.28, 1.18)	0.7 (0.39, 1.25)	0.65 (0.42, 1.01)	-51 (-84, 1)	Direct	Moderate †	Not serious	Serious	Low
Imipenem + Netilmicin vs Cephalosporin	NA	0.71 (0.29, 1.75)	0.71 (0.29, 1.75)	-42 (-103, 109)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Carbapenem vs Cephalosporin	0.97 (0.54, 1.75)	0.65 (0.4, 1.06)	0.77 (0.53, 1.11)	-33 (-68, 16)	Indirect	Moderate †, ‡	Not serious	Serious	Low
Cephalosporin + Aminoglycoside vs Cephalosporin	0.85 (0.49, 1.46)	1.43 (0.57, 3.57)	0.97 (0.62, 1.53)	-4 (-55, 77)	Direct	Low ††	Not serious	Very serious	Very low
Ceftazidime + Pefloxacin vs Cephalosporin	NA	1.89 (0.76, 4.66)	1.89 (0.76, 4.66)	129 (-35, 531)	Indirect	Low ††, ‡	Not serious	Very serious	Very low
Ceftriaxone + Clindamycin vs Cephalosporin	NA	0.18 (0.02, 1.55)	0.18 (0.02, 1.55)	-119 (-142, 80)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Ceftazidime + Linezolid vs Cephalosporin	1.02 (0.84, 1.24)	NA	1.02 (0.6, 1.74)	3 (-58, 107)	Direct	Moderate †	Not serious	Very serious	Very low
Fluoroquinolone vs Cephalosporin	0.85 (0.44, 1.63)	0.85 (0.48, 1.51)	0.85 (0.56, 1.28)	-22 (-64, 41)	Direct	Moderate †	Not serious	Very serious	Very low
Aztreonam + Clindamycin vs Cephalosporin	NA	0.53 (0.12, 2.33)	0.53 (0.12, 2.33)	-68 (-128, 193)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Cephalosporin +Aztreonam vs Cephalosporin	0.7 (0.13, 3.74)	0.59 (0.11, 3.18)	0.64 (0.2, 2.1)	-52 (-116, 160)	Direct	Moderate †	Not serious	Very serious	Very low
Tigecycline vs Cephalosporin	NA	0.81 (0.42, 1.55)	0.81 (0.42, 1.55)	-28 (-84, 80)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Penicillin + Aminoglycoside vs Piperacillin-tazobactam	NA	4.28 (1.88, 9.74)	4.28 (1.88, 9.74)	476 (128, 1000)	Indirect	Moderate†, ‡	Not serious	Serious	Low
Penicillin + Aminoglycoside vs Imipenem + Netilmicin	NA	3.92 (1.25, 12.22)	3.92 (1.25, 12.22)	423 (36, 1000)	Indirect	Moderate †, ‡	Not serious	Serious	Low
Penicillin + Aminoglycoside vs carbapenem	NA	3.63 (1.65, 7.98)	3.63 (1.65, 7.98)	381 (94, 1000)	Indirect	Moderate †, ‡	Not serious	Serious	Low
Penicillin + Aminoglycoside vs Cephalosporin + Aminoglycoside	NA	2.86 (1.24, 6.59)	2.86 (1.24, 6.59)	270 (35, 811)	Indirect	Low ††, ‡	Not serious	Serious	Very low
Penicillin + aminoglycoside vs Ceftazidime + Pefloxacin	NA	1.47 (0.47, 4.62)	1.47 (0.47, 4.62)	68 (-77, 525)	Indirect	Moderate†, ‡	Not serious	Very serious	Very low

Penicillin + Aminoglycoside vs Ceftriaxone + Clindamycin	NA	15.46 (1.61, 148.94)	15.46 (1.61, 148.94)	999 (88, 1000)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Penicillin + Aminoglycoside vs Ceftazidime + Linezolid	NA	2.72 (1.13, 6.57)	2.72 (1.13, 6.57)	249 (19, 808)	Indirect	Moderate †, ‡	Not serious	Serious	Low
Penicillin + Aminoglycoside vs fluoroquinolone	NA	3.28 (1.45, 7.4)	3.28 (1.45, 7.4)	331 (65, 928)	Indirect	Moderate †, ‡	Not serious	Serious	Low
Penicillin + Aminoglycoside vs Aztreonam + Clindamycin	NA	5.23 (1.02, 26.77)	5.23 (1.02, 26.77)	613 (3, 1000)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Penicillin + Aminoglycoside vs Cephalosporin +Aztreonam	NA	4.31 (1.09, 17.04)	4.31 (1.09, 17.04)	480 (13, 1000)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Penicillin + Aminoglycoside vs tigecycline	NA	3.42 (1.33, 8.84)	3.42 (1.33, 8.84)	351 (48, 1000)	Indirect	Moderate †, ‡	Not serious	Serious	Low
Piperacillin-tazobactam vs Imipenem + Netilmicin	NA	0.92 (0.38, 2.22)	0.92 (0.38, 2.22)	-12 (-90, 177)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Piperacillin-tazobactam vs Carbapenem	0.88 (0.6, 1.28)	0.72 (0.31, 1.67)	0.85 (0.61, 1.19)	-22 (-57, 28)	Direct	Moderate †	Not serious	Serious	Low
Piperacillin-tazobactam vs Cephalosporin + Aminoglycoside	NA	0.67 (0.37, 1.2)	0.67 (0.37, 1.2)	-48 (-91, 29)	Indirect	Low ††, ‡	Not serious	Serious	Very low
Piperacillin-tazobactam vs Ceftazidime + Pefloxacin	NA	0.34 (0.13, 0.92)	0.34 (0.13, 0.92)	-96 (-126, -12)	Indirect	Low ††, ‡	Not serious	Serious	Very low
Piperacillin-tazobactam vs Ceftriaxone + Clindamycin	NA	3.62 (0.42, 31.39)	3.62 (0.42, 31.39)	380 (-84, 1000)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Piperacillin-tazobactam vs Ceftazidime + Linezolid	NA	0.64 (0.32, 1.27)	0.64 (0.32, 1.27)	-52 (-99, 39)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Piperacillin-tazobactam vs Fluoroquinolone	NA	0.77 (0.49, 1.2)	0.77 (0.49, 1.2)	-33 (-74, 29)	Indirect	Moderate †, ‡	Not serious	Serious	Low
Piperacillin-tazobactam vs Aztreonam + Clindamycin	1.22 (0.33, 4.58)	NA	1.22 (0.3, 5.01)	32 (-102, 581)	Direct	Moderate †	Not serious	Very serious	Very low
Piperacillin-tazobactam vs Cephalosporin +Aztreonam	NA	1.01 (0.29, 3.52)	1.01 (0.29, 3.52)	1 (-103, 365)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Piperacillin-tazobactam vs Tigecycline	NA	0.8 (0.43, 1.49)	0.8 (0.43, 1.49)	-29 (-83, 71)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Imipenem + Netilmicin vs Carbapenem	0.93 (0.48, 1.78)	NA	0.93 (0.41, 2.1)	-10 (-86, 160)	Direct	Moderate †	Not serious	Very serious	Very low
Imipenem + Netilmicin vs Cephalosporin + Aminoglycoside	NA	0.73 (0.28, 1.94)	0.73 (0.28, 1.94)	-39 (-104, 136)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Imipenem + Netilmicin vs Ceftazidime + Pefloxacin	NA	0.38 (0.11, 1.31)	0.38 (0.11, 1.31)	-90 (-129, 45)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low

Imipenem + Netilmicin vs Ceftriaxone + Clindamycin	NA	3.95 (0.4, 38.99)	3.95 (0.4, 38.99)	428 (-87, 1000)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Imipenem + Netilmicin vs Ceftazidime + Linezolid	NA	0.7 (0.24, 1.98)	0.7 (0.24, 1.98)	-44 (-110, 142)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Imipenem + Netilmicin vs Fluoroquinolone	NA	0.84 (0.35, 2.02)	0.84 (0.35, 2.02)	-23 (-94, 148)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Imipenem + Netilmicin vs Aztreonam + Clindamycin	NA	1.33 (0.25, 7.06)	1.33 (0.25, 7.06)	48 (-109, 879)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Imipenem + Netilmicin vs Cephalosporin +Aztreonam	NA	1.1 (0.25, 4.81)	1.1 (0.25, 4.81)	15 (-109, 552)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Imipenem + Netilmicin vs Tigecycline	NA	0.87 (0.33, 2.31)	0.87 (0.33, 2.31)	-19 (-97, 190)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Carbapenem vs Cephalosporin + Aminoglycoside	0.55 (0.22, 1.36)	0.95 (0.49, 1.83)	0.79 (0.47, 1.34)	-30 (-77, 49)	Direct	Moderate †	Not serious	Very serious	Very low
Carbapenem vs Ceftazidime + Pefloxacin	NA	0.41 (0.16, 1.04)	0.41 (0.16, 1.04)	-86 (-122, 6)	Indirect	Moderate †, ‡	Not serious	Serious	Low
Carbapenem vs Ceftriaxone + Clindamycin	NA	4.27 (0.5, 36.18)	4.27 (0.5, 36.18)	474 (-73, 1000)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Carbapenem vs Ceftazidime + Linezolid	NA	0.75 (0.39, 1.44)	0.75 (0.39, 1.44)	-36 (-88, 64)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Carbapenem vs fluoroquinolone	0.9 (0.61, 1.3)	0.9 (0.41, 2)	0.9 (0.66, 1.25)	-15 (-49, 36)	Direct	Moderate †	Not serious	Serious	Low
Carbapenem vs Aztreonam + Clindamycin	NA	1.44 (0.34, 6.15)	1.44 (0.34, 6.15)	64 (-96, 747)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Carbapenem vs Cephalosporin +Aztreonam	NA	1.19 (0.35, 4.05)	1.19 (0.35, 4.05)	28 (-94, 442)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Carbapenem vs tigecycline	0.92 (0.68, 1.25)	NA	0.94 (0.56, 1.6)	-9 (-64, 87)	Direct	High	Not serious	Very serious	Low
Cephalosporin + Aminoglycoside vs Ceftazidime + Pefloxacin	0.52 (0.28, 0.94)	NA	0.51 (0.24, 1.12)	-71 (-110, 17)	Direct	Moderate †	Not serious	Serious	Low
Cephalosporin + Aminoglycoside vs Ceftriaxone + Clindamycin	NA	5.41 (0.61, 48.26)	5.41 (0.61, 48.26)	639 (-57, 1000)	Indirect	Low ††, ‡	Not serious	Very serious	Very low
Cephalosporin + Aminoglycoside vs Ceftazidime + Linezolid	NA	0.95 (0.47, 1.92)	0.95 (0.47, 1.92)	-7 (-77, 133)	Indirect	Low ††, ‡	Not serious	Very serious	Very low
Cephalosporin + Aminoglycoside vs fluoroquinolone	NA	1.15 (0.65, 2.03)	1.15 (0.65, 2.03)	22 (-51, 149)	Indirect	Low ††, ‡	Not serious	Very serious	Very low
Cephalosporin + Aminoglycoside vs Aztreonam + Clindamycin	NA	1.83 (0.4, 8.42)	1.83 (0.4, 8.42)	120 (-87, 1000)	Indirect	Low ††, ‡	Not serious	Very serious	Very low
Cephalosporin + Aminoglycoside vs Cephalosporin +Aztreonam	1.63 (0.32, 8.15)	1.38 (0.24, 7.84)	1.51 (0.46, 4.9)	74 (-78, 566)	Direct	Moderate †	Not serious	Very serious	Very low
Cephalosporin + Aminoglycoside vs tigecycline	NA	1.2 (0.57, 2.52)	1.2 (0.57, 2.52)	29 (-62, 220)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low

Ceftazidime + Pefloxacin vs Ceftriaxone + Clindamycin	NA	10.5 (1.03, 107.39)	10.5 (1.03, 107.39)	999 (4, 1000)	Indirect	Moderate†, ‡	Not serious	Extremely serious	Very low
Ceftazidime + Pefloxacin vs Ceftazidime + Linezolid	NA	1.85 (0.65, 5.28)	1.85 (0.65, 5.28)	123 (-51, 621)	Indirect	Low ††, ‡	Not serious	Very serious	Very low
Ceftazidime + Pefloxacin vs Fluoroquinolone	NA	2.23 (0.85, 5.86)	2.23 (0.85, 5.86)	178 (-22, 705)	Indirect	Low ††, ‡	Not serious	Serious	Very low
Ceftazidime + Pefloxacin vs Aztreonam + Clindamycin	NA	3.55 (0.64, 19.76)	3.55 (0.64, 19.76)	370 (-52, 1000)	Indirect	Low ††, ‡	Not serious	Very serious	Very low
Ceftazidime + Pefloxacin vs Cephalosporin +Aztreonam	NA	2.93 (0.71, 12.05)	2.93 (0.71, 12.05)	280 (-42, 1000)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Ceftazidime + Pefloxacin vs Tigecycline	NA	2.33 (0.79, 6.85)	2.33 (0.79, 6.85)	193 (-30, 848)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Ceftriaxone + Clindamycin vs Ceftazidime + Linezolid	NA	0.18 (0.02, 1.62)	0.18 (0.02, 1.62)	-119 (-142, 90)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Ceftriaxone + Clindamycin vs Fluoroquinolone	0.21 (0.03, 1.66)	NA	0.21 (0.03, 1.76)	-115 (-141, 110)	Direct	Moderate †	Not serious	Very serious	Very low
Ceftriaxone + Clindamycin vs Aztreonam + Clindamycin	NA	0.34 (0.03, 4.46)	0.34 (0.03, 4.46)	-96 (-141, 502)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Ceftriaxone + Clindamycin vs Cephalosporin +Aztreonam	NA	0.28 (0.02, 3.23)	0.28 (0.02, 3.23)	-104 (-142, 323)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Ceftriaxone + Clindamycin vs Tigecycline	NA	0.22 (0.02, 2)	0.22 (0.02, 2)	-113 (-142, 145)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Ceftazidime + Linezolid vs fluoroquinolone	NA	1.2 (0.61, 2.36)	1.2 (0.61, 2.36)	29 (-57, 197)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Ceftazidime + Linezolid vs Aztreonam + Clindamycin	NA	1.92 (0.4, 9.23)	1.92 (0.4, 9.23)	133 (-87, 1000)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Ceftazidime + Linezolid vs Cephalosporin +Aztreonam	NA	1.58 (0.43, 5.79)	1.58 (0.43, 5.79)	84 (-83, 695)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Ceftazidime + Linezolid vs Tigecycline	NA	1.26 (0.54, 2.91)	1.26 (0.54, 2.91)	38 (-67, 277)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
fluoroquinolone vs Aztreonam + Clindamycin	NA	1.59 (0.36, 7)	1.59 (0.36, 7)	86 (-93, 870)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Fluoroquinolone vs Cephalosporin +Aztreonam	2.79 (1.4, 5.56)	NA	2.78 (1.38, 5.6)	258 (55, 667)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Fluoroquinolone vs Tigecycline	0.57 (0.28, 1.18)	0.7 (0.39, 1.25)	0.65 (0.42, 1.01)	-51 (-84, 1)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Aztreonam + Clindamycin vs Cephalosporin +Aztreonam	NA	0.71 (0.29, 1.75)	0.71 (0.29, 1.75)	-42 (-103, 109)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low
Aztreonam + Clindamycin vs Tigecycline	0.97 (0.54, 1.75)	0.65 (0.4, 1.06)	0.77 (0.53, 1.11)	-33 (-68, 16)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low

Cephalosporin +Aztreonam vs Tigecycline	0.85 (0.49, 1.46)	1.43 (0.57, 3.57)	0.97 (0.62, 1.53)	-4 (-55, 77)	Indirect	Moderate †, ‡	Not serious	Very serious	Very low

RR: relative risk; RD: risk difference; CI: confidence interval, NA: not applicable (no evidence)
[1] Risk difference was calculated through applying the relative risk to the baseline risk that was derived from the median of risk of treatment failure in the cephalosporin arms. In cases that upper limit of confidence interval exceeded 1000, we truncated the value and reported 1000 as the upper limit.
† Due to serious risk of bias.
†† Due to serious risk of bias and inconsistency in effect estimates across trials that informed the direct comparison.
‡ The concern regarding intransitivity was not serious, thus the certainty of indirect evidence is the lowest of the certainty of contributing direct estimates.

Table S12. Direct, indirect, and network estimates and certainty of evidence for all-cause mortality (closest to 30 days after the end of antibiotic therapy); primary analysis

Comparison	Direct estimate	Indirect estimate	Network estimate						
	RR (95% CI)	RR (95%CI)	RR (95%CI)	RD (95%CI) [1]	Starting evidence	Starting certainty	Incoherence	Imprecision	Certainty of evidence
Penicillin + Aminoglycoside (Penicillin G+ Amikacin) vs Cephalosporin	1.5 (0.47, 4.78)	NA	1.5 (0.47, 4.78)	75 (-79.5, 567)	Direct	Moderate †	Not serious	very serious	Very low
Piperacillin-tazobactam vs Cephalosporin	NA	0.95 (0.31, 2.88)	0.95 (0.31, 2.88)	-7.5 (-104, 282)	Indirect	Moderate †, ‡	Not serious	very serious	Very low
Carbapenem (imipenem) vs Cephalosporin	NA	0.65 (0.26, 1.68)	0.65 (0.26, 1.68)	-52.5 (-111, 102)	Indirect	Moderate †, ‡	Not serious	very serious	Very low
Ceftazidime + Linezolid vs Cephalosporin	1.07(0.75, 1.54)	NA	1.07 (0.75, 1.54)	11 (-38, 81)	Direct	High	Not serious	very serious	Low
Fluoroquinolone vs Cephalosporin	0.77 (0.33, 1.82)	NA	0.77 (0.33, 1.82)	-35 (-101, 123)	Direct	Moderate †	Not serious	very serious	Very low
Aztreonam + Clindamycin vs Cephalosporin	NA	0.32 (0.03, 3.54)	0.32 (0.03, 3.54)	-102 (-146, 381)	Indirect	Moderate †, ‡	Not serious	Extremely serious	Very low
Cephalosporin +Aztreonam (Cefazolin +Aztreonam) vs Cephalosporin	1.6 (0.62, 4.1)	NA	1.6 (0.62, 4.1)	90 (-57, 465)	Direct	Moderate †	Not serious	very serious	Very low
Tigecycline vs Cephalosporin	NA	0.64 (0.23, 1.79)	0.64 (0.23, 1.79)	-54 (-116, 119)	Indirect	Moderate †, ‡	Not serious	very serious	Very low
Penicillin + Aminoglycoside (Penicillin G+ Amikacin) vs Piperacillin-tazobactam	NA	1.58 (0.32, 7.89)	1.58 (0.32, 7.89)	87 (-102, 1000)	Indirect	Moderate †, ‡	Not serious	Extremely serious	Very low
Penicillin + Aminoglycoside (Penicillin G+ Amikacin) vs Carbapenem (imipenem)	NA	2.29 (0.51, 10.21)	2.29 (0.51, 10.21)	194 (-74, 1000)	Indirect	Moderate †, ‡	Not serious	Extremely serious	Very low
Penicillin + Aminoglycoside (Penicillin G+ Amikacin) vs Ceftazidime + Linezolid	NA	1.4 (0.42, 4.7)	1.4 (0.42, 4.7)	60 (-87, 555)	Indirect	Moderate †, ‡	Not serious	very serious	Very low
Penicillin + Aminoglycoside (Penicillin G+ Amikacin) vs Fluoroquinolone	NA	1.94 (0.46, 8.18)	1.94 (0.46, 8.18)	141 (-81, 1000)	Indirect	Moderate †, ‡	Not serious	very serious	Very low
Penicillin + Aminoglycoside (Penicillin G+ Amikacin) vs Aztreonam + Clindamycin	NA	4.65 (0.32, 66.46)	4.65 (0.32, 66.46)	548 (-102, 1000)	Indirect	Moderate †, ‡	Not serious	Extremely serious	Very low

Penicillin + Aminoglycoside (Penicillin G+ Amikacin) vs Cephalosporin +Aztreonam (Cefazolin +Aztreonam)	NA	0.94 (0.21, 4.17)	0.94 (0.21, 4.17)	-9 (-119, 476)	Indirect	Moderate †, ‡	Not serious	very serious	Very low
Penicillin + Aminoglycoside (Penicillin G+ Amikacin) vs Tigecycline	NA	2.34 (0.5, 10.99)	2.34 (0.5, 10.99)	201 (-75, 1000)	Indirect	Moderate †, ‡	Not serious	very serious	Very low
Piperacillin-tazobactam vs Carbapenem (imipenem)	1.45 (0.80, 2.60)	NA	1.45 (0.8, 2.6)	67.5 (-30, 240)	Direct	Moderate †	Not serious	very serious	Very low
Piperacillin-tazobactam vs Ceftazidime + Linezolid	NA	0.88 (0.27, 2.83)	0.88 (0.27, 2.83)	-18 (-110, 275)	Indirect	Moderate †, ‡	Not serious	very serious	Very low
Piperacillin-tazobactam vs Fluoroquinolone	NA	1.22 (0.6, 2.48)	1.22 (0.6, 2.48)	33 (-60, 222)	Indirect	Moderate †, ‡	Not serious	very serious	Very low
Piperacillin-tazobactam vs Aztreonam + Clindamycin	2.93 (0.35, 24.47)	NA	2.93 (0.35, 24.47)	290 (-98, 1000)	Direct	Moderate †	Not serious	Extremely serious	Very low
Piperacillin-tazobactam vs Cephalosporin +Aztreonam (Cefazolin +Aztreonam)	NA	0.59 (0.14, 2.54)	0.59 (0.14, 2.54)	-62 (-129, 231)	Indirect	Moderate †, ‡	Not serious	very serious	Very low
Piperacillin-tazobactam vs Tigecycline	NA	1.48 (0.73, 3.01)	1.48 (0.73, 3.01)	72 (-40.5, 302)	Indirect	Moderate †, ‡	Not serious	very serious	Very low
Carbapenem (imipenem) vs Ceftazidime + Linezolid	NA	0.61 (0.22, 1.67)	0.61 (0.22, 1.67)	-59 (-117, 101)	Indirect	Moderate †, ‡	Not serious	very serious	Very low
Carbapenem (imipenem) vs Fluoroquinolone	0.845 (0.57, 1.26)	NA	0.85 (0.57, 1.26)	-23 (-65, 39)	Direct	Moderate †	Not serious	very serious	Very low
Carbapenem (imipenem) vs Aztreonam + Clindamycin	NA	2.03 (0.22, 18.33)	2.03 (0.22, 18.33)	155 (-117, 1000)	Indirect	Moderate †, ‡	Not serious	Extremely serious	Very low
Carbapenem (imipenem) vs Cephalosporin +Aztreonam (Cefazolin +Aztreonam)	NA	0.41 (0.11, 1.55)	0.41 (0.11, 1.55)	-89 (-134, 83)	Indirect	Moderate †, ‡	Not serious	very serious	Very low
Carbapenem (imipenem) vs Tigecycline	1.02 (0.68, 1.53)	NA	1.02 (0.68, 1.52)	3 (-48, 78)	Direct	High	Not serious	very serious	Low
Ceftazidime + Linezolid vs Fluoroquinolone	NA	1.39 (0.55, 3.51)	1.39 (0.55, 3.51)	59 (-68, 377)	Indirect	Moderate †, ‡	Not serious	very serious	Very low
Ceftazidime + Linezolid vs Aztreonam + Clindamycin	NA	3.33 (0.3, 37.45)	3.33 (0.3, 37.45)	350 (-105, 1000)	Indirect	Moderate †, ‡	Not serious	Extremely serious	Very low
Ceftazidime + Linezolid vs Cephalosporin +Aztreonam (Cefazolin +Aztreonam)	NA	0.67 (0.25, 1.84)	0.67 (0.25, 1.84)	-50 (-113, 126)	Indirect	Moderate †, ‡	Not serious	very serious	Very low
Ceftazidime + Linezolid vs Tigecycline	NA	1.67 (0.57, 4.96)	1.67 (0.57, 4.96)	101 (-65, 594)	Indirect	Moderate †, ‡	Not serious	very serious	Very low

fluoroquinolone vs Aztreonam + Clindamycin	NA	2.4 (0.26, 22.45)	2.4 (0.26, 22.45)	210 (-111, 1000)	Indirect	Moderate †, ‡	Not serious	Extremely serious	Very low
Fluoroquinolone vs Cephalosporin +Aztreonam (Cefazolin +Aztreonam)	NA	0.48 (0.14, 1.73)	0.48 (0.14, 1.73)	-78 (-129, 110)	Indirect	Moderate †, ‡	Not serious	very serious	Very low
Fluoroquinolone vs Tigecycline	NA	1.21 (0.69, 2.12)	1.21 (0.69, 2.12)	32 (-47, 168)	Indirect	Moderate †, ‡	Not serious	very serious	Very low
Aztreonam + Clindamycin vs Cephalosporin +Aztreonam (Cefazolin +Aztreonam)	NA	0.2 (0.02, 2.64)	0.2 (0.02, 2.64)	-120 (-147, 246)	Indirect	Moderate †, ‡	Not serious	very serious	Very low
Aztreonam + Clindamycin vs Tigecycline	NA	0.5 (0.05, 4.72)	0.5 (0.05, 4.72)	-75 (-143, 558)	Indirect	Moderate †, ‡	Not serious	very serious	Very low
Cephalosporin +Aztreonam (Cefazolin +Aztreonam) vs Tigecycline	NA	2.5 (0.63, 10.03)	2.5 (0.63, 10.03)	225 (-56, 1000)	Indirect	Moderate †, ‡	Not serious	very serious	Very low

RR: relative risk; RD: risk difference; CI: confidence interval, NA: not applicable (no evidence)
[1] Risk difference was calculated through applying the relative risk to the baseline risk that was derived from the median of risk of all-cause mortality in the cephalosporin arms. In cases that upper limit of confidence interval exceeded 1000, we truncated the value and reported 1000 as the upper limit.
† Due to serious risk of bias.
‡ The concern regarding intransitivity was not serious, thus the certainty of indirect evidence is the lowest of the certainty of contributing direct estimates.

Figure S1. Forest plot of direct comparisons of Piperacillin-tazobactam vs Carbapenem for treatment failure

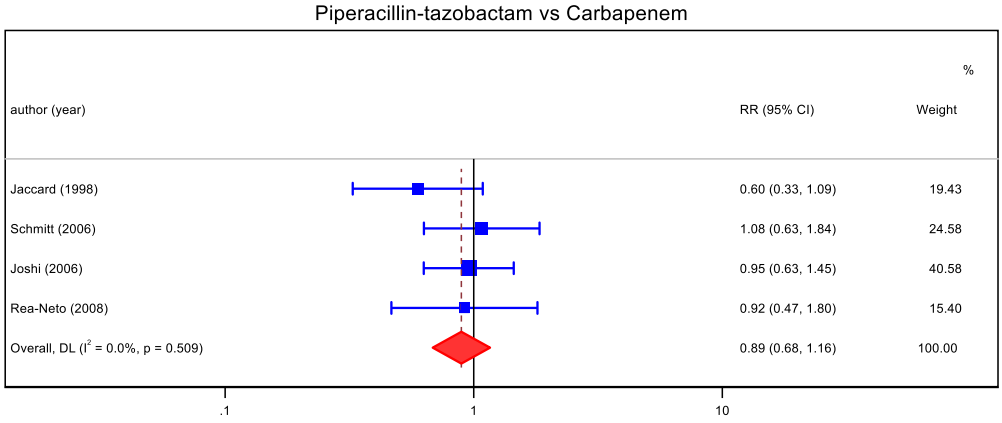


Figure S2. Forest plot of direct comparisons of Carbapenem vs Fluoroquinolone for treatment failure

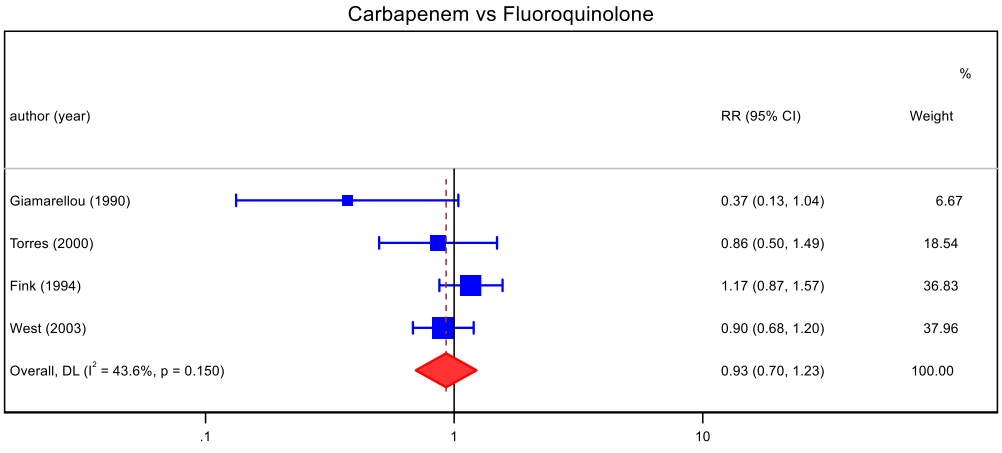


Figure S3. Forest plot of direct comparisons of Cephalosporin vs Fluoroquinolone for treatment failure

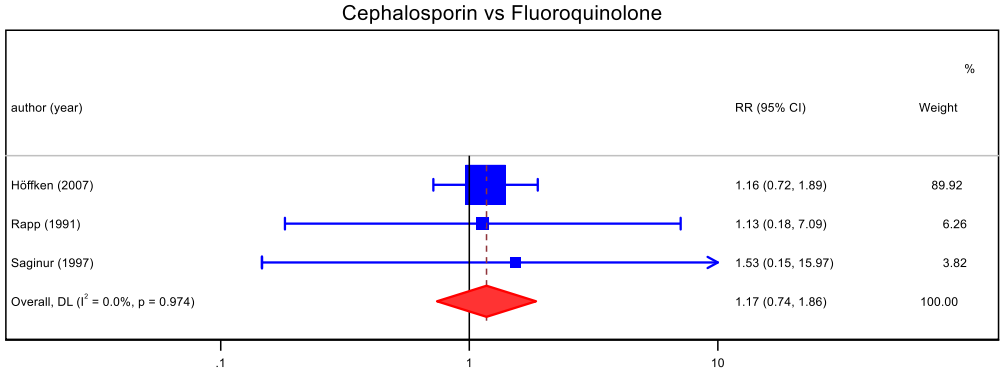


Figure S4. Forest plot of direct comparisons of Penicillin + Aminoglycoside vs Cephalosporin for treatment failure

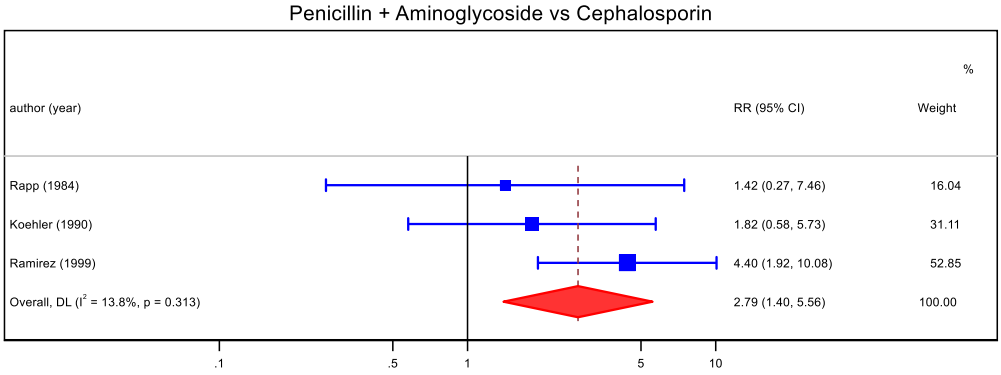


Figure S5. Forest plot of direct comparisons of Carbapenem vs Tigecycline for treatment failure

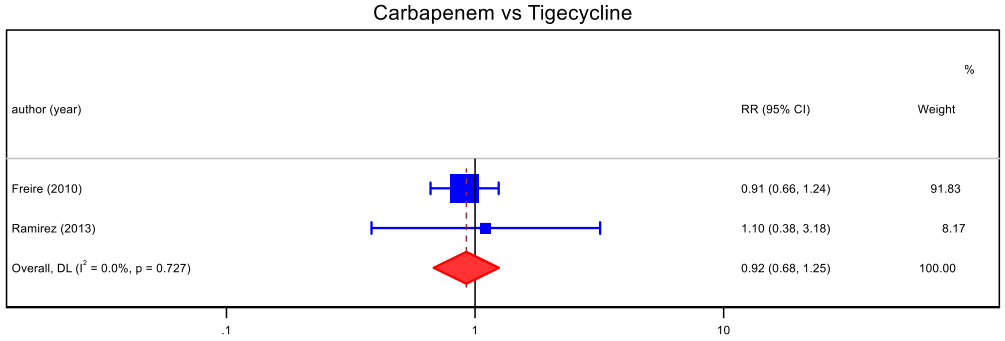


Figure S6. Forest plot of direct comparisons of Carbapenem vs Cephalosporin + Aminoglycoside for treatment failure

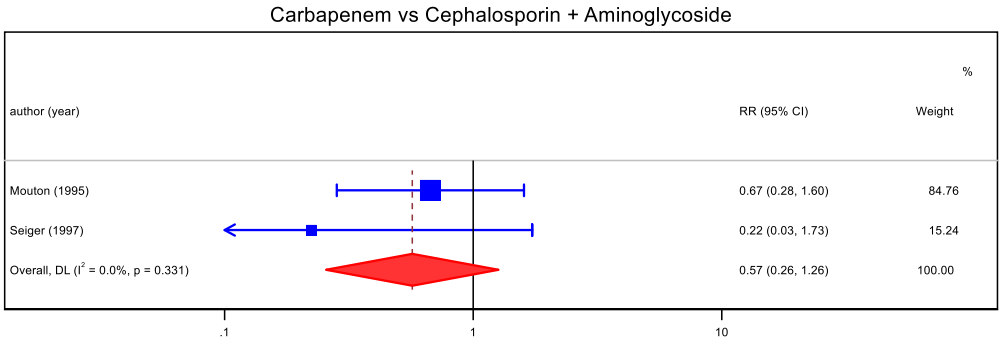


Figure S7. Forest plot of direct comparisons of Cephalosporin + Aminoglycoside vs Cephalosporin for treatment failure

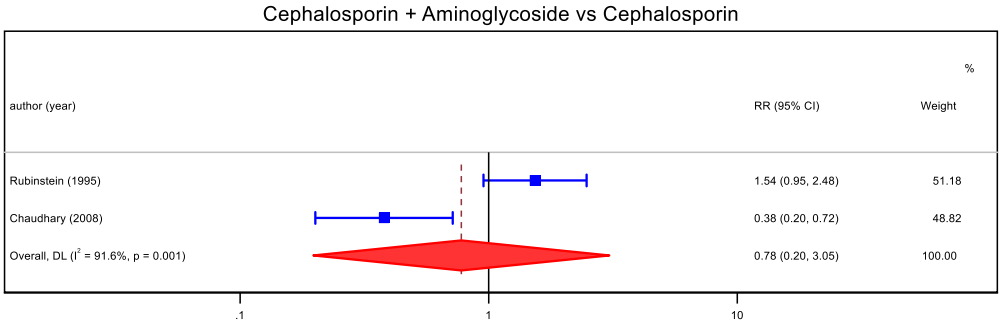


Figure S8. Forest plot of direct comparisons of Carbapenem vs Cephalosporin for treatment failure

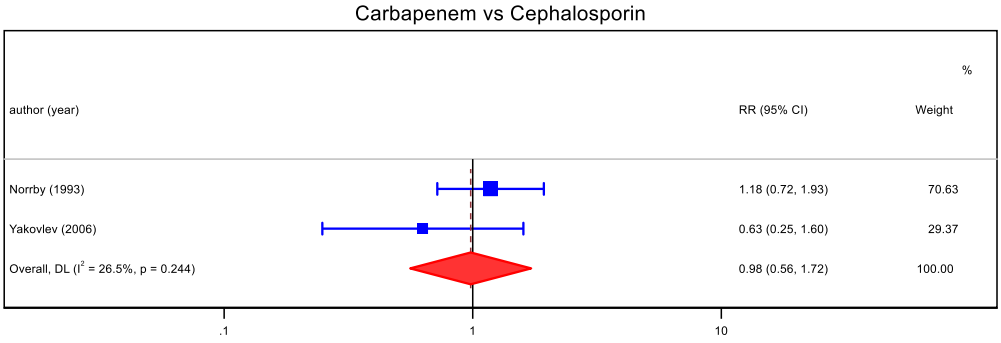


Figure S9. Forest plot of direct comparison of Piperacillin-tazobactam vs Cephalosporin for treatment failure

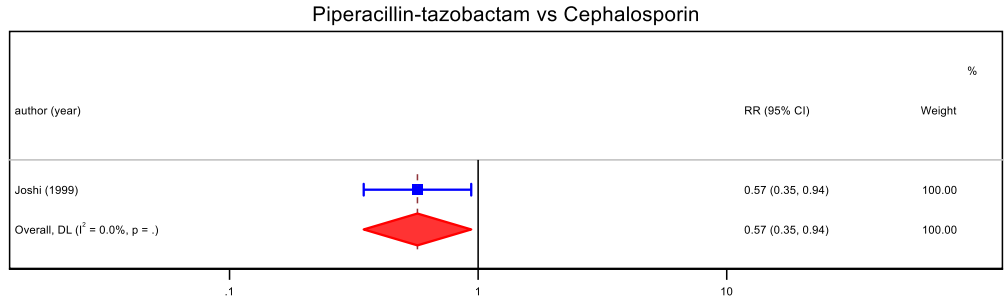


Figure S10. Forest plot of direct comparison of Cephalosporin vs Ceftazidime + Linezolid for treatment failure

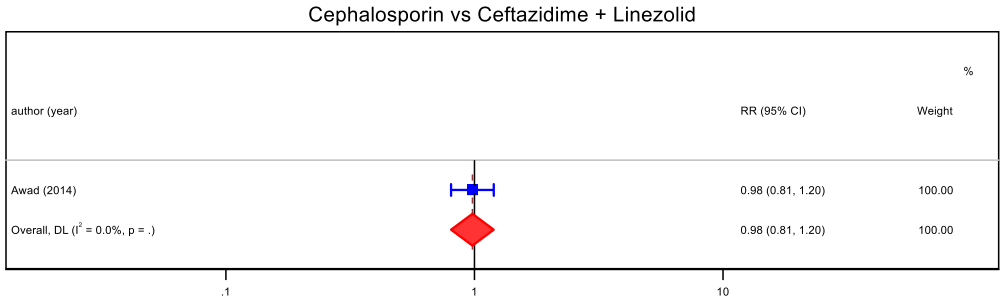


Figure S11. Forest plot of direct comparison of Cephalosporin + Aminoglycoside vs Ceftazidime + Pefloxacin for treatment failure

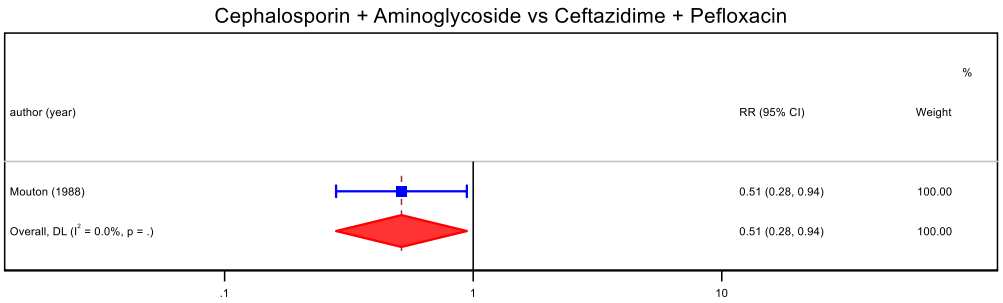


Figure S12. Forest plot of direct comparison of Carbapenem vs Imipenem + Netilmicin for treatment failure

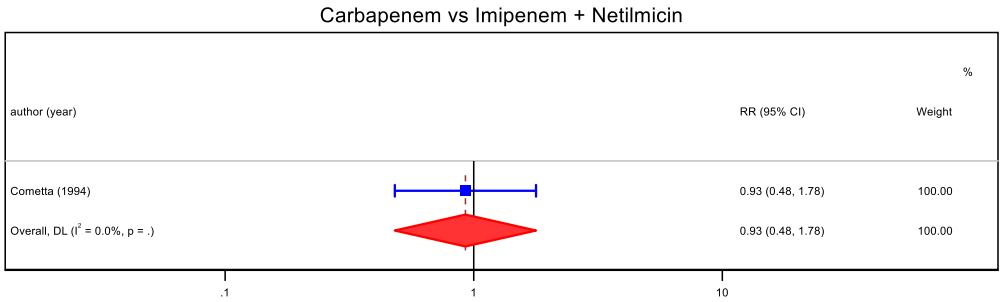


Figure S13. Forest plot of direct comparison of Cephalosporin + Aminoglycoside vs Cephalosporin + Aztreonam for treatment failure

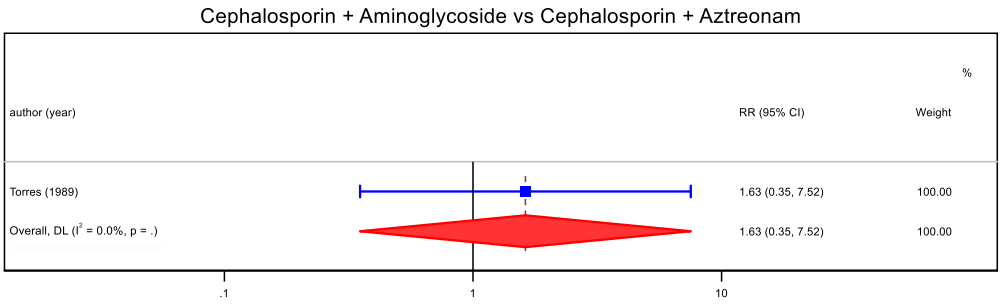


Figure S14. Forest plot of direct comparison of Piperacillin-tazobactam vs Aztreonam + Clindamycin for treatment failure

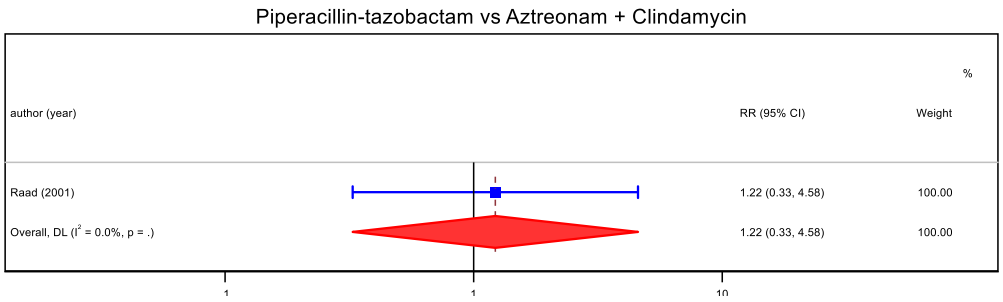


Figure S15. Forest plot of direct comparison of Cephalosporin vs Cephalosporin + Aztreonam for treatment failure

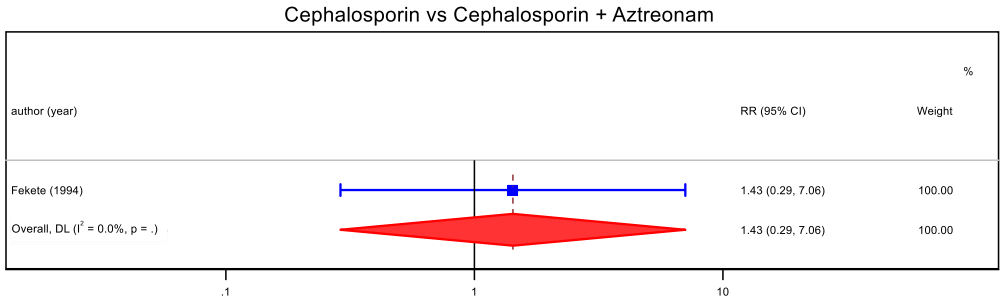


Figure S16. Forest plot of direct comparison of Ceftriaxone + Clindamycin vs Fluoroquinolone for treatment failure

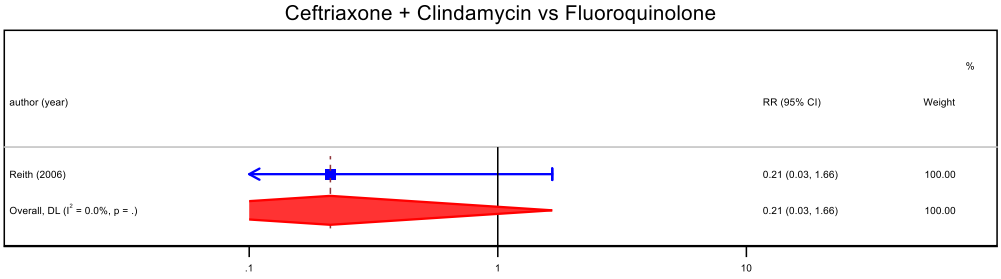


Figure S17. Forest plot of direct comparisons of Carbapenem (imipenem) vs Fluoroquinolone for all-cause mortality

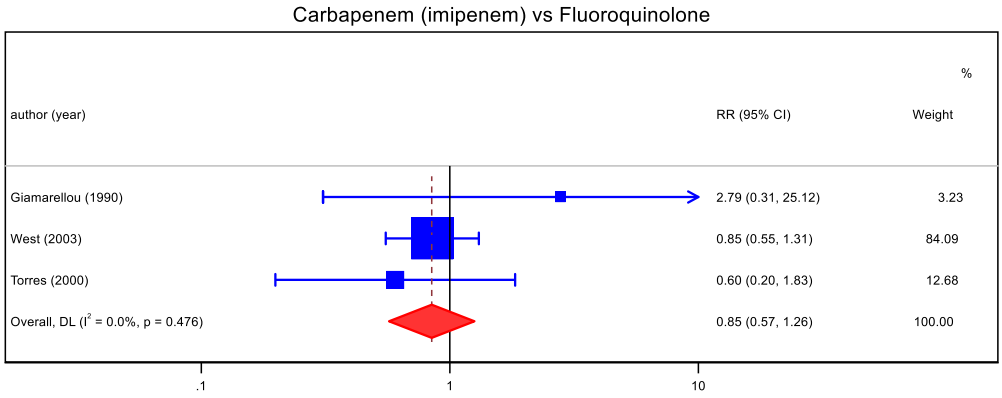


Figure S18. Forest plot of direct comparisons of Piperacillin-tazobactam vs Carbapenem (imipenem) for all-cause mortality

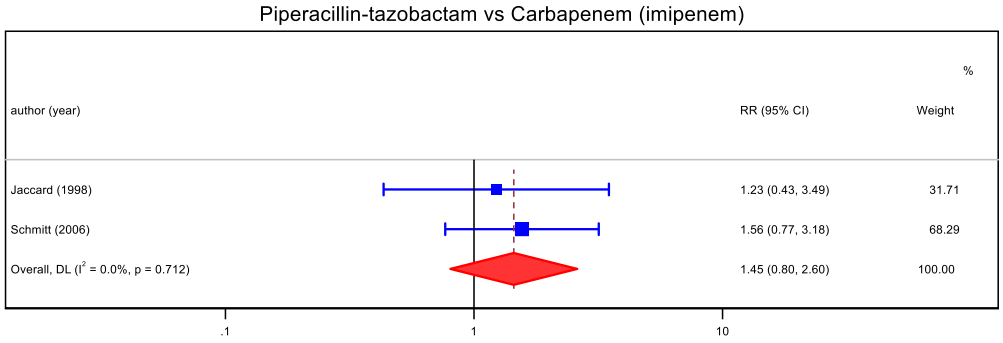


Figure S19. Forest plot of direct comparison of Carbapenem (imipenem) vs Tigecycline for all-cause mortality

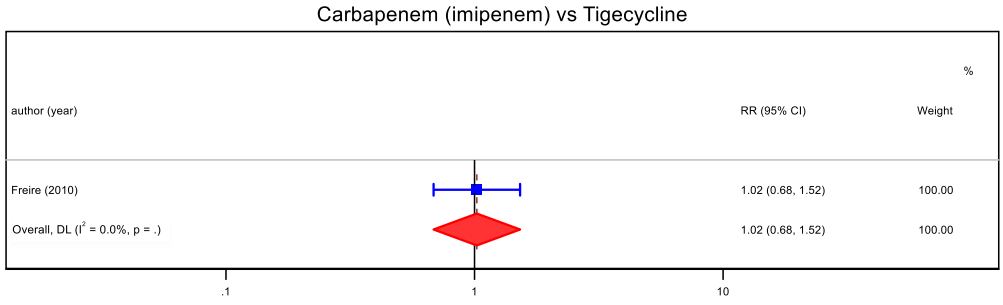


Figure S20. Forest plot of direct comparison of Cephalosporin vs Ceftazidime + Linezolid for all-cause mortality

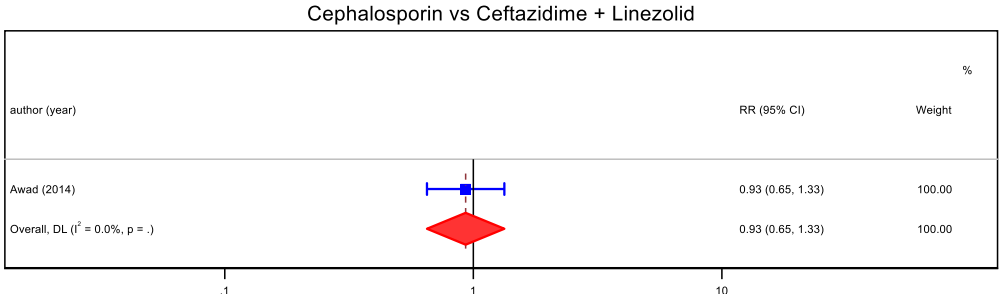


Figure S21. Forest plot of direct comparison of Cephalosporin vs Fluoroquinolone for all-cause mortality

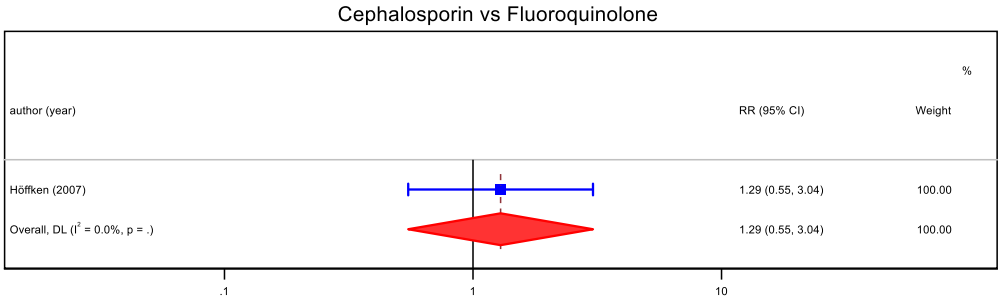


Figure S22. Forest plot of direct comparison of Cephalosporin + Aminoglycoside vs Cephalosporin + Aztreonam for all-cause mortality

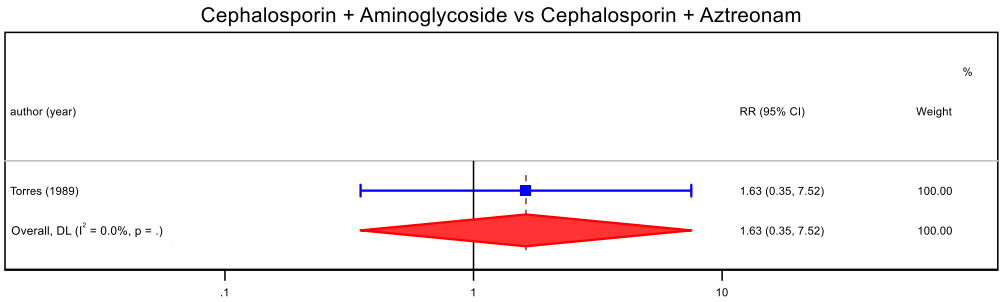


Figure S23. Forest plot of direct comparison of Piperacillin-tazobactam vs Aztreonam + Clindamycin for all-cause mortality

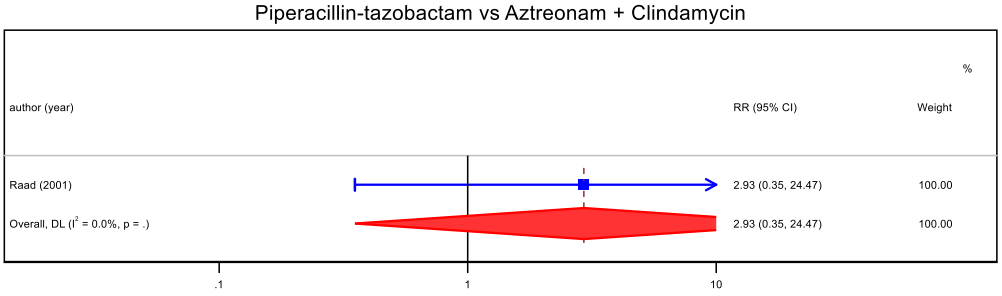


Figure S24. Forest plot of direct comparison of Penicillin + Aminoglycoside vs Cephalosporin for all-cause mortality

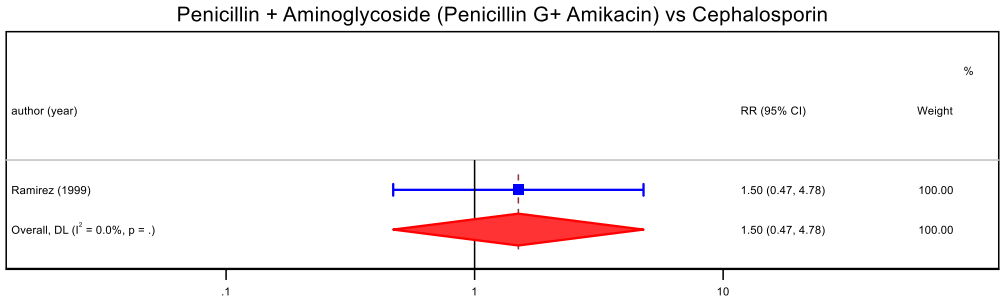
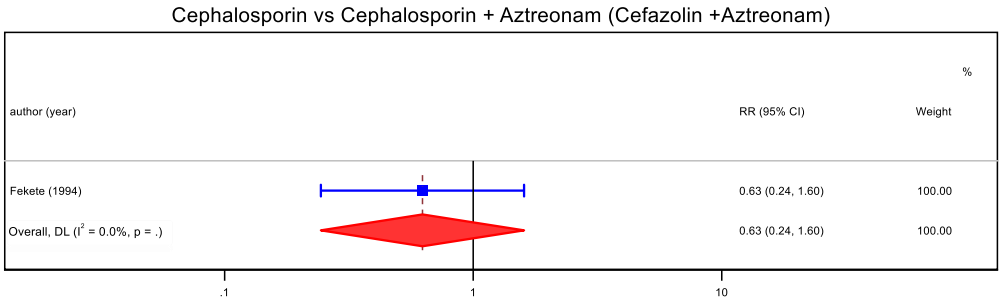


Figure S25. Forest plot of direct comparison of Cephalosporin vs Cephalosporin + Aztreonam for all-cause mortality



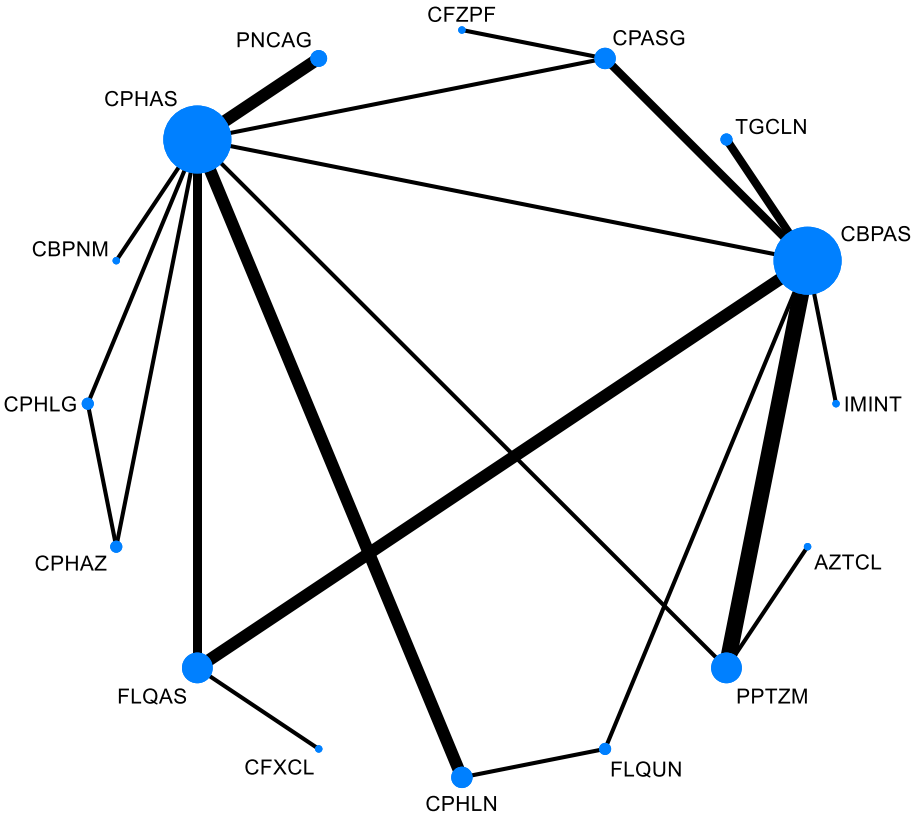


Figure S26. Network plot for treatment failure separating antibiotics within the same class based on activity against *P. aeruginosa* (secondary analysis)

CPHAS: Antipseudomonal cephalosporins; CPASG: Antipseudomonal cephalosporins + Aminoglycoside; CFZPF: Ceftazidime + Pefloxacin; CPHLN: Other cephalosporins; CPHLG: Other cephalosporins + Aminoglycoside; CPHAZ: Other cephalosporins + Aztreonam; CFXCL: Ceftriaxone + Clindamycin; PPTZM: Piperacillin-tazobactam; CBPAS: Antipseudomonal carbapenems; IMINT: Imipenem + Netilmicin; CBPNM: Other carbapenems; FLQAS: Antipseudomonal fluoroquinolones; FLQUN: other fluoroquinolones; AZTCL: Aztreonam + Clindamycin; TGCLN: Tigecycline; PNCAG: Penicillin+ Aminoglycoside .

Table S13. Secondary analysis of treatment failure separating antibiotics within the same class based on activity against *P. aeruginosa* (N = 32 RCTs). Values (network estimates) are relative risk (RR) and 95% CIs for column compared with row

Antipseudomonal cephalosporins	0.76 (0.43,1.34)	0.61 (0.41,0.93) [a]	2.84 (1.48,5.48) [a]	0.66 (0.29,1.49)	1.27 (0.60,2.67)	0.71 (0.45,1.13) [a]	1.32 (0.67,2.59)	1.51 (0.87,2.61) [a]	0.81 (0.25,2.59)	0.62 (0.35,1.10)	1.21 (0.50,2.93)	0.15 (0.02,1.27)	0.63 (0.24,1.68)	0.71 (0.48,1.05) [a]	0.50 (0.12,2.07)
	Tigecycline	0.81 (0.49,1.33)	3.75 (1.59,8.85)[a]	0.86 (0.38,1.97)	1.67 (0.70,3.97)	0.94 (0.58,1.53)	1.73 (0.76,3.96)	1.99 (0.90,4.37) [a]	1.07 (0.29,3.89)	0.82 (0.39,1.72)	1.60 (0.58,4.35)	0.20 (0.02,1.69)	0.83 (0.27,2.58)	0.93 (0.62,1.40) [a]	0.66 (0.16,2.80)
		Piperacillin-tazobactam	4.63 (2.15,9.98) [a]	1.07 (0.49,2.32)	2.07 (0.94,4.55)	1.17 (0.79,1.71)	2.15 (1.02,4.51) [a]	2.46 (1.24,4.87) [a]	1.32 (0.39,4.53)	1.02 (0.53,1.93)	1.97 (0.78,5.02)	0.25 (0.03,2.04)	1.03 (0.36,2.97)	1.15 (0.87,1.54)	0.82 (0.21,3.17)
			Penicillin+ Aminoglycoside	0.23 (0.08,0.65)	0.45 (0.17,1.20)	0.25 (0.11,0.56) [a]	0.46 (0.18,1.18) [a]	0.53 (0.23,1.25)	0.29 (0.08,1.08) [a]	0.22 (0.09,0.52) [a]	0.43 (0.14,1.28)	0.05 (0.01,0.49)	0.22 (0.07,0.72)	0.25 (0.12,0.53) [a]	0.18 (0.04,0.84)
				Imipenem + Netilmicin	1.94 (0.68,5.52)	1.09 (0.51,2.35)	2.01 (0.73,5.55)	2.30 (0.86,6.16) [a]	1.24 (0.30,5.12)	0.95 (0.37,2.44)	1.85 (0.58,5.90)	0.23 (0.03,2.12)	0.96 (0.27,3.45)	1.08 (0.53,2.22)	0.77 (0.16,3.65)
					other fluoroquinolones	0.56 (0.25,1.25)	1.04 (0.61,1.76)	1.19 (0.47,2.99)	0.64 (0.16,2.54)	0.49 (0.20,1.21)	0.95 (0.31,2.95)	0.12 (0.01,1.10) [a]	0.50 (0.15,1.70)	0.56 (0.26,1.19)	0.40 (0.08,1.90)
						Antipseudomonal fluoroquinolones	1.84 (0.86,3.93) [a]	2.11 (1.04,4.30) [a]	1.13 (0.33,3.95)	0.87 (0.45,1.67)	1.69 (0.66,4.34)	0.21 (0.03,1.69)	0.88 (0.30,2.59)	0.99 (0.76,1.29)	0.70 (0.17,2.87)
							Other cephalosporins	1.15 (0.48,2.74)	0.62 (0.16,2.36)	0.47 (0.20,1.13) [a]	0.92 (0.31,2.76)	0.12 (0.01,1.05) [a]	0.48 (0.15,1.57)	0.54 (0.26,1.10) [a]	0.38 (0.08,1.79)
								Other cephalosporins + Aminoglycoside	0.54 (0.17,1.71)	0.41 (0.19,0.91) [a]	0.80 (0.28,2.27)	0.10 (0.01,0.90)	0.42 (0.14,1.28)	0.47 (0.24,0.92) [a]	0.33 (0.07,1.52)
									Other cephalosporins + Aztreonam	0.77 (0.21,2.80)	1.49 (0.35,6.43)	0.19 (0.02,2.11)	0.78 (0.17,3.55)	0.87 (0.26,2.97)	0.62 (0.10,3.86)
										Antipseudomonal cephalosporins + Aminoglycoside	1.94 (0.99,3.82)	0.24 (0.03,2.15)	1.01 (0.33,3.13)	1.14 (0.62,2.09)	0.81 (0.18,3.61)
											Ceftazidime + Pefloxacin	0.13 (0.01,1.22)	0.52 (0.14,1.94)	0.58 (0.24,1.45)	0.41 (0.08,2.15)
												Ceftriaxone + Clindamycin	4.16 (0.40,43.18)	4.67 (0.58,37.89)	3.31 (0.27,40.75)
													Other carbapenems	1.12 (0.39,3.22)	0.80 (0.14,4.46)
														Antipseudomonal carbapenems	0.71 (0.18,2.83)
															Aztreonam + Clindamycin

[a] Low certainty evidence; all other comparisons are at very low certainty evidence.

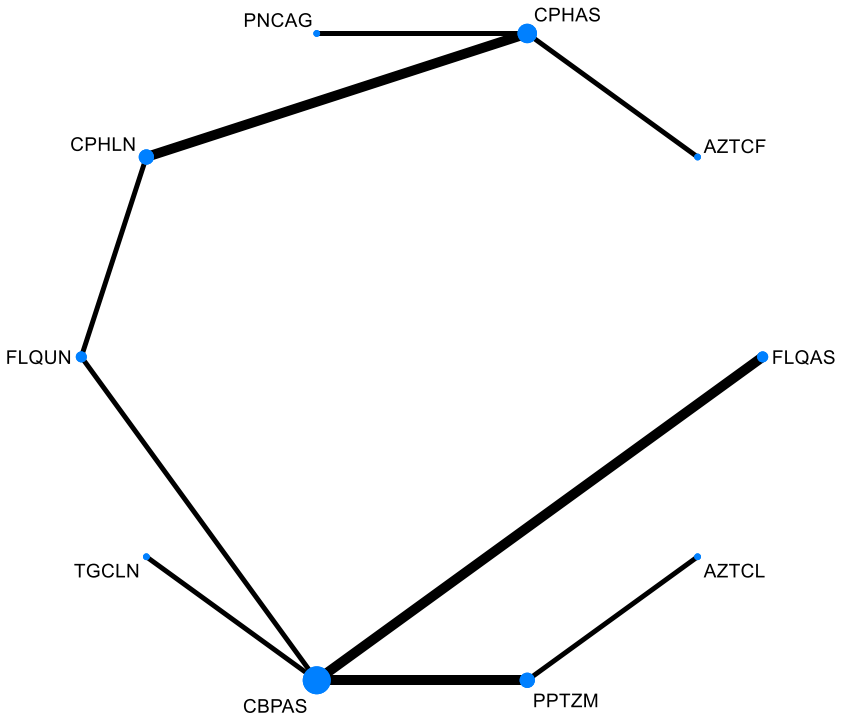


Figure S27. Network plot for all-cause mortality separating antibiotics within the same class based on activity against *P. aeruginosa* (secondary analysis)

CPHAS: Antipseudomonal cephalosporins; CPHLN: Other cephalosporins; PPTZM: Piperacillin-tazobactam; CBPAS: Antipseudomonal carbapenems; FLQAS: Antipseudomonal fluoroquinolones; FLQUN: other fluoroquinolones; AZTCL: Aztreonam + Clindamycin; AZTCF: Aztreonam + Cefazolin; TGCLN: Tigecycline; PNCAG: Penicillin+ Aminoglycoside.

Table S14. Secondary analysis of all-cause mortality separating antibiotics within the same class based on activity against *P. aeruginosa* (N = 12 RCTs). Values (network estimates) are relative risk (RR) and 95% CIs for column compared with row

Antipseudomonal carbapenems	0.98 (0.66,1.46) [a]	1.45 (0.80,2.60)	0.84 (0.05,13.63)	0.36 (0.04,3.24)	1.23 (0.82,1.84)	0.46 (0.04,4.91)	0.56 (0.04,7.06)	0.49 (0.05,4.45)	0.90 (0.06,13.37)
	Tigecycline	1.48 (0.73,3.01)	0.86 (0.05,14.33)	0.37 (0.04,3.43)	1.26 (0.71,2.22)	0.47 (0.04,5.19)	0.57 (0.04,7.44)	0.50 (0.05,4.72)	0.92 (0.06,14.07)
		Piperacillin-tazobactam	0.58 (0.03,10.02)	0.25 (0.03,2.42)	0.85 (0.42,1.73)	0.32 (0.03,3.65)	0.39 (0.03,5.22)	0.34 (0.04,2.84)	0.62 (0.04,9.85)
			Penicillin+ Aminoglycoside	0.43 (0.08,2.35)	1.46 (0.09,24.31)	0.55 (0.13,2.41)	0.67 (0.21,2.13)	0.58 (0.02,20.33)	1.07 (0.24,4.75)
				other fluoroquinolones	3.43 (0.37,32.07)	1.29 (0.55,3.04)	1.57 (0.45,5.47)	1.37 (0.06,30.84)	2.50 (0.52,11.98)
					Antipseudomonal fluoroquinolones	0.38 (0.03,4.13)	0.46 (0.04,5.92)	0.40 (0.04,3.75)	0.73 (0.05,11.19)
						Other cephalosporins	1.21 (0.49,3.02)	1.06 (0.04,26.81)	1.94 (0.52,7.19)
							Antipseudomonal cephalosporins	0.88 (0.03,25.10)	1.60 (0.62,4.10)
								Aztreonam + Clindamycin	1.82 (0.06,59.38)
									Aztreonam + Cefazolin

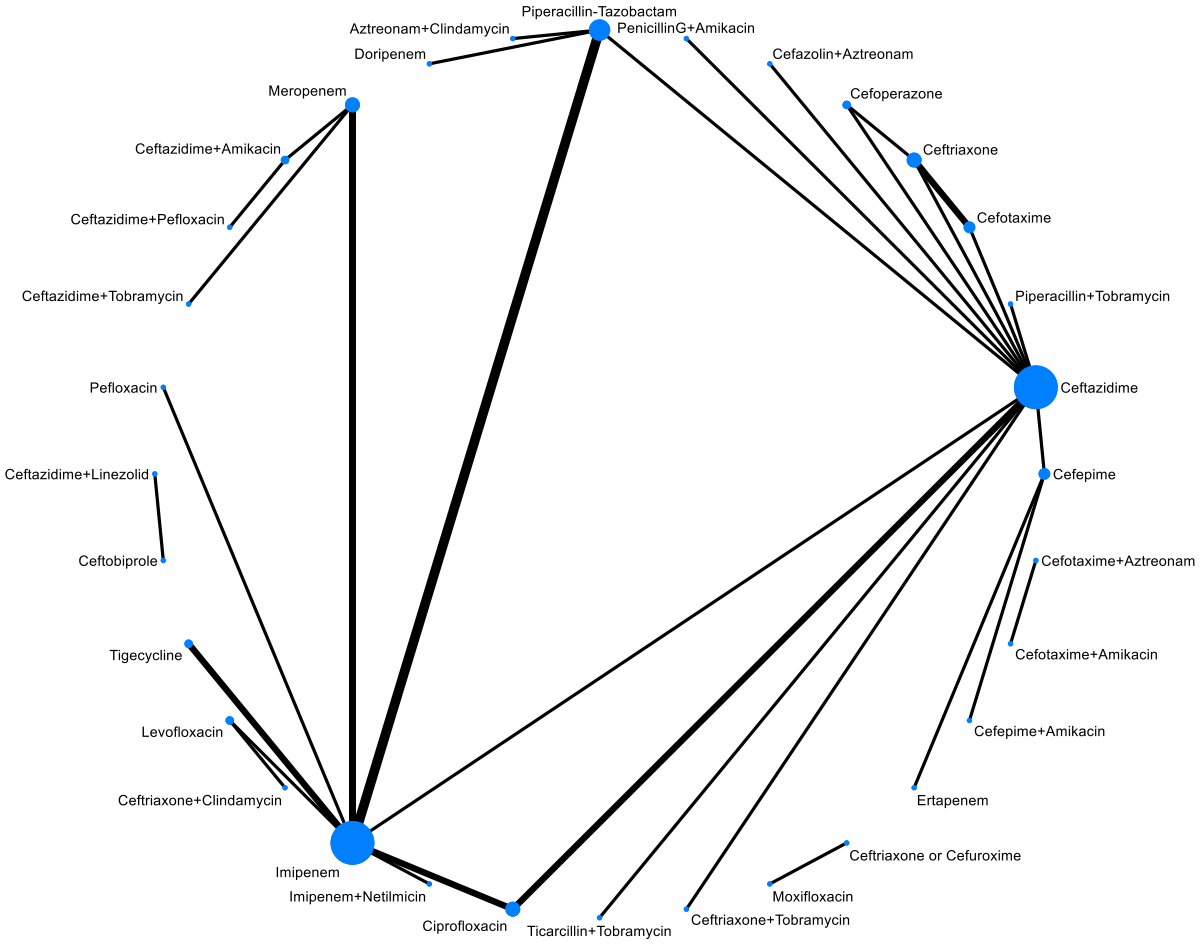


Figure S28. Network plot for treatment failure with individual antibiotics in separate nodes

Table S15. Effects of cephalosporins on treatment failure. Values (network estimates) are relative risk (RR) and 95% CIs for column compared with row

Ceftazidime				
0.78 (0.32,1.93)	**Ceftriaxone**			
0.88 (0.29,2.68)	1.13 (0.57,2.24)	**Cefotaxime**		
1.50 (0.15,15.37)	1.92 (0.16,23.31)	1.70 (0.13,22.44)	**Cefepime**	
0.76 (0.39,1.49)	0.98 (0.44,2.17)	0.87 (0.31,2.44)	0.51 (0.05,5.73)	**Cefoperazone**

Table S16. Effects of carbapenems on treatment failure. Values (network estimates) are relative risk (RR) and 95% CIs for column compared with row

Imipenem			
1.97 (0.72,5.38)	**Meropenem**		
2.16 (0.17,27.43)	1.10 (0.07,16.91)	**Ertapenem**	
1.13 (0.53,2.40)	0.58 (0.16,2.02)	0.52 (0.04,7.29)	**Doripenem**

Table S17. Effects of fluoroquinolones on treatment failure. Values (network estimates) are relative risk (RR) and 95% CIs for column compared with row

Ciprofloxacin		
0.83 (0.54,1.29)	**Levofloxacin**	
0.34 (0.12,1.01)	0.41 (0.14,1.22)	**Pefloxacin**

Table S18. Effects of combinations of a cephalosporin and an aminoglycoside on treatment failure. Values (network estimates) are relative risk (RR) and 95% CIs for column compared with row

Ceftriaxone + Tobramycin			
0.74 (0.07,7.95)	**Ceftazidime + Tobramycin**		
2.24 (0.51,9.82)	3.01 (0.32,28.05)	**Ceftazidime + Amikacin**	
6.08 (0.51,71.76)	8.18 (0.29,232.63)	2.72 (0.17,44.21)	**Cefepime + Amikacin**

Table S19. Effects of combinations of a penicillin and an aminoglycoside on treatment failure. Values (network estimates) are relative risk (RR) and 95% CIs for column compared with row

Penicillin G + Amikacin		
2.42 (0.58,10.15)	**Piperacillin + Tobramycin**	
3.11 (0.48,20.16)	1.28 (0.17,9.79)	**Ticarcillin + Tobramycin**

Table S20. Results from included trials on outcomes for which network meta-analysis or pairwise meta-analysis was not performed

Comparison	N of analysed participants	MD (95% CI) / RR (95% CI)
Length of hospital stay (day)		
Raad, 2001 piperacillin-tazobactam vs aztreonam + clindamycin	52	-1.55 (-4.85, 1.75)
Adverse events leading to discontinuation		
Schmitt, 2006 piperacillin-tazobactam vs imipenem	221	1.82 (1.02, 3.22)
West, 2003 levofloxacin vs imipenem	438	1.32 (0.47, 3.70)
Höffken, 2007 moxifloxacin vs cephalosporin (ceftriaxone or cefuroxime)	159	2.13 (0.40, 11.11)
Koehler, 1990 Piperacillin + tobramycin vs ceftazidime	146	0.34 (0.01, 8.27)
Fekete, 1994 aztreonam + cefazolin vs ceftazidime	68	1.19 (0.02, 50.00)
All/any gastrointestinal adverse events		
Höffken, 2007 moxifloxacin vs cephalosporin (ceftriaxone or cefuroxime)	159	1.69 (0.83, 3.57)
Diarrhoea		
Schmitt, 2006 piperacillin-tazobactam vs imipenem	221	3.70 (1.06, 12.90)
West, 2003 levofloxacin vs imipenem	438	0.79 (0.42, 1.49)
Höffken, 2007 moxifloxacin vs cephalosporin (ceftriaxone or cefuroxime)	159	1.59 (0.47, 5.56)
Raad, 2001 piperacillin-tazobactam vs aztreonam + clindamycin	52	0.25 (0.01,5.80)
Nausea and/or vomiting		
Schmitt, 2006 piperacillin-tazobactam vs imipenem	221	0.25 (0.06, 1.16)
West, 2003 levofloxacin vs imipenem	438	0.63 (0.25, 1.59)
Allergic reactions		
West, 2003 levofloxacin vs imipenem	438	0.77 (0.29, 2.04)
Raad, 2001 piperacillin-tazobactam vs aztreonam + clindamycin	52	0.73 (0.05, 11.10)

RR: relative risk; MD: mean difference; CI: confidence interval

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[3] Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence—inconsistency. J Clin Epidemiol. 2011;64:1294-302. DOI: https://doi.org/10.1016/j.jclinepi.2011.03.017.

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Chapter 5: Empiric antibiotic therapy for moderate-to-severe community-acquired pneumonia: a systematic review and network meta-analysis

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Systematic review

Empiric antibiotic therapy for moderate-to-severe community-acquired pneumonia: a systematic review and network meta-analysis

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ABSTRACT

Background: The optimal empiric antibiotic regimen for moderate-to-severe community-acquired pneumonia (CAP) is uncertain.
Objectives: To compare the effects of antibiotics for empiric therapy of moderate-to-severe CAP using a network meta-analysis.
Data sources: Medline, EMBASE, Cochrane CENTRAL, Web of Science, and CINAHL from inception to 03 July 2024.
Study eligibility criteria: Randomized controlled trials (RCT).
Participants: Adults with moderate-to-severe CAP.

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Keywords:
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Interventions: Any empiric antibiotic regimen vs. another, placebo, or no treatment.
Assessment of risk of bias: Paired reviewers independently assessed risk of bias using a modified Cochrane tool for assessing risk of bias in randomized trials.
Methods of data synthesis: We conducted frequentist random-effect network meta-analyses addressing patient-important outcomes and assessed the certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation approach.
Results: In total, 143 RCTs involving 29,157 participants proved eligible. Effects are in comparison with respiratory fluoroquinolones alone. Penicillins alone (relative risks [RR]: 1.25, 95% CI: 0.93–1.67; risk difference [RD]: 33 more per 1000, 95% CI: 9 fewer to 88 more), second-generation cephalosporins alone (RR: 1.34, 95% CI: 0.89–2.02; RD: 45 more per 1000, 95% CI: 15 fewer to 135 more), and third-generation cephalosporins alone (RR: 1.32, 95% CI: 0.99–1.77; RD: 42 more per 1000, 95% CI: 1 fewer to 102 more) or combined with a macrolide (RR: 1.34, 95% CI: 0.98–1.84; RD: 45 more per 1000, 95% CI: 3 fewer to 111 more) may be inferior in reducing treatment failure (all low certainty). The evidence among other antibiotic regimens for treatment failure and among all regimens for all-cause mortality, duration of hospitalization, and adverse events suggested little to no difference (in most cases with low certainty) or was very low certainty.
Conclusions: For empiric treatment of moderate-to-severe CAP, none of the antibiotic regimens provided convincing evidence of important differences in any of the outcomes.
Trial registration number: PROSPERO (CRD42022297216). **Maryam Ghadimi, Clin Microbiol Infect 2025;■:1**

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Introduction

Community-acquired pneumonia (CAP) is one of the most common reasons for adult hospitalizations [1]. The clinical presentation of CAP ranges from mild to severe disease [2]. Treatment failure increases with severity [3,4] and is associated with a longer hospital stay and increased mortality rate [3].

Clinicians treating CAP typically administer empiric antibiotic therapy effective against the most likely pathogens. The choice, however, remains controversial: substantial variability exists in antibiotic selection both in practice [4,5] and among clinical practice guidelines [6–9]. For example, for adults with moderate severity CAP, the American Thoracic Society/Infectious Diseases Society of America recommendations include monotherapy with a respiratory fluoroquinolone [6], whereas the National Institute for Health and Care Excellence guideline recommends amoxicillin with or without a macrolide [7], and a Dutch professional society recommends monotherapy with penicillin or amoxicillin [8].

Summarizing available evidence from randomized controlled trials (RCTs) using a network meta-analysis (NMA) may help address this uncertainty. Previous NMAs that evaluated antibiotics for empiric management of CAP failed to address the certainty of evidence [10] and used ranking probability to interpret findings [10,11]. To address these limitations, we conducted an NMA comparing the efficacy and safety of antibiotic regimens for empiric therapy of adults with moderate-to-severe CAP.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses with NMA extension [12,13] and registered this review in PROSPERO (CRD42022297216) (Supplementary S1).

Eligibility criteria

We included RCTs comparing any empiric antibiotic or antibiotic combination to an alternative antibiotic regimen, a placebo, or no treatment in patients aged 18 years or older with clinical suspicion of moderate-to-severe CAP. In eligible trials, at least 50% of participants were in Pneumonia Severity Index (PORT) class III, IV, or V, or were explicitly characterized as having moderate and/or severe CAP. If data on the severity of pneumonia were unavailable, we included trials if, at randomization, at least 50% of enrolled patients were hospitalized for management of CAP. We included trials regardless of language, year of publication, and publication status as long as at least 80% of enrolled patients were adults, had CAP, were not immunocompromised, and were treated empirically or reported outcomes of interest separately for eligible participants.

Search strategy and study selection

We searched Medline, EMBASE, Cochrane CENTRAL, Web of Science, and CINAHL from their inception through 03 July 2024 (Supplementary S2). We reviewed the reference lists from relevant systematic reviews and eligible trials. Using Covidence [14], pairs of reviewers independently screened titles and abstracts of retrieved citations, followed by full texts of potentially eligible studies. A third reviewer (M.G.) adjudicated disagreements.

Data extraction

Pairs of reviewers independently extracted data from each eligible trial, including country of origin, sources of funding, patient characteristics, intervention and comparator, and outcomes of interest. For severity of pneumonia, we extracted the proportion of patients identified as having severe CAP or classified in PORT class V. If authors did not provide this information, we abstracted the proportion of patients who were mechanically ventilated or in shock at randomization or, if this information was also unavailable, the proportion of patients admitted to an intensive care unit. Reviewers resolved discrepancies by consensus and, when necessary, through discussion with a third reviewer (M.G.).

We classified treatment failure as defined by each study and all-cause mortality, both closest to 30 days after the end of the antibiotic therapy, as critical outcomes. Important outcomes, all at the longest available follow-up, included need for mechanical

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ventilation, duration of hospitalization, discontinuation of antibiotics due to adverse events, diarrhoea, nausea and/or vomiting, any allergic reactions, and acute kidney injury. We extracted outcome data from the intention-to-treat (ITT) population and, if not reported, in preferred order, modified ITT, per-protocol, and as-treated population.

Risk of bias assessment

For each eligible trial, paired reviewers independently assessed the risk of bias for each outcome using a modified Cochrane tool, resolving disagreements through adjudication with a third reviewer (M.G.) [15]. Supplementary S3 provides details regarding the risk of bias assessment. When all the domains were low or probably at low risk, we rated the overall risk of bias as 'low'; otherwise, we rated the overall risk of bias as 'high'.

Data synthesis and analysis

We pooled dichotomous outcomes using relative risks (RRs) and associated 95% CIs. We calculated risk difference (RD) per 1000 patients using the baseline risk derived from the median risk of an event across the reference intervention arms, which for each network was the intervention most connected to others (i.e. respiratory fluoroquinolones alone). For the duration of hospitalization, we calculated the mean difference and corresponding 95% CI. For trials that did not report standard deviation for duration of hospitalization, we imputed standard deviations according to Ma et al. [16].

For outcomes in which ten or more trials contributed data, we performed frequentist random-effect NMA assuming a common heterogeneity across all comparisons under the multivariate meta-analysis models [17]. To obtain direct estimates, we performed pairwise meta-analyses using the DerSimonian–Laird random-effect model [18]. We used design-by-treatment models and Wald's test to assess incoherence at the entire network level [19] and the node-splitting approach to assess incoherence within each closed loop of evidence and obtain indirect estimates [20]. We grouped individual antibiotics within the same class into a single treatment node, splitting different generations of cephalosporins and separating respiratory fluoroquinolones from fluoroquinolones that lack reliable activity against *Streptococcus pneumoniae* and atypical respiratory pathogens. For critical outcomes, we planned to conduct secondary analyses using individual antibiotics. If more than 20% of participants in a study arm received antibiotics administered based on the discretion of the treating physician, we included those antibiotics in our characterizations of the nodes.

We explored two prespecified effect modifiers: for critical outcomes, we hypothesized that treatment effects would differ across trials with higher vs. lower proportion of patients with severe CAP. For all outcomes, we hypothesized that trials at high vs. low risk of bias would show larger treatment effects. We tested these hypotheses using multivariate random-effects network meta-regression, assuming common heterogeneity [21], and assessed the credibility of any apparent effect modification using the Instrument for assessing the Credibility of Effect Modification Analyses [22]. For the subgroup hypothesis related to severity, as data proved insufficient to conduct a network meta-regression, we conducted *post hoc* subgroup analyses by severe vs. moderate, using the threshold of 80% for the proportion of patients with severe CAP. Additional *post hoc* variables considered for network meta-regression for critical outcomes included study year and geographical region as proxies for the local distribution of pathogens and resistance patterns across studies, follow-up time for reporting the outcomes, and age. We further performed sensitivity analyses for critical outcomes to explore whether treatment effects would differ if trials in which at least 80% of participants had severe CAP were excluded from the analysis. We implemented all analyses in Stata 17.0 (StataCorp, College Station, TX).

Assessment of the certainty of the evidence

We assessed the certainty of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [23,24] with the target of certainty rating as a non-zero effect [25] and rated the certainty for each comparison and outcome as 'high', 'moderate', 'low', or 'very low'. We included risk of bias [26], inconsistency [27,28], indirectness [29], and publication bias [30] for assessment of direct estimates and intransitivity [31] for assessment of indirect estimates. The certainty of network estimates was based on the direct or indirect evidence that most contributed to the network estimate, with further consideration for incoherence between direct and indirect estimates [32] and imprecision of network estimates [33].

Classification of antibiotics

When interpreting the results, we used a modification of a previously suggested GRADE approach [34], focusing on whether the point estimate comparing an antibiotic to the reference showed an important effect using the minimal important difference thresholds. We categorized an antibiotic as 'among the best' if the point estimate in comparison to respiratory fluoroquinolones alone and at least two other antibiotics represented an important benefit. We classified antibiotics as 'among the worst' if the point estimate in comparison to respiratory fluoroquinolones alone and at least two other antibiotics represented an important harmful effect. We classified antibiotics as 'not different from respiratory fluoroquinolones alone' if the point estimate in comparison to respiratory fluoroquinolones alone proved an unimportant beneficial or harmful effect. We then separated antibiotics into two groups based on the certainty of the evidence. We limited the categorization to antibiotics with low or high certainty evidence compared with the reference.

Results

We identified 41,136 citations, of which 143 RCTs involving 29,157 participants proved eligible (Fig. 1). Supplementary S4 presents the characteristics of each study. Trials were published between 1971 and 2024, mostly conducted in Europe and North America, and funded by the pharmaceutical industry. Trials included participants with a median of mean age of 60.2 years. The median proportion of participants with severe CAP was 3.2 %; more than 80% of enrolled patients had severe CAP in 16 (11.2%) trials. Table 1 summarizes the characteristics of the studies. Trials evaluated 32 classes of antibiotic regimens (Supplementary S5).

Supplementary S6 presents risk of bias assessment at the outcome level: 4% to 23% of trials were at overall low risk of bias. Inadequate allocation concealment and unblinded patients or healthcare providers were the most frequent limitations.

NMA and GRADE certainty ratings

Because both arms were classified within the same treatment nodes, several trials could not be included in the primary analyses (Supplementary S4). Table 2 presents a summary of the effects and classification of routinely administered antibiotics. Fig. 2 presents network plots for treatment failure and all-cause mortality, and

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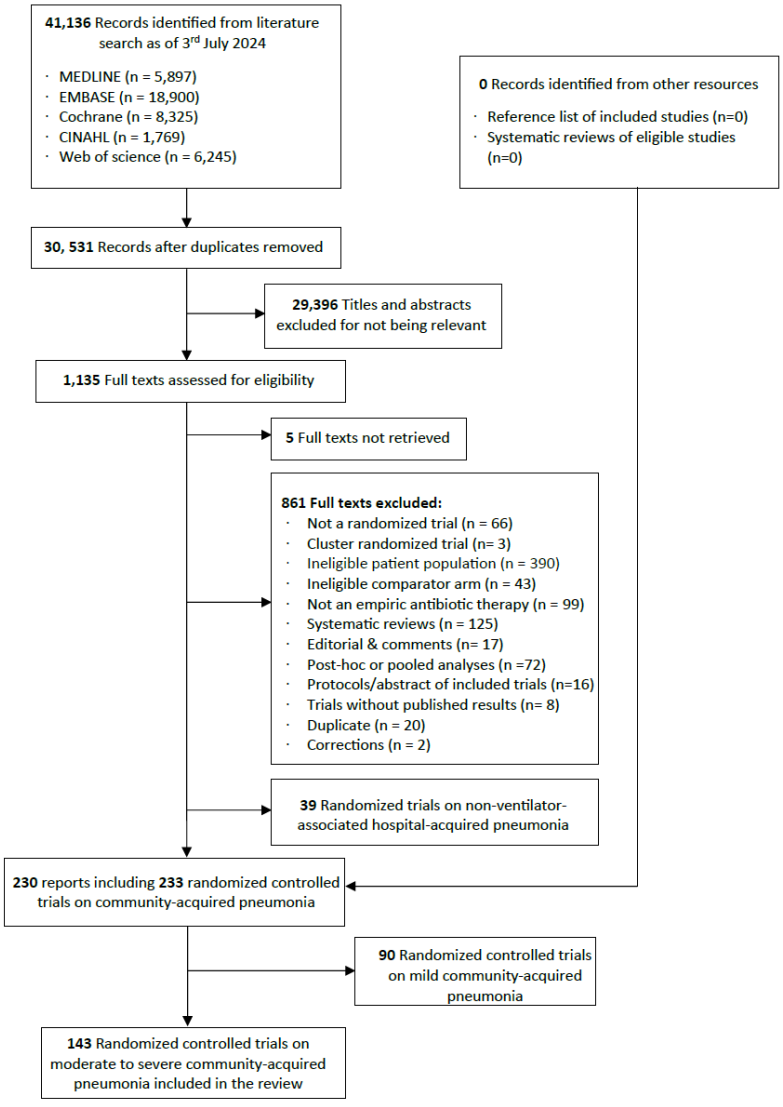

Fig. 1. Study selection flowchart.

Supplementary S7 includes network plots for other outcomes. Supplementary S8 presents forest plots for direct comparisons, and Supplementary S9–S15 report direct, indirect, and network estimates, as well as assessments of the certainty of the evidence.

We rated down certainty due to inconsistency for one comparison for duration of hospitalization and one for nausea and/or vomiting. There was no evidence of publication bias for most comparisons. Because none of the prespecified effect modifiers proved credible, we had no serious concerns regarding intransitivity. We did not identify important evidence of global or comparison-specific incoherence in any of the networks except for one comparison for treatment failure and one for duration of hospitalization.

Treatment failure

The 106 trials involving 22,725 participants and 52 direct comparisons informed effects on treatment failure (Fig. 2(a)). The median follow-up was 14 days (interquartile range [IQR]: 3–21 days) after the end of antibiotic therapy, with the risk of treatment failure ranging from 0.7% to 41.2%. Treatment failure was mostly defined as a lack of improvement or worsening of signs and symptoms of CAP after initiation of treatment that required the need for initiation of an antibiotic regimen other than study antibiotics (Supplementary S16). Effects are in comparison with respiratory fluoroquinolones alone. The following may be inferior in reducing treatment failure (low certainty): penicillins alone

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Table 1
Summary of characteristics of included studies

Characteristics	Measure
Number of eligible studies	143
Number of randomized patients; median (IQR)	107 (60–279)
Year of publication, *n* (%)	
1971–1999	66 (46.1)
2000–2009	46 (32.2)
2010–2020	25 (17.5)
2020–3 July 2024	6 (4.2)
Region of origin, *n* (%)	
Europe	35 (24.5)
North America	34 (23.8)
Western Pacific region	31 (21.7)
Multinational	31 (21.7)
South America	4 (2.8)
Eastern Mediterranean	4 (2.8)
Africa	3 (2.0)
South-East Asia	1 (0.7)
Funding source, *n* (%)	
Pharmaceutical industry	82 (57.3)
Other sources	6 (4.2)
Not reported	55 (38.5)
Mean age (y), median (IQR)	60.2 (54.4–66.1)
Male (%), median (IQR)	62.1 (54.6–68.5)
Severe pneumonia (%), median (IQR)	3.2 (0–28.9)
Admitted to ICU at baseline (%), median (IQR)	0 (0–7.4)
Mechanically ventilated at baseline (%), median (IQR)	0 (0–22.4)
Prevalence of atypical pathogens (%), median (IQR)	11.5 (5.5–19.6)
Previous unsuccessful antibiotic treatment (%), median (IQR)	13.9 (0–27.1)
Duration of antibiotic therapy (d), median (IQR)	10 (7–11)

ICU, intensive care unit; IQR, interquartile range.

(RR: 1.25; 95% CI: 0.93–1.67; RD: 33 more per 1000; 95% CI: 9 fewer to 88 more), second-generation cephalosporins alone (RR: 1.34; 95% CI: 0.89–2.02; RD: 45 more per 1000; 95% CI: 15 fewer to 135 more), and third-generation cephalosporins alone (RR: 1.32 95% CI: 0.99–1.77; RD: 42 more per 1000; 95% CI: 1 fewer to 102 more) or combined with a macrolide (RR: 1.34, 95% CI: 0.98–1.84; RD: 45 more per 1000; 95% CI: 3 fewer to 111 more). The evidence for all other antibiotic regimens suggested little to no difference (moderate-to-low certainty) or was very low certainty (Table 2).

Among fifth-generation cephalosporins, ceftaroline probably reduced the risk of treatment failure compared with ceftobiprole (RR: 0.59; 95% CI: 0.42–0.89; RD: 54 fewer per 1000 patients; 95% CI: 77–22 fewer, moderate certainty). Within other classes, we did not find convincing differences between antibiotics (Supplementary S17).

All-cause mortality

The 71 trials involving 19,121 participants and 39 direct comparisons informed effects on all-cause mortality (Fig. 2(b)). The median follow-up was 14 days (IQR: 4–28 days) after the end of antibiotic therapy, with the risk of all-cause mortality ranging from 0.6% to 19.6% with a median of 3.8%. Antibiotic regimens provided low certainty evidence of little to no difference in reducing all-cause mortality compared with respiratory fluoroquinolones alone, or the evidence was very low certainty (Table 2). Because most effect estimates were very imprecise, we did not conduct a secondary analysis separating antibiotics within the same class.

Need for mechanical ventilation

Only one trial involving 378 participants reported effects on the need for mechanical ventilation. The pairwise comparison provided very low certainty evidence comparing β-lactam/β-lactamase inhibitors alone with third-generation cephalosporins alone (RR: 1.05; 95% CI: 0.45–2.47).

Duration of hospitalization

The 19 trials involving 4,289 participants that informed effects on length of hospital stay included 19 direct comparisons. Antibiotic regimens provided moderate-to-low certainty evidence of little to no difference in reducing duration of hospitalization compared with respiratory fluoroquinolones alone, or the evidence was very low certainty (Table 2).

Discontinuation due to adverse events

The 60 trials involving 17,741 participants that informed effects on discontinuation due to adverse events included 37 direct comparisons. Antibiotic regimens provided moderate-to-low certainty evidence of little to no difference in increasing discontinuation for adverse events compared with respiratory fluoroquinolones alone, or the evidence was very low certainty (Table 2).

Diarrhoea

The 48 trials involving 16,540 participants that informed effects on diarrhoea included 31 direct comparisons. Antibiotic regimens provided high-to-low certainty evidence of little to no difference in increasing diarrhoea compared with respiratory fluoroquinolones alone, or the evidence was very low certainty (Table 2).

Nausea and/or vomiting

The 43 trials involving 15,879 participants that informed effects on nausea and/or vomiting included 27 direct comparisons.

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Table 2
Classification of antibiotics based on the effect estimates for the comparison of an antibiotic regimen vs. respiratory fluoroquinolones alone and certainty of evidence

Antibiotic regimen vs respiratory fluoroquinolones alone	Treatment failure; RD (95%CI)	All-cause mortality; RD (95%CI)	Duration of hospitalization; MD (95%CI)	Discontinuation due to adverse events; RD (95%CI)	Diarrhoea; RD (95%CI)	Nausea and/or vomiting; RD (95%CI)	Any allergic reactions; RD (95%CI)
Baseline risk [a]	132 per 1000 patients	23 per 1000 patients	8.9 days	48 per 1000 patients	43 per 1000 patients	45 per 1000 patients	24 per 1000 patients
Minimal important difference [b]	20 per 1000 patients	5 per 1000 patients	1 day	30 per 1000 patients	50 per 1000 patients	50 per 1000 patients	40 per 1000 patients
Lefamulin	-3 (-44, 57)			-16 (-35, 29)	-39 (-42, -25)	15 (-26, 146)	
β-Lactam/β-lactamase inhibitors alone	13 (-20, 58)	0 (-11, 21)	-1.67 (-5.23, 1.88)	6 (-20, 54)	77 (23, 176)	30 (-15, 144)	-2 (-16, 39)
A β-lactam/β-lactamase inhibitor plus a macrolide	20 (-17, 70)	12 (-5, 43)	0.92 (-2.46, 4.30)	-4 (-23, 29)	405 (84, 1000)	-1 (-31, 93)	-15 (-22, 24)
Fifth-generation cephalosporins alone	4 (-37, 61)	0 (-12, 25)		11 (-18, 65)	50 (3, 144)	23 (-18, 128)	-8 (-19, 28)
Carbapenems alone	18 (-29, 87)	-1 (-12, 21)	0.18 (-1.68, 2.04) [c]	-8 (-35, 73)	48 (-3, 163)	12 (-36, 81)	3 (-18, 109)
Penicillins alone	33 (-9, 88)	3 (-10, 32)	1.07 (-5.45, 7.60)	-1 (-26, 52)	0 (-28, 80)	-9 (-34, 75)	4 (-14, 51)
Third-generation cephalosporins alone	42 (-1, 102)	1 (-8, 14)	0 (-0.41, 0.41) [c]	0 (-19, 31)	11 (-9, 42)	-10 (-27, 25)	-12 (-19, 4)
A third-generation cephalosporin plus a macrolide	45 (-3, 111)	-4 (-12, 8)	1.13 (-0.46, 2.72)	20 (-5, 59)	20 (-17, 107)	-14 (-31, 25)	-4 (-14, 17)
Second-generation cephalosporins alone	45 (-15, 135)	8 (-10, 52)	1.37 (-3.88, 6.63)	-13 (-37, 67)	46 (-9, 189)	23 (-27, 215)	-15 (-21, 6)
Tetracyclines alone [d]	-29 (-69, 38)	26 (-8, 130)		-9 (-25, 19)	-37 (-41, -25)	-13 (-30, 24) [e]	-8 (-19, 33)
A second-generation cephalosporin plus a macrolide	9 (-32, 65)	-9 (-18, 12)	-0.20 (-0.94, 0.54) [c]	55 (0, 169)	32 (-9, 123)	113 (26, 310)	-16 (-24, 173)
Fourth-generation cephalosporins alone	29 (-25, 110)	4 (-9, 32)		-4 (-35, 103)	62 (-7, 268)		-19 (-24, 28)
A third-generation cephalosporin plus a respiratory fluoroquinolone	-28 (-61, 22)	-8 (-15, 9)		-20 (-32, 3)	-22 (-33, 2) [e]	0 (-29, 84)	
A carbapenem plus a macrolide	8 (-50, 110)	34 (0, 119)	-0.80 (-2.56, 0.96) [c]	-5 (-47, 1000)	484 (83, 1000)		-21 (-26, 84)
Third-generation cephalosporin/β-lactamase inhibitors alone	-84 (-115, -1)	0 (-23, 1000)		-2 (-47, 1000)		-9 (-39, 165)	
A second-generation cephalosporin plus a tetracycline	9 (-62, 154)						

CI: confidence interval; MD: mean difference; RD: risk difference. Numbers in the colored cells are the estimated RDs and 95% CI per 1000 patients MDs and 95% CI in days comparing each antibiotic regimen versus respiratory fluoroquinolones alone.
[a] The baseline risks was derived from the median of risk of event across the arms that randomized patients to the respiratory fluoroquinolones alone.
[b] We decided on the minimal important difference thresholds based on a consensus among the clinical experts in the team.
[c] Best estimate of effect was obtained from the direct evidence.
[d] The network estimates on the effects of tetracyclines alone versus respiratory fluoroquinolones alone were dominantly informed by the direct evidence which came from a single trial that used omadacycline.
[e] The certainty of the evidence was high.

	Among the best	Not different from respiratory fluoroquinolones alone	Among the worst
High / Moderate certainty	(Probably) better than respiratory fluoroquinolones alone and some alternatives	(Probably) results in little or no difference compared with respiratory fluoroquinolones alone	(Probably) inferior to respiratory fluoroquinolones alone and some alternatives
Low certainty	May be better than respiratory fluoroquinolones alone and some alternatives	May result in little or no difference compared with respiratory fluoroquinolones alone	May be inferior to respiratory fluoroquinolones alone and some alternatives
Ver low certainty	We are very uncertain regarding the effect of the antibiotic		
No evidence			

Antibiotic regimens provided high-to-low certainty evidence of little to no difference in increasing nausea and/or vomiting compared with respiratory fluoroquinolones alone, or the evidence was very low certainty (Table 2).

Any allergic reactions

The 38 trials involving 8,202 participants that informed effects on any allergic reactions included 27 direct comparisons. Antibiotic regimens provided moderate-to-low certainty evidence of little to no difference in increasing allergic reactions compared with respiratory fluoroquinolones alone, or the evidence was very low certainty (Table 2).

Acute kidney injury

Twelve trials reported effects on acute kidney injury, of which three trials compared antibiotics within the same class. We did not perform an NMA due to the limited number of trials. Supplementary S18 presents the pairwise comparisons for this outcome.

Network meta-regression and sensitivity analyses

Analyses revealed no credible differential effects based on the severity of CAP, risk of bias, study year, geographical region, follow-up time, and age (Supplementary S19 and S20). The

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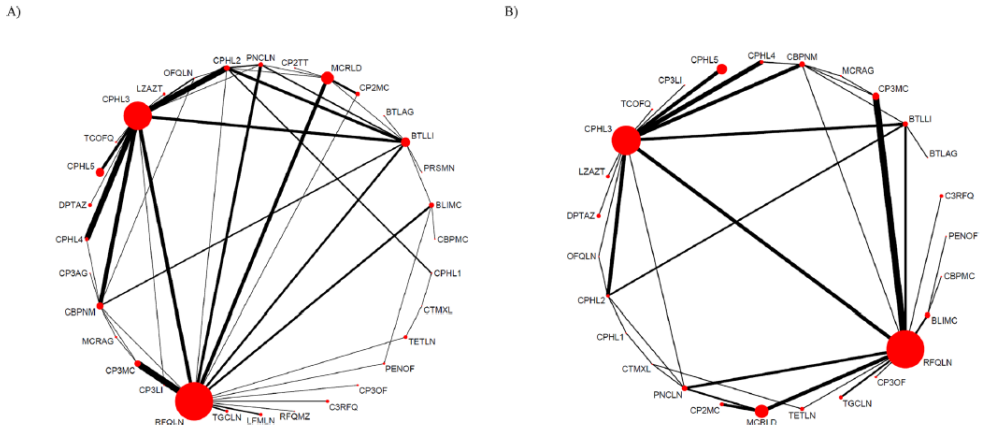

Fig. 2. Network plots of (a) treatment failure and (b) all-cause mortality. The size of the nodes is proportional to the number of participants randomized to each antibiotic regimen, and the lines link nodes are weighted according to the number of trials informed a specific direct comparison. BTLLI, β-lactam/β-lactamase inhibitors alone; BLIMC, a β-lactam/β-lactamase inhibitor plus a macrolide; BTLAG, a β-lactam/β-lactamase inhibitor plus an aminoglycoside; CBPMC, a carbapenem plus a macrolide; CP3AG, a third-generation cephalosporin plus an aminoglycoside; CBPNM, carbapenems alone; CP3MC, a third-generation cephalosporin plus a macrolide; CPHL3, third-generation cephalosporins alone; CP3LI, third-generation cephalosporin/β-lactamase inhibitors alone; CPHL4, fourth-generation cephalosporins alone; CPHL5, fifth-generation cephalosporins alone; CPHL2, second-generation cephalosporins alone; CPHL1, first-generation cephalosporins alone; CTMXL, cotrimoxazole; DPTAZ, daptomycin plus aztreonam; LZAZT, linezolid plus aztreonam; MCRAG, a macrolide plus an aminoglycoside; MCRLD, macrolides alone; CP2TT, a second-generation cephalosporin plus a tetracycline; OFQLN, other fluoroquinolones alone; PENOF, a penicillin plus an other fluoroquinolone; PNCLN, penicillins alone; PRSMN, pristinamycin; RFQLN, respiratory fluoroquinolones lone; C3RFQ, a third-generation cephalosporin plus a respiratory fluoroquinolone; LFMLN, lefamulin; CP2MC, a 2second-generation cephalosporin plus a macrolide; CP3OF, a third-generation cephalosporin plus an other fluoroquinolone; RFQMZ, a respiratory fluoroquinolone plus a metronidazole; TCOFQ, teicoplanin plus an other fluoroquinolone; TETLN, tetracyclines alone; TGCLN, tigecycline.

findings were robust when we excluded trials in which at least 80% of participants had severe CAP (Supplementary S21).

Discussion

This NMA summarizes the comparative effects of antibiotics used for the empiric management of adults with moderate-to-severe CAP. We found no moderate or high certainty evidence of important differences in any of the outcomes for any of the antibiotic regimens. However, low certainty evidence suggests that penicillins alone, second-generation cephalosporins alone, and third-generation cephalosporins alone or combined with a macrolide may be among the worst regimens for treatment failure. All other antibiotic regimens either showed effects similar to respiratory fluoroquinolones alone (in most cases with low certainty), or the evidence remains very uncertain regarding their effects.

Strengths and limitations

The strengths of our NMA include a comprehensive and up-to-date synthesis of evidence regarding the benefits and harms of empiric antibiotics for moderate-to-severe CAP. For studies with available information on the severity of CAP, rather than using the site of care, we used severity data to classify trials. To minimize bias, pairs of reviewers independently conducted the screening process, data abstraction, and risk of bias assessment. We applied the GRADE methodology to assess the certainty of evidence and classified antibiotics using a modification of the GRADE approach to optimally inform decision-making [34].

This review has several limitations. Firstly, there was limited direct evidence resulting in imprecision of effect estimates, most of the trials suffered from risk of bias, and these limitations resulted in low or very low certainty evidence for most comparisons. Secondly, when data on severity of pneumonia were unavailable, we used the site of care to decide whether trials were eligible. As several ineligible trials suggested that patients with mild CAP may receive inpatient care, it is possible that some patients enrolled in the trials included in our NMA may have had mild pneumonia. Thirdly, we assumed similar effects between antibiotics within the same class and/or generation. We explored the difference between the effects of individual antibiotics only for treatment failure, and for most antibiotics, the evidence was very uncertain. Thus, it is possible that our findings may not be generalizable to all antibiotics within the same class. Fourthly, the median duration of antibiotic therapy across the included studies was 10 days, whereas a shorter duration of therapy is now recommended for patients with CAP with uncomplicated disease [6]. However, the longer duration is unlikely to impact the relative effect of the antibiotics. Fifthly, we did not find any evidence of credible effect modification by severity of CAP; however, the majority of patients in the trials included in our review had moderate severity CAP. Thus, the applicability of our results for patients with severe CAP remains uncertain. Finally, although the local distribution of pathogens and resistance patterns may influence antibiotic effects, we did not identify differential effects based on study year and geographical region. However, given the overrepresentation of certain regions, our findings may not be applicable worldwide. If available, the local prevalence of underlying pathogens and resistance patterns should inform empiric antibiotic selection. Most regions, however, do not have seroepidemiological data to inform the prevalence of particular pathogens.

Relation to other studies

We are aware of two other similar NMAs to ours [10,11]. These NMAs included trials that enrolled patients hospitalized for CAP management. Hospitalization as a surrogate criterion for the

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severity of CAP might be misleading, as in several trials on inpatient CAP, more than 50% of enrolled patients were in PORT class I or II (i.e. had mild pneumonia) [35–37]; we excluded such trials.

Previous NMAs either assessed the effects of specific antibiotic classes without evaluating the certainty of evidence [10] or did not include all eligible trials [11]. The NMA that included a broader range of antibiotics [11] specified treatment nodes as individual antibiotics, further splitting based on dosing and thus resulting in disconnected networks and inability to provide an informative conclusion. Our approach in grouping antibiotics and node definition while proving still be limited, allowed more useful inferences. These NMAs offered conclusions based on ranking probabilities with surface under the cumulative ranking curve, a limited approach that ignores both imprecision in effect estimates and certainty of evidence [38].

Implications for practice and research

This NMA highlights the uncertain evidence on the comparative efficacy and safety of antibiotic regimens for empiric therapy of moderate-to-severe CAP. However, our findings may offer useful insights for empiric antibiotic selection, particularly among patients with moderate severity CAP. Firstly, among β-lactams, β-lactams/β-lactamase inhibitors (e.g. Amoxicillin-clavulanate or Ampicillin-sulbactam) may be more effective than penicillins and second- or third-generation cephalosporins in reducing treatment failure. Secondly, routine coverage against atypical pathogens may not offer additional benefits in reducing treatment failure and all-cause mortality. Combination therapy with macrolides may be more effective in cases of suspected infection due to atypical pathogens in settings with a low prevalence of resistance to macrolides or in patients with more severe disease [39,40]. Thirdly, monotherapy with respiratory fluoroquinolones may not offer additional benefit in reducing treatment failure compared with β-lactams/β-lactamase inhibitors monotherapy or combined with a macrolide. Respiratory fluoroquinolones should be reserved for patients with more severe CAP and risk factors for macrolide-resistant atypical pathogens [40], or in settings with a high prevalence of multidrug-resistant *S. pneumonia*. Finally, routine coverage of *Pseudomonas aeruginosa* may not offer additional benefits in reducing treatment failure compared with antibiotics that cover common CAP pathogens.

The evidence on moderate-to-severe CAP is dominated by trials of respiratory fluoroquinolones, while investigators seldom addressed non-fluoroquinolone antibiotics that are of interest to clinicians. Future RCTs should focus on addressing the comparative efficacy and safety of regimens that thus far underrepresented such as monotherapy with a β-lactam/β-lactamase inhibitor vs. a penicillin in patients with moderate severity CAP, or a β-lactam/β-lactamase inhibitor combined with a macrolide vs. a second- or third-generation cephalosporin combined with a macrolide in patients with more severe disease. Such trials should enrol patients based on the severity of CAP, which is assessed through a standardized approach, and include a greater proportion of patients with severe disease. Future RCTs should consider the need for mechanical ventilation and duration of hospitalization as outcomes and evaluate outcomes at longer follow-up. Additionally, RCTs should adequately conceal the allocation of antibiotic regimens and properly blind patients and healthcare providers.

In conclusion, this systematic review and NMA found no convincing evidence that antibiotic regimens prescribed for empiric therapy of moderate-to-severe CAP importantly differ in any of the patient-important outcomes.

Author contributions

M.G., G.G., and R.A.C.S. were responsible for conceptualization. M.G., G.G., R.A.C.S., M.L., B.S., and R.B-P. were responsible for methodology. M.G. and R.C. were responsible for resources. M.G., J. P.L., D.A., H.G., Y.W., A.A.H., J.B., L.Y., W.S.H.K., A.G., A.A., A.T., T.T., S. M., G.A-G., K.K., G.E.U.M.S., S.Z., A.D., V.M., F.M., and V.L. were responsible for investigation. M.G. was responsible for data curation, writing-original draft, visualization and project administration. All authors were responsible for writing-review and editing. G.G., R.A.C.S., M.L., B.S., and R.B-P. were responsible for supervision.

Transparency declaration

Potential conflict of interest

M.L. is on AMMI-Canada Working Group on Antibiotic Guidelines and participated in advisory boards for AVIR pharma and Xediton Pharmaceuticals. A.T. received personal fees from Eisai and Shionogi outside the submitted work. The other authors declare that they have no conflicts of interest.

Data availability

The dataset of this review is available in Supplementary file S2.

Financial report

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2025.06.033.

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Supplementary Appendix C5

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Supplement 1. Deviations from the protocol

1) We initially developed the protocol "PROSPERO (CRD42022297216)" for community-acquired pneumonia (inpatient and outpatient), but in the course of the review, we changed our plan to conduct two separate NMAs for inpatient and outpatient CAP. However, as mentioned in the manuscript, reviewing inpatient trials showed in some trials more than 50% of enrolled patients had mild CAP and thus may show different effects compared with trials in which most patients had moderate to severe CAP. To deal with this issue and avoid relying on site of care for inclusion of trials, we classified trials as mild versus moderate to severe CAP based on the severity data reported in the trials. In this manuscript, we focused on moderate to severe CAP.

2) Among moderate to severe CAP trials, we found only 10 trials (7.0%) that enrolled adults with healthcare-associated pneumonia (not hospital-acquired pneumonia); the proportion ranged from 1.2 to 100%. Due to the insufficient variability in the data, we were unable to perform network meta-regression or subgroup analysis by the type of pneumonia.

3) We performed network meta-regression for each domain of risk of bias and as we found no apparent effect modification by high risk of bias arising from randomization process or due to inadequate allocation concealment versus low risk of bias, we did not perform a sensitivity analysis by restricting studies to randomized trials with concealment.

4) Our critical outcomes included treatment failure and all-cause mortality, both closest to 30 days after the end of the antibiotic therapy. However, we observed variability in the assessment time of these outcomes across the studies and thus performed a post-hoc network meta-regression by follow up time for reporting the outcomes.

5) As requested by reviewers, for critical outcomes, we conducted post-hoc network meta-regression by study year, geographical region, and age and sensitivity analyses by excluding trials in which at least 80% of participants had severe CAP from the analysis.

Supplement 2. Search strategy

OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

1 exp Pneumonia/
2 Respiratory Tract Infections/
3 Pneumonia, Pneumococcal/
4 Pleuropneumonia/
5 (pneumon* or bronchopneumon* or pleuropneumon*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
6 (respiratory adj2 infection*).mp.
7 or/1-6
8 Tetracycline/ or tetracycline*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
9 exp Lincosamides/ or lincosamide*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
10 exp Macrolides/ or macrolide*.mp.
11 Ketolides/ or Ketolide*.mp.
12 exp Aminoglycosides/ or Aminoglycoside*.mp.
13 exp Oxazolidinones/ or Oxazolidinone*.mp.
14 exp Glycopeptides/ or Glycopeptide*.mp.
15 exp beta-Lactams/ or Beta-lactam*.mp.
16 exp Penicillins/ or Penicillin*.mp.
17 Carbapenem*.mp. or exp Carbapenems/
18 exp Cephalosporins/ or Cephalosporin*.mp.
19 exp Monobactams/ or Monobactam*.mp.
20 exp Folic Acid Antagonists/ or Antifolate*.mp.
21 exp sulfonamide/ or Sulfonamide*.mp.
22 exp Fluoroquinolones/ or Fluoroquinolone*.mp.
23 (Piperacillin-tazobactam or Amoxicillin or Ampicillin or Ampicillin-sulbactam or Amoxicillin-clavulanate or Pivampicillin or Hetacillin or Bacampicillin or Metampicillin or Talampicillin or Epicillin or Carbenicillin or Ticarcillin or Temocillin or Ureidopenicillins or Azlocillin or Mezlocillin or Cyclacillin or Sulbenicillin or Aspoxicillin or Amdinocillin or Penicillin G Benzathine or Procaine benzylpenicillin or Azidocillin or Phenoxymethylpenicillin or Cloxacillin or Dicloxacillin or Flucloxacilli or Oxacillin or Meticillin or Nafcillin or Ampicillin-flucloxacillin or Sultamicillin or Ticarcillin-clavulanate).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
24 (Aztreonam or Aztreonam-avibactam or Lefamulin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word,

organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
25 (Cefepime or Ceftazidime or Cefotaxime or Ceftriaxone or Cefpodoxime or Cefuroxime or Ceftaroline or Ceftolozane-tazobactam or Ceftazidime-avibactam or Ceftaroline-avibactam or cefoperazone-sulbactam or Ceftobiprole medocaril or Ceftazidime-avibactam or Cefazolin or Cefacetrile or Cefadroxil or Cefalexin or Cephaloridine or Cefalotin or Cefatrizine or Cefazedone or Cefradine or Cefroxadine or Cefaclor or Cefamandole or Cefminox or Cefonicid or Ceforanide or Cefotiam or Cefprozil or Cefbuperazone or Cefuzonam or cephamycin or Cefoxitin or Cefotetan or Cefmetazole or Loracarbef or Cefixime or Cefoperazone or Cefcapene or Cefdinir or Cefditoren or Cefetamet or Cefmenoxime or Cefodizime or Cefpimizole or Cefpiramide or Cefpodoxime or Cefsulodin or Cefteram or Ceftibuten or Ceftizoxime or oxacephem or Flomoxef or Latamoxef or Moxalactam or Cefiderocol or Cefozopran or Cefpirome or Ceftobiprole or Ceftolozane or Carumonam or Nocardicin A).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
26 (Imipenem or Meropenem or Ertapenem or Imipenem-relebactam or Meropenem-vaborbactam or Doripenem or Biapenem or Ertapenem or Panipenem).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
27 (levofloxacin or Ciprofloxacin or Moxifloxacin or Omadacycline or Lascufloxacin or Zabofloxacin or Gatifloxacin or Grepafloxacin or Trovafloxacin or Enoxacin or Fleroxacin or Lomefloxacin or Nadifloxacin or Ofloxacin or Norfloxacin or Pefloxacin or Rufloxacin or Balofloxacin or Pazufloxacin or Sparfloxacin or Temafloxacin or Tosufloxacin or Clinafloxacin or Garenoxacin or Sitafloxacin or Prulifloxacin or Nemonoxacin or Alatrofloxacin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
28 (Gentamicin or Amikacin or Tobramycin or Plazomicin or Streptomycin or Dihydrostreptomycin or Ribostamycin or Kanamycin or Arbekacin or Netilmicin or Sisomicin or Isepamicin or Verdamicin or Eperezolid or Bekanamycin or Dibekacin or Micronomicin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
29 (Vancomycin or Linezolid or Telavancin or Oritavancin or Teicoplanin or Dalbavancin or Daptomycin or Posizolid or Radezolid or Tedizolid or Ranbezolid).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
30 (Azithromycin or Clarithromycin or Erythromycin or Nafithromycin or Dirithromycin or Flurithromycin or Josamycin orMidecamycin or Miocamycin or Rokitamycin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
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Eravacycline).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
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33 (Sulfamethizole or Sulfathiazole or Sulfapyridine or Prontosil or Sulfanilamide or Sulfadiazine or Sulfalene or Sulfamethoxazole or Sulfamerazine or Sulfametrole or Trimethoprim-sulfamethoxazole or septra or cotrimoxazole or Sulfisoxazole or Sulfamethazine or Iclaprim or Brodimoprim).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
34 (Metronidazole or Tinidazole or Ornidazole).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
35 (Streptogramin or Quinupristin-dalfopristin or Chloramphenicol or Fusidic acid or Fosfomycin or Murepavidin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
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37 or/8-36
38 7 and 37
39 systematic review.mp. or "Systematic Review"/
40 MEDLINE.tw.
41 meta-analysis.pt.
42 39 or 40 or 41
43 38 and 42
44 random:.tw. or placebo:.mp. or double-blind:.tw.
45 ((treatment or control) adj3 group*).ab.
46 (allocat* adj5 group*).ab.
47 ((clinical or control*) adj3 trial).ti,ab,kw.
48 or/44-47
49 38 and 48
50 43 or 49
51 exp animals/ not humans.sh.
52 50 not 51

EMBASE
Database: Embase <1974 to Present>

1 exp pneumonia/
2 respiratory tract infection/
3 Streptococcus pneumonia/
4 (pneumon* or bronchopneumon* or pleuropneumon*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
5 (respiratory adj2 infection*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
6 or/1-5
7 tetracycline/ or tetracycline*.mp.
8 lincosamide/ or lincosamide*.mp.
9 exp macrolide/ or macrolide*.mp.
10 exp ketolide/ or Ketolide*.mp.
11 aminoglycoside/ or Aminoglycoside*.mp.
12 oxazolidinone derivative/ or Oxazolidinone*.mp.
13 exp glycopeptide/ or Glycopeptide*.mp.
14 exp beta lactam antibiotic/ or Beta-lactam*.mp.
15 Penicillin*.mp. or exp penicillin derivative/
16 carbapenem derivative/ or Carbapenem*.mp.
17 exp cephalosporin derivative/ or Cephalosporin*.mp.
18 exp monobactam derivative/ or Monobactam*.mp.
19 exp folic acid antagonist/
20 sulfonamide/ or Sulfonamide*.mp.
21 Fluoroquinolone*.mp.
22 (Piperacillin-tazobactam or Amoxicillin or Ampicillin or Ampicillin-sulbactam or Amoxicillin-clavulanate or Pivampicillin or Hetacillin or Bacampicillin or Metampicillin or Talampicillin or Epicillin or Carbenicillin or Ticarcillin or Temocillin or Ureidopenicillins or Azlocillin or Mezlocillin or Cyclacillin or Sulbenicillin or Aspoxicillin or Amdinocillin or Penicillin G Benzathine or Procaine benzylpenicillin or Azidocillin or Phenoxymethylpenicillin or Cloxacillin or Dicloxacillin or Flucloxacilli or Oxacillin or Meticillin or Nafcillin or Ampicillin-flucloxacillin or Sultamicillin or Ticarcillin-clavulanate).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
23 (Aztreonam or Aztreonam-avibactam or Lefamulin).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
24 (Cefepime or Ceftazidime or Cefotaxime or Ceftriaxone or Cefpodoxime or Cefuroxime or Ceftaroline or Ceftolozane-tazobactam or Ceftazidime-avibactam or Ceftaroline-avibactam or cefoperazone-sulbactam or Ceftobiprole medocaril or Ceftazidime-avibactam or Cefazolin or Cefacetrile or Cefadroxil or Cefalexin or Cephaloridine or Cefalotin or Cefatrizine or Cefazedone or Cefradine or Cefroxadine or Cefaclor or Cefamandole or Cefminox or Cefonicid or Ceforanide or Cefotiam or Cefprozil or Cefbuperazone or Cefuzonam or cephamycin or Cefoxitin or Cefotetan or Cefmetazole or Loracarbef or Cefixime or Cefoperazone or Cefcapene or Cefdinir or Cefditoren or Cefetamet or Cefmenoxime or Cefodizime or Cefpimizole or Cefpiramide or Cefpodoxime or

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25 (Imipenem or Meropenem or Ertapenem or Imipenem-relebactam or Meropenem-vaborbactam or Doripenem or Biapenem or Ertapenem or Panipenem).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
26 (levofloxacin or Ciprofloxacin or Moxifloxacin or Omadacycline or Lascufloxacin or Zabofloxacin or Gatifloxacin or Grepafloxacin or Trovafloxacin or Enoxacin or Fleroxacin or Lomefloxacin or Nadifloxacin or Ofloxacin or Norfloxacin or Pefloxacin or Rufloxacin or Balofloxacin or Pazufloxacin or Sparfloxacin or Temafloxacin or Tosufloxacin or Clinafloxacin or Garenoxacin or Sitafloxacin or Prulifloxacin or Nemonoxacin or Alatrofloxacin).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
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29 (Azithromycin or Clarithromycin or Erythromycin or Nafithromycin or Dirithromycin or Flurithromycin or Josamycin orMidecamycin or Miocamycin or Rokitamycin).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
30 (Doxycycline or Tigecycline or Chlortetracycline or Demeclocycline or Lymecycline or Meclocycline or Metacycline or Minocycline or Penimepicycline or Rolitetracycline or Eravacycline).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
31 (Clindamycin or Solithromycin or Telithromycin or Cethromycin or Lincomycin or Roxithromycin or Spiramycin or Troleandomycin).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
32 (Sulfamethizole or Sulfathiazole or Sulfapyridine or Prontosil or Sulfanilamide or Sulfadiazine or Sulfalene or Sulfamethoxazole or Sulfamerazine or Sulfametrole or Trimethoprim-sulfamethoxazole or septra or cotrimoxazole or Sulfisoxazole or Sulfamethazine or Iclaprim or Brodimoprim).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
33 (Metronidazole or Tinidazole or Ornidazole).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

34 (Streptogramin or Quinupristin-dalfopristin or Chloramphenicol or Fusidic acid or Fosfomycin or Murepavidin).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
35 (Rifampicin or Rifabutin or Rifapentine).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
36 or/7-35
37 6 and 36
38 "systematic review".mp. or "systematic review"/
39 meta-analysis.mp. or meta analysis/
40 38 or 39
41 37 and 40
42 random:.tw. or placebo:.mp. or double-blind:.tw.
43 ((treatment or control) adj3 group*).ab.
44 (allocat* adj5 group*).ab.
45 ((clinical or control*) adj3 trial).ti,ab,kw.
46 or/42-45
47 37 and 46
48 41 or 47
49 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/
50 Animal experiment/ not (human experiment/ or human/)
51 49 or 50
52 48 not 51

Cochrane Library

#1 MeSH descriptor: [Pneumonia] explode all trees
#2 MeSH descriptor: [Respiratory Tract Infections] this term only
#3 MeSH descriptor: [Pneumococcal Infections] explode all trees
#4 MeSH descriptor: [Pleuropneumonia] explode all trees
#5 (pneumon* or bronchopneumon* or pleuropneumon*):ti,ab,kw (Word variations have been searched)
#6 MeSH descriptor: [Respiratory Distress Syndrome] explode all trees
#7 (ARDS):ti,ab,kw (Word variations have been searched)
#8 (respiratory near/2 (infection*))
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 Piperacillin-tazobactam or Amoxicillin or Ampicillin or Ampicillin-sulbactam or Amoxicillin-clavulanate or Pivampicillin or Hetacillin or Bacampicillin or Metampicillin or Talampicillin or Epicillin or Carbenicillin or Ticarcillin or Temocillin or Ureidopenicillins or Azlocillin or Mezlocillin or Cyclacillin or Sulbenicillin or Aspoxicillin or Amdinocillin or Penicillin G Benzathine or Procaine benzylpenicillin or Azidocillin or Phenoxymethylpenicillin or Cloxacillin or Dicloxacillin or Flucloxacilli or Oxacillin or Meticillin or Nafcillin or Ampicillin-flucloxacillin or Sultamicillin or Ticarcillin-clavulanate or Aztreonam or Aztreonam-avibactam or Lefamulin or Cefepime or Ceftazidime or Cefotaxime or Ceftriaxone or Cefpodoxime or Cefuroxime or Ceftaroline or Ceftolozane-tazobactam or Ceftazidime-avibactam or Ceftaroline-

avibactam or cefoperazone-sulbactam or Ceftobiprole medocaril or Ceftazidime-avibactam or Cefazolin or Cefacetrile or Cefadroxil or Cefalexin or Cephaloridine or Cefalotin or Cefatrizine or Cefazedone or Cefradine or Cefroxadine or Cefaclor or Cefamandole or Cefminox or Cefonicid or Ceforanide or Cefotiam or Cefprozil or Cefbuperazone or Cefuzonam or cephamycin or Cefoxitin or Cefotetan or Cefmetazole or Loracarbef or Cefixime or Cefoperazone or Cefcapene or Cefdinir or Cefditoren or Cefetamet or Cefmenoxime or Cefodizime or Cefpimizole or Cefpiramide or Cefpodoxime or Cefsulodin or Cefteram or Ceftibuten or Ceftizoxime or oxacephem or Flomoxef or Latamoxef or Moxalactam or Cefiderocol or Cefozopran or Cefpirome or Ceftobiprole or Ceftolozane or Carumonam or Nocardicin A or Imipenem or Meropenem or Ertapenem or Imipenem-relebactam or Meropenem-vaborbactam or Doripenem or Biapenem or Ertapenem or Panipenem or levofloxacin or Ciprofloxacin or Moxifloxacin or Omadacycline or Lascufloxacin or Zabofloxacin or Gatifloxacin or Grepafloxacin or Trovafloxacin or Enoxacin or Fleroxacin or Lomefloxacin or Nadifloxacin or Ofloxacin or Norfloxacin or Pefloxacin or Rufloxacin or Balofloxacin or Pazufloxacin or Sparfloxacin or Temafloxacin or Tosufloxacin or Clinafloxacin or Garenoxacin or Sitafloxacin or Prulifloxacin or Nemonoxacin or Alatrofloxacin or Gentamicin or Amikacin or Tobramycin or Plazomicin or Streptomycin or Dihydrostreptomycin or Ribostamycin or Kanamycin or Arbekacin or Netilmicin or Sisomicin or Isepamicin or Verdamicin or Eperezolid or Bekanamycin or Dibekacin or Micronomicin or Vancomycin or Linezolid or Telavancin or Oritavancin or Teicoplanin or Dalbavancin or Daptomycin or Posizolid or Radezolid or Tedizolid or Ranbezolid or Azithromycin or Clarithromycin or Erythromycin or Nafithromycin or Dirithromycin or Flurithromycin or Josamycin orMidecamycin or Miocamycin or Rokitamycin or Doxycycline or Tigecycline or Chlortetracycline or Demeclocycline or Lymecycline or Meclocycline or Metacycline or Minocycline or Penimepicycline or Rolitetracycline or Eravacycline or Clindamycin or Solithromycin or Telithromycin or Cethromycin or Lincomycin or Roxithromycin or Spiramycin or Troleandomycin or Sulfamethizole or Sulfathiazole or Sulfapyridine or Prontosil or Sulfanilamide or Sulfadiazine or Sulfalene or Sulfamethoxazole or Sulfamerazine or Sulfametrole or Trimethoprim-sulfamethoxazole or septra or cotrimoxazole or Sulfisoxazole or Sulfamethazine or Iclaprim or Brodimoprim or Metronidazole or Tinidazole or Ornidazole or Streptogramin or Quinupristin-dalfopristin or Chloramphenicol or Fusidic acid or Fosfomycin or Murepavidin or Rifampicin or Rifabutin or Rifapentine

#11 tetracycline* or lincosamide* or macrolide* or ketolide* or Aminoglycoside* or Oxazolidinone* or Glycopeptide or Beta-lactam* or Penicillin* or Carbapenem* or Cephalosporin or Monobactam* or Antifolate* or sulfonamide* or Fluoroquinolone*

#12 #10 or #11

#13 #9 and #12

CINAHL

S62 S44 OR S61

S61 S40 AND S60

S60 S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59

S59 (MH "Randomized Controlled Trials")

S58 (MH "Double-Blind Studies")

S57 (MH "Single-Blind Studies")

S56 (MH "Random Assignment")

S55 (MH "Pretest-Posttest Design")

S54 (MH "Cluster Sample")
S53 TI (randomised OR randomized)
S52 AB (random*)
S51 TI (trial)
S50 MH (sample size) AND AB (assigned OR allocated OR control)
S49 MH (placebos)
S48 PT (randomized controlled trial)
S47 AB (CONTROL W5 GROUP)
S46 MH (CROSSOVER DESIGN) OR MH (COMPARATIVE STUDIES)
S45 AB (CLUSTER W3 RCT)
S44 S40 AND S43
S43 S41 OR S42
S42 (MH "Meta Analysis") OR "meta-analysis"
S41 (MH "Systematic Review") OR "systematic review"
S40 S8 AND S39
S39 S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38
S38 TX Rifampicin or Rifabutin or Rifapentine
S37 TX Streptogramin or Quinupristin-dalfopristin or Chloramphenicol or Fusidic acid or Fosfomycin or Murepavidin
S36 TX Metronidazole or Tinidazole or Ornidazole
S35 TX Sulfamethizole or Sulfathiazole or Sulfapyridine or Prontosil or Sulfanilamide or Sulfadiazine or Sulfalene or Sulfamethoxazole or Sulfamerazine or Sulfametrole or Trimethoprim-sulfamethoxazole or septra or cotrimoxazole or Sulfisoxazole or Sulfamethazine or Iclaprim or Brodimoprim
S34 TX Clindamycin or Solithromycin or Telithromycin or Cethromycin or Lincomycin or Roxithromycin or Spiramycin or Troleandomycin
S33 TX Doxycycline or Tigecycline or Chlortetracycline or Demeclocycline or Lymecycline or Meclocycline or Metacycline or Minocycline or Penimepicycline or Rolitetracycline or Eravacycline
S32 TX Azithromycin or Clarithromycin or Erythromycin or Nafithromycin or Dirithromycin or Flurithromycin or Josamycin orMidecamycin or Miocamycin or Rokitamycin
S31 TX Vancomycin or Linezolid or Telavancin or Oritavancin or Teicoplanin or Dalbavancin or Daptomycin or Posizolid or Radezolid or Tedizolid or Ranbezolid
S30 TX Gentamicin or Amikacin or Tobramycin or Plazomicin or Streptomycin or Dihydrostreptomycin or Ribostamycin or Kanamycin or Arbekacin or Netilmicin or Sisomicin or Isepamicin or Verdamicin or Eperezolid or Bekanamycin or Dibekacin or Micronomicin
S29 TX levofloxacin or Ciprofloxacin or Moxifloxacin or Omadacycline or Lascufloxacin or Zabofloxacin or Gatifloxacin or Grepafloxacin or Trovafloxacin or Enoxacin or Fleroxacin or Lomefloxacin or Nadifloxacin or Ofloxacin or Norfloxacin or Pefloxacin or Rufloxacin or Balofloxacin or Pazufloxacin or Sparfloxacin or Temafloxacin or Tosufloxacin or Clinafloxacin or Garenoxacin or Sitafloxacin or Prulifloxacin or Nemonoxacin or Alatrofloxacin
S28 TX Imipenem or Meropenem or Ertapenem or Imipenem-relebactam or Meropenem-vaborbactam or Doripenem or Biapenem or Ertapenem or Panipenem
S27 TX Cefepime or Ceftazidime or Cefotaxime or Ceftriaxone or Cefpodoxime or Cefuroxime or Ceftaroline or Ceftolozane-tazobactam or Ceftazidime-avibactam or Ceftaroline-avibactam or cefoperazone-sulbactam or Ceftobiprole medocaril or Ceftazidime-avibactam or Cefazolin or

Cefacetrile or Cefadroxil or Cefalexin or Cephaloridine or Cefalotin or Cefatrizine or Cefazedone or Cefradine or Cefroxadine or Cefaclor or Cefamandole or Cefminox or Cefonicid or Ceforanide or Cefotiam or Cefprozil or Cefbuperazone or Cefuzonam or cephamycin or Cefoxitin or Cefotetan or Cefmetazole or Loracarbef or Cefixime or Cefoperazone or Cefcapene or Cefdinir or Cefditoren or Cefetamet or Cefmenoxime or Cefodizime or Cefpimizole or Cefpiramide or Cefpodoxime or Cefsulodin or Cefteram or Ceftibuten or Ceftizoxime or oxacephem or Flomoxef or Latamoxef or Moxalactam or Cefiderocol or Cefozopran or Cefpirome or Ceftobiprole or Ceftolozane or Carumonam or Nocardicin A

S26 TX Aztreonam or Aztreonam-avibactam or Lefamulin

S25 TX Piperacillin-tazobactam or Amoxicillin or Ampicillin or Ampicillin-sulbactam or Amoxicillin-clavulanate or Pivampicillin or Hetacillin or Bacampicillin or Metampicillin or Talampicillin or Epicillin or Carbenicillin or Ticarcillin or Temocillin or Ureidopenicillins or Azlocillin or Mezlocillin or Cyclacillin or Sulbenicillin or Aspoxicillin or Amdinocillin or Penicillin G Benzathine or Procaine benzylpenicillin or Azidocillin or Phenoxymethylpenicillin or Cloxacillin or Dicloxacillin or Flucloxacilli or Oxacillin or Meticillin or Nafcillin or Ampicillin-flucloxacillin or Sultamicillin or Ticarcillin-clavulanate

S24 (MH "Antiinfective Agents, Fluoroquinolone") OR "Fluoroquinolone*"

S23 (MH "Sulfonamides") OR "sulfonamide*"

S22 (MH "Folic Acid Antagonists+")

S21 "Antifolate*"

S20 "Monobactam*"

S19 (MH "Cephalosporins") OR "Cephalosporin*"

S18 "Carbapenem*" OR (MH "Carbapenems+")

S17 (MH "Penicillins+") OR "Penicillin*"

S16 (MH "Antibiotics, Lactam+") OR "Beta-lactam*"

S15 "Glycopeptide*"

S14 "Oxazolidinone*"

S13 (MH "Aminoglycosides+") OR "Aminoglycoside*"

S12 "ketolide*"

S11 (MH "Antibiotics, Macrolide+") OR "macrolide*"

S10 "lincosamide*"

S9 (MH "Tetracycline") OR "tetracycline*"

S8 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7

S7 TX (respiratory N2 (infection* or distress))

S6 "ARDS"

S5 (MH "Respiratory Distress Syndrome")

S4 TX pneumon* or bronchopneumon* or pleuropneumon*

S3 (MH "Pneumococcal Infections+")

S2 (MH "Respiratory Tract Infections")

S1 (MH "Pneumonia+")

Web of Science

16 #14 not #15

15 TOPIC: (TOPIC: (Rat OR rats OR mouse OR mice OR rodent OR murine OR canine OR porcine OR pig OR hog OR dog OR rabbit*))

14 #13 AND #7

13 #12 OR #11 OR #10 OR #9 OR #8

12 TOPIC: ((random: OR placebo: OR double-blind:))

11 TOPIC: (((treatment OR control) NEAR/3 group*))
10 TOPIC: (((clinical OR control*) NEAR/3 trial))
9 TOPIC: ((allocat* NEAR/5 group*))
8 TOPIC: ((("systematic review" or meta-analysis)))
7 #6 AND #3
6 #5 OR #4
5 TOPIC: (((Piperacillin-tazobactam or Amoxicillin or Ampicillin or Ampicillin-sulbactam or Amoxicillin-clavulanate or Pivampicillin or Hetacillin or Bacampicillin or Metampicillin or Talampicillin or Epicillin or Carbenicillin or Ticarcillin or Temocillin or Ureidopenicillins or Azlocillin or Mezlocillin or Cyclacillin or Sulbenicillin or Aspoxicillin or Amdinocillin or Penicillin G Benzathine or Procaine benzylpenicillin or Azidocillin or Phenoxymethylpenicillin or Cloxacillin or Dicloxacillin or Flucloxacilli or Oxacillin or Meticillin or Nafcillin or Ampicillin-flucloxacillin or Sultamicillin or Ticarcillin-clavulanate or Aztreonam or Aztreonam-avibactam or Lefamulin or Cefepime or Ceftazidime or Cefotaxime or Ceftriaxone or Cefpodoxime or Cefuroxime or Ceftaroline or Ceftolozane-tazobactam or Ceftazidime-avibactam or Ceftaroline-avibactam or cefoperazone-sulbactam or Ceftobiprole medocaril or Ceftazidime-avibactam or Cefazolin or Cefacetrile or Cefadroxil or Cefalexin or Cephaloridine or Cefalotin or Cefatrizine or Cefazedone or Cefradine or Cefroxadine or Cefaclor or Cefamandole or Cefminox or Cefonicid or Ceforanide or Cefotiam or Cefprozil or Cefbuperazone or Cefuzonam or cephamycin or Cefoxitin or Cefotetan or Cefmetazole or Loracarbef or Cefixime or Cefoperazone or Cefcapene or Cefdinir or Cefditoren or Cefetamet or Cefmenoxime or Cefodizime or Cefpimizole or Cefpiramide or Cefpodoxime or Cefsulodin or Cefteram or Ceftibuten or Ceftizoxime or oxacephem or Flomoxef or Latamoxef or Moxalactam or Cefiderocol or Cefozopran or Cefpirome or Ceftobiprole or Ceftolozane or Carumonam or Nocardicin A or Imipenem or Meropenem or Ertapenem or Imipenem-relebactam or Meropenem-vaborbactam or Doripenem or Biapenem or Ertapenem or Panipenem or levofloxacin or Ciprofloxacin or Moxifloxacin or Omadacycline or Lascufloxacin or Zabofloxacin or Gatifloxacin or Grepafloxacin or Trovafloxacin or Enoxacin or Fleroxacin or Lomefloxacin or Nadifloxacin or Ofloxacin or Norfloxacin or Pefloxacin or Rufloxacin or Balofloxacin or Pazufloxacin or Sparfloxacin or Temafloxacin or Tosufloxacin or Clinafloxacin or Garenoxacin or Sitafloxacin or Prulifloxacin or Nemonoxacin or Alatrofloxacin or Gentamicin or Amikacin or Tobramycin or Plazomicin or Streptomycin or Dihydrostreptomycin or Ribostamycin or Kanamycin or Arbekacin or Netilmicin or Sisomicin or Isepamicin or Verdamicin or Eperezolid or Bekanamycin or Dibekacin or Micronomicin or Vancomycin or Linezolid or Telavancin or Oritavancin or Teicoplanin or Dalbavancin or Daptomycin or Posizolid or Radezolid or Tedizolid or Ranbezolid or Azithromycin or Clarithromycin or Erythromycin or Nafithromycin or Dirithromycin or Flurithromycin or Josamycin or Midecamycin or Miocamycin or Rokitamycin or Doxycycline or Tigecycline or Chlortetracycline or Demeclocycline or Lymecycline or Meclocycline or Metacycline or Minocycline or Penimepicycline or Rolitetracycline or Eravacycline or Clindamycin or Solithromycin or Telithromycin or Cethromycin or Lincomycin or Roxithromycin or Spiramycin or Troleandomycin or Sulfamethizole or Sulfathiazole or Sulfapyridine or Prontosil or Sulfanilamide or Sulfadiazine or Sulfalene or Sulfamethoxazole or Sulfamerazine or Sulfametrole or Trimethoprim-sulfamethoxazole or septra or cotrimoxazole or Sulfisoxazole or Sulfamethazine or Iclaprim or Brodimoprim or Metronidazole or Tinidazole or Ornidazole or Streptogramin or Quinupristin-dalfopristin or Chloramphenicol or Fusidic acid or Fosfomycin or Murepavidin or Rifampicin or Rifabutin or Rifapentine)))
4

TOPIC: (((tetracycline* or lincosamide* or macrolide* or ketolide* or Aminoglycoside* or Oxazolidinone* or Glycopeptide or Beta-lactam* or Penicillin* or Carbapenem* or Cephalosporin or Monobactam* or Antifolate* or sulfonamide* or Fluoroquinolone*)))
3 #2 OR #1
2 TOPIC: ((respiratory near/2 infection*))
1 TOPIC: (((pneumon* or bronchopneumon* or pleuropneumon*))

Supplement 3. Risk of bias assessment instruction (modified Cochrane ROB 1.0)

1. Was the allocation sequence adequately generated?

Definitely YES >>> Trial explicitly stated use of an adequate method of randomization: e.g., random number generator, random number table, coin tossing, shuffling cards or envelopes, throwing dice, drawing of lots, minimization with or without random element.

Probably YES >>> Trial is described as "randomized" without further description on the method of randomization.

Probably NO >>> Trial is described as randomized but there is substantial imbalance in baseline characteristics or key prognostic factor (severity of pneumonia) based on all randomized participants that suggest problem with randomization process, or trial described as randomized but there are substantial differences between intervention group sizes, compared with the intended allocation ratio.

Definitely NO >>> Trial used quasi-randomization: e.g., sequence generated by odd or even date of birth, date (or day) of admission or hospital or clinic record number, alteration between treatment arms.

2. Was the allocation adequately concealed?

Definitely YES >>> Trial used central allocation (including telephone, web-based), or trial is blinded and explicitly stated that drug prepared by pharmacist, or trial used sequentially numbered drug containers of identical appearance.

Probably YES >>> Trial described as double or triple blind, or trial explicitly stated that patients and healthcare providers/ investigators are blinded, or trial used sequentially numbered opaque sealed envelopes.

Probably NO >>> Trial is described as single blind or unblinded and no information or insufficient information on allocation concealment (e.g., if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque, and sealed.)

Definitely NO >>> Trial used an open random allocation schedule (e.g., a list of random numbers), assignment envelopes without appropriate safeguards (e.g., if envelopes were unsealed or non-opaque or not sequentially numbered), or trial used a quasi-randomization method.

3. Blinding: Was knowledge of the allocated interventions adequately prevented?

3.a. Were patients blinded?

Definitely YES >>> Trial explicitly stated that patients were blinded.

Probably YES >>> There is no explicit statement about blinding of patients, but trial is described as placebo-controlled trial or active control drug trial (A vs. B) and mention of "double dummy" or that medications were identical or matched, or trial is described as single-blind or double-blind or triple-blind.

Probably NO >>> There is no explicit statement about blinding of patients, but trial is described as active control drug trial (A vs. B) and no mention of "double dummy" or that medications were identical or matched.

Definitely NO >>> Trial explicitly stated that patients were not blinded, or trial is described as open-label or unblinded.

3.b. Were healthcare providers blinded?

Definitely YES >>> Trial explicitly stated that healthcare providers were blinded.

Probably YES >>> Trial explicitly stated that investigators were blinded, or there is no explicit statement about blinding of healthcare providers, but trial described as placebo-controlled trial or active control drug trial (A vs. B) and mention of "double dummy" or that medications were identical or matched, or trial is described as double-blind or triple-blind.

Probably NO >>> There is no explicit statement about blinding of healthcare providers, but trial described as active control drug trial (A vs. B) and no mention of "double dummy" or that medications were identical or matched, trial is described as single-blind.

Definitely NO >>> Trial explicitly stated that healthcare providers were not blinded, trial is described as open-label or unblinded.

3.c. Were data collectors blinded?

Definitely YES >>> Trial explicitly stated that data collectors were blinded.

Probably YES >>> Trial explicitly stated that investigators were blinded, there is no explicit statement about blinding of data collectors, but trial described as placebo-controlled trial or active control drug trial (A vs. B) and mention of "double dummy" or that medications were identical or matched, or trial is described as double-blind or triple-blind.

Probably NO >>> There is no explicit statement about blinding of data collectors, but trial described as active control drug trial (A vs. B) and no mention of "double dummy" or that medications were identical or matched, trial is described as single-blind.

Definitely NO >>> Trial explicitly stated that data collectors were not blinded, or trial is described as open-label or unblinded.

3.d. Were outcome assessors blinded?

Definitely YES >>> Trial explicitly stated that outcome assessors or adjudicators were blinded, or outcome assessors were not blinded but outcomes are objective (outcome measurement are not likely influenced by lack of blinding) [treatment failure if measured via objective criteria, mortality, need for mechanical ventilation, length of hospital stay].

Probably YES >>> There is no explicit statement about blinding of outcome assessors or adjudicators, but trial described as placebo-controlled trial or active control drug trial (A vs. B) and mention of "double dummy" or that medications were identical or matched, or trial is described as double-blind or triple-blind.

Probably NO >>> There is no explicit statement about blinding of outcome assessors or adjudicators, but trial described as active control drug trial (A vs. B) and no mention of "double dummy" or that medications were identical or matched, or trial described as single-blind.

Definitely NO >>> Trial explicitly stated that outcome assessors were not blinded, or trial is described as open-label or unblinded.

3.e. Were data analysts blinded?

Definitely YES >>> Trial explicitly stated that data analysts were blinded.

Probably NO >>> There is no explicit statement about blinding status of data analysts, or trial is described as single-blind or double-blind or triple-blind.

Definitely NO >>> Trial explicitly stated that data analysts were not blinded, or trial is described as open-label or unblinded.

4. Was loss to follow-up (missing outcome data) infrequent?

Definitely YES >>> no missing outcome data (outcome measured in all randomized participants) or loss to follow-up < 5% (including outcome data that has been imputed)

Probably YES >>> loss to follow-up 5 – 10 % (including outcome data that has been imputed) and there is no compelling reason to think that missing outcome data is related to the true outcome and there is no substantial imbalance in numbers of or reasons for missing data across intervention groups and authors provide explicit information regarding reasons for missing outcome data across groups.

Probably NO >>> loss to follow-up 5-10 % (including outcome data that has been imputed) and there is compelling reason to think that missing outcome data is related to the true outcome or there are substantial imbalances in numbers of or reasons for missing data across intervention groups or authors fail to provide explicit information regarding reasons for missing outcome data across groups.

Definitely NO >>> loss to follow-up ≥ 10 % (including outcome data that has been imputed) or authors do not specify and there are reasons to think the loss to follow-up was substantial.

5. Is the continuous outcome free of competing effect due to death?

Definitely YES >>> Results are very unlikely to have been affected by competing risk due to death. For example, the intervention arm increased the risk of death, but the duration of hospitalization is shorter in the control arm.

Probably YES >>> Results are unlikely to have been affected by competing risk due to death. For example, the intervention arm increased the risk of death, but the duration of hospitalization is slightly shorter in the control arm or there is no appreciable difference between arms.

Probably NO >>> Results are likely to have been affected by competing risk due to death. For example, the intervention arm increased the risk of death, and the duration of hospitalization is appreciably lower in the intervention arm.

Definitely NO >>> Results are very likely to have been affected by competing risk due to death. For example, the intervention arm increased the risk of death, and the duration of hospitalization is much lower in the intervention arm.

Supplement 4. Characteristics of included studies in the review

First author, year	Country	Language	Inpatient (%)	Admitted to ICU (%)	Mechanically ventilated (%)	Shock state (%)	Severe pneumonia (%)	Previous unsuccessful antibiotic treatment (%)	Mean age (years)	Percent Male (%)	Atypical pathogens (%)	Antibiotics compared and dosing [b]	Number of randomized participants	Outcomes of interest (time of measurement)
Anzueto, 2006 [1] [a]	United States	English	100	NR	0	0	5.7	NR	77.6	49.8	NR	Moxifloxacin 400 mg IV q24h vs Levofloxacin 500 mg IV q24h for a mean of 10 days	401	Treatment failure (21 days after EOT), all-cause mortality, diarrhea, nausea/vomiting, duration of hospitalization (30 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Aquino, 1994 [2] [a]	Philippines	English	100	NR	NR	NR	NR	NR	38.7	71.9	NR	Ceftriaxone 1 g IV q24h/q12h vs Ceftazidime 1 g IV q12h for 7 days	22	Treatment failure, all-cause mortality (14 days after EOT)
Aubier, 1998 [3]	Multinational	English	100	NR	0	0	0	NR	42.2	86.9	2.7	Sparfloxacin 200 mg PO q24h vs Amoxicillin 1 g PO q8h for a mean of 10.8 days	329	Treatment failure (EOT), all-cause mortality, diarrhea, nausea/vomiting, allergic reactions (21 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Aufiero, 1997 [4]	Italy	English	100	NR	NR	NR	0	NR	60	79	NR	Cefepime 1 g IV q12h vs Ceftazidime 1 g IV q12h for a mean of 7.4 days	31	Treatment failure (14 days after EOT)
Barrera, 2016 [5]	United States	English	NR	NR	NR	NR	0	NR	57.6	53	23.7	Solithromycin 800 mg PO q24h on day 1, 400 mg PO q24h on days 2–5 vs Moxifloxacin 400 mg PO q24h for 7 days	860	Treatment failure (10 days after EOT), all-cause mortality, diarrhea, nausea/vomiting (30 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Bartolon i, 1999 [6] [a]	Italy	English	100	NR	NR	NR	NR	NR	NR	67.4	NR	Meropenem 500 mg IV q8h vs imipenem1 g IV q12h for a mean of 9.8 days	144	Treatment failure, all-cause mortality, adverse events leading to discontinuation of treatment (EOT)
Bergallo, 2009 [7]	Multinational	English	100	0	0	0	0	NR	54.8	58.4	11	Tigecycline initial dose of 100 mg IV followed by 50 mg IV q12h vs Levofloxacin 500 mg IV q24h for a mean of 10 days	425	Treatment failure, all-cause mortality, diarrhea, nausea/vomiting, duration of hospitalization (23 days after EOT)
Berman, 1997 [8]	United States	English	100	14.2	33.6	NR	18.1	27.1	62.1	67.1	NR	Meropenem 500 mg IV q8h vs Ceftazidime 1 gr IV q8h for a mean of 7.3 days	295	Treatment failure (2 days after EOT), all-cause mortality, diarrhea, nausea/vomiting, allergic reactions (28 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Bertrand , 1988 [9] [a]	France	French	100	NR	NR	NR	NR	NR	63	62.6	5.2	Roxithromycin 150mg PO q12h vs Erythromycin 1g PO q12h for at least 5 days	132	Treatment failure, diarrhea, nausea/vomiting, adverse events leading to discontinuation of treatment (EOT)

Bittner, 1986 [10]	United States	English	100	NR	NR	NR	NR	NR	66.4	97.4	NR	Ceftriaxone 1 g IV q12h vs Cefamandole 1.5 g IV q6h for a mean of 8.5 days	38	Treatment failure, all-cause mortality (EOT)
Bonfitto, 1999 [11]	Italy	English	100	NR	NR	NR	NR	NR	63.5	66.2	NR	Ceftazidime 2 g IV q8h vs Cefepime 2 g IV q12h for a mean of 10 days	148	Treatment failure (EOT)
Brambilla, 1992 [12]	Multinational	English	100	NR	0	NR	0	NR	63.5	67.7	NR	Cefuroxime 750 mg IV q8h vs Amoxicillin-clavulanate 1.2 g IV q8h for at least 5 days	271	Treatment failure (EOT)
Carbon, 1992 [13]	France	English	100	NR	NR	0	0	NR	55.1	67.6	5	Temafloxacin 600 mg PO q12h vs Amoxicillin 500 mg PO q12h for a mean of 10 days	246	Treatment failure, all-cause mortality, diarrhea, nausea/vomiting, allergic reactions, acute kidney injury (9 days after EOT)
Castro, 1986 [14]	Belgium	English	100	NR	NR	NR	100	NR	66	59.5	NR	Cefadroxil 1 g PO q12h vs Cotrimoxazole 800/160 mg PO q12h for a mean of 12 days	17	Treatment failure, all-cause mortality, adverse events leading to discontinuation of treatment (EOT)
Chaudhary, 2018 [15]	India	English	100	NR	NR	NR	0	NR	46.9	30.1	NR	Ceftriaxone-sulbactam 3 g IV q24h vs Ceftriaxone 2 g IV q24h for 3-10 days	93	Treatment failure, all-cause mortality, nausea/vomiting, adverse events leading to discontinuation of treatment (EOT)
Chen, 2014 [16] [a]	China	Chinese	100	NR	100	NR	100	NR	55	NR	NR	Biapenem 300 mg IV q12h vs Meropenem 500 mg IV q8h for 7-14 days	48	Treatment failure (EOT)
Colardyn, 1996 [17] [a]	Multinational	English	100	67	59	NR	100	NR	55.5	67.2	NR	Meropenem 1g IV q8h vs Imipenem 1g IV q8h for a mean of 11.1 days	15	Treatment failure (EOT)
Correa, 2003 [18]	Multinational	English	100	NR	0	NR	0	NR	57.3	45.2	NR	Gatifloxacin 400 mg IV q24h vs Ceftriaxone 1- 2 g q24h + Erythromycin 500 mg or 1g PO q6h or Clarithromycin 500 mg PO q12h for 7 to 14 days	170	Treatment failure, all-cause mortality, diarrhea, nausea/vomiting, allergic reactions (14 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Covington, 2013 [19] [a]	Multinational	English	100	NR	NR	NR	NR	NR	NR	NR	NR	Avarofloxacin 150 mg IV q12h vs Moxifloxacin 400 mg IV q24h	32	Treatment failure, all-cause mortality (30 days after EOT)
Dal Negro, 2001 [20] [a]	Italy	English	100	NR	NR	NR	NR	NR	59.5	66.2	NR	Ceftazidime 1 g IV q12h vs Ceftriaxone 1 g IV q24h for 7 days	68	Treatment failure, all-cause mortality, adverse events leading to discontinuation of treatment (EOT)
Dall, 1986 [21]	United States	English	100	NR	NR	NR	NR	NR	59	64	1.7	Cefamandole 1g IV q6h vs Cefazolin 1g IV q6h for a mean of 6.6 days	115	Treatment failure, all-cause mortality, nausea/vomiting, adverse events leading to discontinuation of treatment (EOT)
de Celis, 2002 [22] [a]	Andorra	English	100	0	0	NR	0	NR	64	68.4	NR	Erythromycin 1g IV q6h vs Clarithromycin 500mg IV q6h	57	Treatment failure, all-cause mortality (EOT)
Ebright, 1983 [23]	United States	English	100	NR	NR	NR	NR	NR	NR	79.3	NR	Ceftizoxime 1g IV q12h vs Cefamandole 1g IV q6h for a mean of 9.5 days	29	Treatment failure, all-cause mortality (EOT)

Edelstein, 1991 [24]	United States	English	100	NR	NR	NR	NR	NR	63	98.3	NR	Cefepime 1 g IV q12h vs Ceftazidime 1 g IV q8h for a mean of 7 days	65	Treatment failure, all-cause mortality, diarrhea, allergic reactions (14 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Etemadi, 2011 [25]	Iran	English	100	NR	NR	NR	NR	NR	NR	NR	NR	Azithromycin 500 mg IV q24h vs Ceftriaxone 2 g IV q12h + Clarithromycin 500 mg PO q12h for 14 days	63	None
Fang, 2019 [26]	China	English	NR	NR	NR	NR	NR	NR	51.2	52	NR	Azithromycin 500 mg IV q24h vs Cefuroxime1.5 g IV q12h for a mean of 14 days	102	Treatment failure (EOT)
Feldman, 2001 [27]	Multinational	English	100	NR	NR	0	NR	NR	42.9	63.8	NR	Sitafloxacin 400mg IV q24h vs Imipenem 500 mg IV q8h for a mean of 8 days	69	Treatment failure, all-cause mortality (35 days after EOT)
File, 1983 [28]	United States	English	100	0	NR	NR	NR	NR	58.5	56.5	14	Cefoperazone 2 g IV q12h vs Cefamandole 1 g IV q6h for a mean of 7.6 days	73	Treatment failure, diarrhea, nausea/vomiting (21 days after EOT), adverse events leading to discontinuation of treatment (EOT)
File, 2011 [29]	Multinational	English	100	NR	NR	NR	28.9	NR	61.1	63	NR	Ceftaroline 600 mg IV q12h vs Ceftriaxone 1 g IV q24h for a mean of 6.5 days	613	Treatment failure (15 days after EOT), all-cause mortality, diarrhea, nausea/vomiting, acute kidney injury (35 days after EOT), adverse events leading to discontinuation of treatment (EOT)
File, 2016 [30]	Multinational	English	NR	NR	NR	NR	0.7	NR	60.1	51.9	12.2	Solithromycin 400 mg IV q24h vs Moxifloxacin 400 mg IV q24h for 7 days	863	Treatment failure (10 days after EOT), all-cause mortality, diarrhea, nausea/vomiting (28 days after EOT), adverse events leading to discontinuation of treatment (EOT)
File, 2019 [31]	United States	English	NR	NR	0	NR	1.3	NR	60.3	59.9	16.7	Lefamulin 150 mg IV q12h vs Moxifloxacin 400 mg IV q24h for a mean of 7 days	551	Treatment failure, diarrhea, nausea/vomiting (10 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Finch, 2002 [32]	Multinational	English	100	NR	NR	NR	51.1	NR	55.6	NR	7.2	Moxifloxacin 400 mg IV q24h vs Amoxicillin-clavulanate 1.2 g IV q8h vs Amoxicillin-clavulanate 1.2 g IV q8h + Clarithromycin 500 mg IV/PO q12h for 7-14 days	628	Treatment failure, all-cause mortality, duration of hospitalization (28 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Fink, 1994 [33]	United States	English	100	79.9	79	NR	100	NR	59.7	70.1	NR	Ciprofloxacin 400 mg IV q8h vs Imipenem 1g IV q8h for a mean of 10.3 days	88	Treatment failure (28 days after EOT)
Fogarty, 2004 [34]	United States	English	100	NR	20.7	NR	100	NR	60.7	68	21.9	Levofloxacin 500 mg IV vs Ceftriaxone 1–2 g IV/IM q24h + Erythromycin 500–1000 mg IV q6h for a mean of 10.4 days	269	Treatment failure, all-cause mortality (12 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Forbes, 1971 [35]	Zimbabwe	English	100	0	NR	NR	0	NR	34.6	70.5	NR	Penicillin G 1 MU IM q6h vs Cotrimoxazole 800/160 mg PO q12h	61	All-cause mortality, duration of hospitalization (28 days after EOT),

														adverse events leading to discontinuation of treatment (EOT)
Frank, 2002 [36]	United States	English	100	NR	NR	NR	2.5	NR	67.6	71.2	NR	Levofloxacin 500 mg PO or IV q24hr vs Ceftriaxone 1g q24hr + Azithromycin 500 mg IV q24hr for up to 10 days	236	Treatment failure, all-cause mortality, diarrhea, nausea/vomiting, allergic reactions (7 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Gaillat, 1994 [37]	France	English	100	NR	24	NR	100	NR	62.8	NR	1.7	Penicillin G 3 MU IM q6h + Ofloxacin 200 mg IV q12h vs Amoxicillin-clavulanate 1g IV q6h + Erythromycin 1 g IV q8h for a mean of 14 days	117	Treatment failure, all-cause mortality, diarrhea, nausea/vomiting, allergic reactions (14 days after EOT)
Garcìa-Contreras, 2000 [38] [a]	Mexico	Spanish	100	NR	0	NR	8	11.8	57.5	51.8	NR	Ceftriaxone 1 g IV q24h vs Cefotaxime 1 g IV q8h for 7 days	110	Treatment failure, all-cause mortality, duration of hospitalization (EOT)
Geckler, 1984 [39] [a]	United States	English	100	NR	NR	NR	4	NR	65.5	60	NR	Cefonicid 1 g IV q24h vs Cefamandole 1 g IV q6h for a mean of 7 days	108	Treatment failure, all-cause mortality, diarrhea (EOT)
Geerts, 1971 [40]	Belgium	French	100	NR	NR	NR	NR	NR	NR	66	NR	Cotrimoxazole 400/80 mg PO q4-6h vs Tetracycline 150 mg PO q4-6h for up to 15 days	47	Treatment failure, nausea/vomiting, allergic reactions (15 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Genne, 1997 [41]	Switzerland	English	100	NR	NR	NR	NR	NR	70	61.6	14.3	Clarithromycin 500 mg IV q12h vs Amoxicillin-clavulanate 1.2 g IV q6h for at least 10 days	112	Treatment failure, diarrhea, nausea/vomiting, allergic reactions, acute kidney injury (21 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Gotfried, 1997 [42] [a]	United States	English	100	NR	NR	NR	33.3	NR	56.6	50	20	Cefuroxime 750 mg IV q8h + Clarithromycin 500 mg PO q12h vs Cefuroxime 750 mg IV q8h + Erythromycin 500mg IV q6h for at least 5 days	20	Treatment failure, all-cause mortality, duration of hospitalization, diarrhea, nausea/vomiting (14 days after EOT)
Grieco, 1982 [43]	United States	English	100	NR	NR	NR	NR	NR	64.2	66.7	5.5	Ceftizoxime 1 g IM/IV q12h vs Cefamandole 1 g IM/IV q6h for a mean of 8 days	16	Treatment failure, diarrhea (5 days after EOT)
Grossman, 1999 [44]	Canada	English	100	NR	NR	NR	NR	NR	77.8	54.7	NR	Cefepime 2g IV q12h vs Ceftriaxone 1g IV q12h for a mean of 6.2 days	151	Treatment failure (EOT), all-cause mortality (14 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Hirata-Dulas, 1991 [45]	United States	English	100	NR	NR	NR	NR	NR	79.4	62	NR	Ciprofloxacin 200mg IV q12h vs Ceftriaxone 2g IV q24h for 14 days	50	Treatment failure, all-cause mortality, diarrhea, duration of hospitalization, adverse events leading to discontinuation of treatment (EOT)
Ho, 1997 [46]	Hong Kong	English	100	NR	30	13	30	NR	68.4	63.3	3.3	Ceftazidime 1 g IV q8h vs Imipenem 500 mg IV q8h for 7 days	60	Treatment failure, all-cause mortality, adverse events leading to discontinuation of treatment (EOT)

Hongyun, 2007 [47]	China	Chinese	100	NR	0	NR	NR	4.5	NR	NR	19.6	Gatifloxacin 400mg IV q24h vs Cefuroxime 2 g IV q12h for 14 days	107	Treatment failure (14 days after EOT)
Horcajada, 2019 [48] [a]	Multinational	English	100	NR	NR	NR	1.4	NR	60	58.7	NR	Delafloxacin 300 mg IV q12h vs Moxifloxacin 400 mg IV q24 h for a mean day of 9 days	859	Treatment failure, all-cause mortality, diarrhea, nausea/vomiting, allergic reactions, acute kidney injury, adverse events leading to discontinuation of treatment (EOT)
Huang, 2023 [49]	China	English	NR	NR	NR	NR	NR	NR	NR	NR	NR	Lefamulin 150 mg IV q12h vs Moxifloxacin 400 mg IV q24h	124	Treatment failure (10 days after EOT)
Huys, 1972 [50]	Rwanda	French	100	NR	NR	NR	NR	NR	NR	100	4.3	Cotrimoxazole 800/160 mg PO q8h vs Tetracycline 300mg PO q8h for 6 days	38	All-cause mortality, nausea/vomiting, adverse events leading to discontinuation of treatment (EOT)
Ito, 2010 [51]	Japan	English	100	NR	NR	NR	32.5	NR	84.8	51.5	9.8	Piperacillin-tazobactam 5 g IV q12h + Erythromycin 500 mg IV q12h vs Imipenem 1 g IV q12h + Erythromycin 500 mg IV q12h for a mean of 10.8 days	163	Treatment failure, all-cause mortality, diarrhea, allergic reactions, acute kidney injury (21 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Izadi, 2018 [52]	Iran	English	100	NR	0	NR	0	0	65.9	40.7	NR	Levofloxacin 750 mg PO q24h vs Ceftriaxone 1 g IV q12h + Azithromycin 250 mg PO q24h for 7-10 days	150	Treatment failure, all-cause mortality, allergic reactions (10 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Jardim, 2003 [53]	Multinational	Spanish	52.8	NR	NR	NR	NR	0	50.1	51.2	17.1	Moxifloxacin 400mg PO q24h vs Amoxicillin 1 g PO q8h for 10 days	84	Treatment failure (28 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Kalbermatte, 2000 [54]	Argentina	Spanish	100	NR	0	NR	0	NR	60.3	48.8	NR	Amoxicillin-clavulanate 1.2 g IV q8h vs Ceftriaxone 1 g IV q12h vs Levofloxacin 500 mg PO q24h for 7-10 days	84	Treatment failure, all-cause mortality (3 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Keeton, 1983 [55]	South Africa	English	NR	NR	NR	NR	NR	NR	38	NR	NR	Cefamandole 1.5 g IV q8h vs Ceftazidime 1g IV q8h for a minimum of 5 days	59	Treatment failure, all-cause mortality (EOT)
Kouno, 2003 [56]	Japan	Japanese	40.6	NR	NR	NR	0	NR	NR	54.6	3.8	Telithromycin 600 mg PO q24h vs Levofloxacin 100 mg PO q8h for 7 days	250	Treatment failure (7 days after EOT)
Kouno, 2011 [57]	Japan	Japanese	100	NR	NR	NR	8.5	NR	58.7	59.5	9.8	Levofloxacin 500 mg IV q24h vs Ceftriaxone1 g IV q12h for 7-14 days	260	Treatment failure, diarrhea, nausea/vomiting (EOT)
Kuzman, 2005 [58]	Multinational	English	100	NR	NR	NR	0	NR	54.4	66.7	37.2	Azithromycin 500 mg IV q24h for a mean of 6.2 days vs Cefuroxime 1.5 g IV q8h + Doxycycline 100 mg PO q12h for a mean of 10 days	180	Treatment failure (31 days after EOT)
LeFrock, 1982 [59]	United States	English	100	NR	NR	NR	NR	NR	48.2	53.2	NR	Ceftizoxime 1-2 g IV q8h vs Cefamandole 1-2 g IV q6h for a mean of 7.2 days	53	Treatment failure, allergic reactions, adverse events leading to discontinuation of treatment (EOT)

Leophonte, 1993 [60]	Multinational	English	100	NR	5.3	NR	5.3	NR	69.5	80.9	NR	Cefepime 1 g IV q12h vs Ceftazidime 1 g IV q8h for a mean of 8.6 days	99	Treatment failure, all-cause mortality (14 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Leophonte, 2004 [61]	Multinational	English	93.9	NR	NR	NR	16.3	NR	54.3	63.4	19.8	Gemifloxacin 320 mg PO q24h for 7 days vs Amoxicillin-clavulanate 1.125 g PO q8h for 10 days	324	Treatment failure, all-cause mortality, diarrhea, nausea/vomiting, allergic reactions (20 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Leroy, 2005 [62]	Multinational	English	100	100	51	0	100	NR	59.5	68	4.9	Levofloxacin 500 mg IV q12h vs Cefotaxime 1g IV q8h + Ofloxacin 200 mg IV q12h for a mean of 11.3 days	398	Treatment failure, all-cause mortality, allergic reactions (45 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Leuenberger, 1983 [63]	Switzerland	English	100	NR	NR	NR	85.3	NR	66.3	73.5	NR	Cefaclor 500 mg PO q8h vs Amoxicillin 750 mg PO q8h for 7 days	34	Treatment failure, diarrhea, allergic reactions (EOT)
Li, 2024 [64] [a]	China	English	100	NR	NR	NR	0	NR	57.3	62.3	NR	Nemonoxacin 500 mg IV q24h vs Levofloxacin 500 mg IV q24h for a mean of 9.1 days	525	Treatment failure, all-cause mortality, nausea/vomiting (14 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Lin, 2007 [65]	China	Chinese	100	NR	0	0	NR	NR	43.5	52.2	29.1	Levofloxacin 300 mg IV q24h vs Cefoperazone-sulbactam 4g IV q24h for 5-14 days	52	Treatment failure (EOT)
Lin, 2007 [66]	Taiwan	English	100	NR	NR	NR	0.4	NR	68.1	73.3	NR	Levofloxacin 500 mg IV q24h vs Amoxicillin-clavulanate 600 mg IV q8h + Clarithromycin 500 mg PO q12h for 7-14 days	50	Treatment failure (7 days after EOT)
Lin, 2007 [67] [a]	China	Chinese	NR	0	NR	NR	NR	NR	NR	NR	2	Moxifloxacin 400mg IV q24h vs Levofloxacin 400mg IV q24h for 7 days	65	Treatment failure, nausea/vomiting, allergic reactions (7 days after EOT)
Lode, 2002 [68]	Multinational	English	100	NR	NR	NR	0.9	NR	58.9	55.3	NR	Gemifloxacin 320 mg PO q24h vs Ceftriaxone 2 g IV q24h + Macrolide (clarithromycin or azithromycin or erythromycin or roxithromycin or spiramycin) for a mean of 10.3 days	345	Treatment failure, all-cause mortality, diarrhea, allergic reactions, duration of hospitalization (30 days after EOT), adverse events leading to discontinuation of treatment (EOT)
López-Véjar, 2013 [69]	Mexico	Spanish	100	NR	NR	NR	8.3	NR	61.5	56.9	25.8	Ceftriaxone 1 g IV q12h + Clarithromycin 500 mg PO q12h vs Levofloxacin 750 mg IV/PO q24h for 7 days	72	Treatment failure, all-cause mortality, duration of hospitalization (15 days after EOT)
Low, 2011 [70]	Multinational	English	100	NR	8.3	NR	31.9	NR	61.3	62.4	NR	Ceftaroline 600 mg IV q12h vs Ceftriaxone 1 g IV q24h for a mean of 6.5 days	622	Treatment failure, all-cause mortality, diarrhea, nausea/vomiting, acute kidney injury (15 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Macfarlane, 1983 [71]	United Kingdom	English	100	0	NR	NR	NR	NR	50.3	70.3	15.9	Ampicillin 500 mg IV q6h vs Erythromycin 300 mg IV q6h for 7 days	91	All-cause mortality, allergic reactions (EOT)

McCabe, 1993 [72]	Multinational	English	67	NR	NR	NR	0	NR	48	62.8	18.7	Ceftibuten 200 mg PO q12h vs Cefaclor 500 mg PO q8h for 5-14 days	187	Treatment failure, all-cause mortality, diarrhea, nausea/vomiting, allergic reactions (14 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Miyazaki, 2019 [73] [a]	Japan	English	71	NR	NR	NR	6.7	NR	77	58.8	NR	Sitafloxacin 100 mg PO q24h vs Garenoxacin 400 mg PO q24h for a mean of 7.5 days	120	Treatment failure (10 days after EOT)
Moola, 1999 [74]	Multinational	English	57	NR	NR	NR	7	NR	48.5	59.5	NR	Grepafloxacin 600 mg PO q24h vs Clarithromycin 500 mg PO q12h for 10 days	278	Treatment failure, all-cause mortality, diarrhea, nausea/vomiting (35 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Morganroth, 2005 [75] [a]	United States	English	100	NR	NR	NR	6.6	NR	77.8	51.3	11.3	Moxifloxacin 400 mg IV q24h vs Levofloxacin 500 mg IV q24h for a mean of 9 days	401	All-cause mortality (EOT)
Mouton, 1995 [76]	Multinational	English	100	NR	0	0	42.2	NR	61	70.5	NR	Meropenem 1 g IV q8h vs Ceftazidime 2 g IV q8h + Amikacin 15 mg/kg/day IV for a mean of 8.5 days	89	Treatment failure (EOT)
Ni, 2012 [77]	China	Chinese	100	NR	44.7	NR	100	NR	77	55.4	NR	Ertapenem 1 g IV q24h vs Ceftizoxime 3-4.5 g IV q12h for 10-14 days	83	Treatment failure, all-cause mortality, duration of hospitalization (14 days after EOT)
Nicholson, 2012 [78]	Multinational	English	100	NR	NR	NR	1.7	0	54.5	57.4	NR	Ceftobiprole 500 mg IV q8h vs Ceftriaxone 2 g IV q24h for a mean of 9.3 days	638	Treatment failure (14 days after EOT), all-cause mortality, nausea/vomiting (30 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Nicolle, 1996 [79]	Canada	English	NR	NR	NR	NR	NR	0	82.4	48.6	6.9	Ampicillin 1g IV q8h vs Ceftriaxone 1g IV q24h for at least 7 days	37	Treatment failure, all-cause mortality (EOT)
Norbby, 1998 [80]	Multinational	English	100	NR	NR	NR	20	NR	65	65	NR	Levofloxacin 500 mg IV q12h for vs Ceftriaxone 4 g IV q24h for a mean of 8.5 days	625	Treatment failure, all-cause mortality, diarrhea, duration of hospitalization (21 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Oh, 1996 [81]	Singapore	English	100	NR	NR	NR	0	NR	41.3	66.6	NR	Cefuroxime 750 mg IV q8h vs Amoxicillin-clavulanate 1.2 g IV q8h for a mean of 7 days	47	Treatment failure, nausea/vomiting, allergic reactions (14 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Oi, 2020 [82]	Japan	English	100	0	NR	NR	28.9	NR	85.4	51.3	10.4	Cefepime 1 g IV q8h vs Meropenem 500 mg IV q8h for a mean of 10.5 days	101	Treatment failure, all-cause mortality, diarrhea, allergic reactions (7 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Ortiz-Ruiz, 2002 [83]	Multinational	English	100	NR	0	0	3.2	NR	56.6	57	NR	Ertapenem 1g IV q24h vs Ceftriaxone 1g IV q24h for a mean of 12 days	498	Treatment failure, diarrhea, nausea/vomiting (14 days after EOT), adverse events leading to discontinuation of treatment (EOT)

Ortqvist, 1996 [84]	Multinational	English	75	NR	NR	NR	0	NR	47	43	26.1	Sparfloxacin 400 mg PO day 1, then 200 mg PO q24h vs Roxithromycin 150mg PO q12h for a mean of 10.1 days	304	Treatment failure, all-cause mortality, diarrhea, nausea/vomiting, allergic reactions (42 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Paladino, 2007 [85]	United States	English	100	0	0	NR	0	NR	86	75	NR	Cefepime 1 g IM q24h vs Ceftriaxone 1 g IM q24h for 10 - 14 days	61	Treatment failure, all-cause mortality (14 days after EOT)
Pariente, 1988 [86] [a]	France	French	100	NR	NR	NR	18.2	NR	61.6	77.9	NR	Cefuroxime 500mg PO q12h vs Cefaclor 500mg PO q8h for 7-10 days	77	Treatment failure, all-cause mortality, nausea/vomiting (EOT)
Peng, 2006 [87] [a]	China	Chinese	NR	NR	NR	NR	NR	NR	37.5	65.6	NR	Moxifloxacin 400mg IV q24h vs Levofloxacin 200 mg IV q12h for 7-14 days	32	Treatment failure (7 days after EOT)
Pertel, 2008 [88]	Multinational	English	100	NR	NR	0	0.1	NR	55.2	58.5	NR	Daptomycin 4 mg/kg IV q24h + Aztreonam vs Ceftriaxone 2g IV q24h for 5-14 days	936	Treatment failure, all-cause mortality, diarrhea, nausea/vomiting (14 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Peterma nn, 2001 [89]	Multinational	English	100	NR	NR	NR	18.6	NR	58	65.8	5.1	Clinafloxacin 200 mg IV q24h vs Ceftriaxone 2 g IV q24h for a mean of 9.5 days	527	Treatment failure (9 days after EOT), all-cause mortality, diarrhea, nausea/vomiting, allergic reactions (21 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Peterson, 1988 [90]	United States	English	100	0	0	NR	0	NR	81.1	48.3	NR	Ciprofloxacin 750 mg PO q12h vs Cefamandole 1 g IM q6h for 14 days	60	Treatment failure, all-cause mortality, allergic reactions, duration of hospitalization (42 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Phillips, 1993 [91] [a]	United States	English	100	0	0	NR	0	NR	80.6	86.5	NR	Cefoperazone 1g IM q12h vs Ceftriaxone 1g IM q24h for a mean of 10 days	104	Treatment failure, all-cause mortality, diarrhea (EOT)
Plouffe, 2000 [92]	United States	English	100	NR	0	0	0.7	NR	62.5	33	16.4	Azithromycin 500 mg IV q24h for a mean of 8.6 days vs Cefuroxime 750 mg q8h + Erythromycin 500-1000 mg PO/IV q6h for a mean of 10.3 days	403	Treatment failure, all-cause mortality, diarrhea, nausea/vomiting (42 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Poirier, 1991 [93] [a]	France	English	100	0	NR	NR	7.7	NR	54.8	70.8	NR	Clarithromycin 250 mg PO q12h vs Roxithromycin 150mg PO q12h for up to 14 days	77	Treatment failure, acute kidney injury (2 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Poirier, 1999 [94]	France	French	100	NR	NR	0	0	NR	52.5	NR	6.1	Pristinamycin 1g PO q12h vs Amoxicillin-clavulanate 500 mg PO q6h for 10 to 14 days	180	Treatment failure (33 days after EOT)
Portier, 1996 [95]	France	English	100	0	0	NR	0	17.9	60	63	NR	Sparfloxacin 400 mg PO on the first day, followed by a 200 mg PO q24h vs Amoxycillin 1 g IV	213	All-cause mortality (20 days after EOT)

											q8h + Ofloxacin 200 mg PO q12h for a mean of 10 days		
Portier, 2005 [96]	France	English	100	0	NR	0	0	62	60.9	72.5	9	Moxifloxacin 400 mg PO q24h vs Amoxicillin-clavulanate 1.125 g PO q8h + Roxithromycin 150 mg PO q12h for 10 days	349	Treatment failure, all-cause mortality, diarrhea, nausea/vomiting, allergic reactions (28 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Rahlwes, 1988 [97]	Germany	English	100	0	NR	NR	0	NR	53.5	54.6	NR	Amoxycillin 750mg PO q8h vs Roxithromycin 150mg PO q12h for a mean of 9.4	33	Treatment failure, all-cause mortality, diarrhea, allergic reactions, adverse events leading to discontinuation of treatment (EOT)
Rizzato, 1992 [98]	Italy	English	100	NR	NR	NR	NR	30	69.4	61.9	NR	Ticarcillin-clavulanate 1.2 g IM q8h vs Piperacillin 2g IM q8h for a mean of 9.1 days	15	Treatment failure (EOT)
Rizzato, 1993 [99] [a]	Italy	English	100	NR	NR	NR	NR	NR	73.2	62.5	NR	Meropenem 500 mg IV q12h vs Imipenem 500 mg IV q12h for 5 to 14 days	18	Treatment failure (EOT)
Rizzato, 1995 [100] [a]	Italy	English	100	NR	NR	NR	0	NR	46	72.5	45	Azithromycin 500 mg PO q24h for 3 days vs Clarithromycin 250 mg PO q12h for at least 8 days	40	Treatment failure, duration of hospitalization (EOT)
Rizzato, 1997 [101]	Italy	English	100	NR	NR	NR	100	NR	68.5	65.8	NR	Teicoplanin 40mg IV q24h + Ciprofloxacin 50mg PO q12h vs Ceftriaxone 2 g IV q24h for a mean of 10 days	240	Treatment failure, all-cause mortality, allergic reactions, acute kidney injury, duration of hospitalization, adverse events leading to discontinuation of treatment (EOT)
Romanelli, 2002 [102]	Italy	English	100	0	NR	NR	100	NR	75.8	43.1	NR	Meropemem 500 mg IV q8h vs Imipenem 500 mg q8h vs Clarithromycin 500 mg IV q12h + Ceftriaxone 1 g q12h vs Clarithromycin 500 mg IV q12h + Amikacin 250 mg IV q12h for a mean of 10 days	152	Treatment failure, all-cause mortality, diarrhea, nausea/vomiting, allergic reactions, duration of hospitalization (28 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Roson, 2001 [103]	Spain	English	100	7.4	5.3	3.2	5.3	NR	67.4	71.5	8.2	Amoxicillin-clavulanate 2.2 g IV q8h vs Ceftriaxone 1 g IV q24h for a mean of 10.5 days	378	Treatment failure, all-cause mortality, need for mechanical ventilation, duration of hospitalization (30 days after EOT)
Rossoff, 1995 [104]	United States	English	100	NR	NR	NR	NR	NR	66	44.6	NR	Ampicillin-sulbactam 3 g IV q6h vs Cefuroxime 1.5 g IV q8h for a mean of 7 days	103	Treatment failure, all-cause mortality, nausea/vomiting, allergic reactions, duration of hospitalization (14 days after EOT)
Samsonov, 2023 [105] [a]	Russia	English	100	0	NR	NR	0	NR	42.6	60.6	NR	Nemonoxacin 500 mg IV q24h vs Levofloxacin 500 mg IV q24h	342	Treatment failure, all-cause mortality, diarrhea (23 days after EOT), adverse events leading to discontinuation of treatment (EOT)
San Pedro, 2002 [106]	Multinational	English	100	NR	NR	NR	NR	NR	54.7	58.5	NR	Linezolid 600 mg IV q12h + Aztreonam 1–2 g IV q8h vs Ceftriaxone 1 g IV q12h for a mean of 11 days	747	Treatment failure, all-cause mortality, diarrhea, nausea/vomiting (28 days after EOT), adverse events leading to discontinuation of treatment (EOT)

Seki, 2009 [107]	Japan	English	100	NR	NR	NR	4.9	NR	70.4	59.8	NR	Piperacillin 2 g IV q12h vs Ampicillin-sulbactam 3 g IV q12 for a mean of 8.3 days	102	Treatment failure (EOT)
Shao, 2008 [108]	China	Chinese	NR	NR	NR	NR	1.1	NR	49.5	53.7	NR	Levofloxacin 500mg IV q24h vs Cefuroxime 1.5 g IV q12h + Azithromycin 500mg PO q8h for a mean of 10.5 days	398	Treatment failure, diarrhea, nausea/vomiting, allergic reactions, duration of hospitalization (14 days after EOT)
Shlaes, 1994 [109] [a]	Multinational	English	100	NR	NR	0	0	NR	57.1	78.3	NR	Piperacillin-tazobactam 3.375 g IV q6h vs Ticarcillin-clavulanate 3.1 g IV q6h for a mean of 7.3 days	299	Treatment failure, all-cause mortality, diarrhea (14 days after EOT)
Speich, 1998 [110]	Switzerland	English	100	NR	NR	0	100	NR	64.6	NR	NR	Piperacillin-tazobactam 4.5 g IV q8h vs Amoxicillin-clavulanate 2.2 g IV q8h + Netilmicin or Gentamicin single dose of 3-6 mg/kg IV for a mean of 10.1 days	89	Treatment failure, all-cause mortality, acute kidney injury (14 days after EOT)
Stein, 2011 [111] [a]	United States	English	100	0	NR	NR	0	NR	63	60	NR	Levofloxacin 750 mg IV q24h vs Moxifloxacin 400 mg IV q24h	10	None
Stets, 2019 [112]	Multinational	English	99.5	0	NR	0	13.1	NR	62	55.2	28.9	Omadacycline 100 mg IV q12h for two doses, then 100 mg IV q24h vs Moxifloxacin 400 mg IV q24h for a mean of 9.6 days	774	Treatment failure (10 days after EOT), all-cause mortality, diarrhea, nausea/vomiting, allergic reactions, acute kidney injury (30 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Stille, 2000 [113]	Germany	German	100	10.9	0	NR	0	43.5	61.9	57.6	NR	Ceftriaxone 1 g IV q24h vs Cefuroxime 1.5g IV q8h for 2-5 days	92	Treatment failure (10 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Sturm, 1998 [114]	Multinational	English	100	NR	NR	NR	100	NR	NR	NR	NR	Ertapenem 1-2 g IV q24h vs Ceftriaxone 2g IV q24h	57	Treatment failure (14 days after EOT)
Sun, 2014 [115]	China	English	NR	0	NR	0	0	23.1	NR	90.9	16.8	Moxifloxacin 400 mg IV q24h vs Moxifloxacin 400 mg IV q24h + Metronidazole 500 mg IV q8h for 2 to 4 weeks	37	Treatment failure (14 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Tanaseanu, 2009 [116]	Multinational	English	100	NR	NR	NR	0.9	NR	49.8	61.7	NR	Tigecycline100 mg IV, followed by 50 mg IV q12h vs Levofloxacin 500 mg IV q24h/q12h for 7-14 days	434	Treatment failure, all-cause mortality, diarrhea, nausea/vomiting (21 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Thadepalli, 1991 [117]	United States	English	100	NR	0	0	100	NR	45.3	72.7	3.9	Enoxacin 400 mg IV q12h vs Ceftazidime2 g IV q8h for a mean of 11 days	33	Treatment failure, adverse events leading to discontinuation of treatment (EOT)
Torres, 2008 [118]	Multinational	English	100	9.7	NR	NR	11.3	13.9	65.4	62.4	11.7	Moxifloxacin 400 mg PO q24h vs Ceftriaxone 2g IV q24h + Levofloxacin 500 mg IV q24h for a mean of 11.5 days	738	Treatment failure, all-cause mortality, diarrhea, nausea/vomiting (14 days after EOT), adverse events leading to discontinuation of treatment (EOT)

Tremolieres, 1998 [119]	Multinational	English	75	NR	NR	NR	NR	NR	52.3	65.5	13.2	Trovafloxacin 200 mg PO q24h vs Amoxicillin 1 g PO q8h for a mean of 10 days	342	Treatment failure, all-cause mortality (25 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Vergis, 2000 [120]	United States	English	100	NR	NR	NR	NR	NR	NR	NR	28.4	Azithromycin 500 mg IV q24h vs Cefuroxime 750 mg IV q8h + Erythromycin 500-1000 mg IV/PO q6h for a mean of 9 days	169	Treatment failure, all-cause mortality (42 days after EOT)
Vetter, 1997 [121]	Multinational	English	100	NR	NR	NR	NR	NR	NR	NR	NR	Clarithromycin 500 mg IV q12h vs Erythromycin 1g IV q8h + Cefuroxime 1.5 g q8h for a mean of 9.6 days	235	Treatment failure, all-cause mortality, diarrhea, nausea/vomiting (42 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Vetter, 2002 [122]	Multinational	English	100	NR	NR	NR	6.3	NR	57.7	61.2	7.7	Ertapenem 1 g IV q24h vs Ceftriaxone 1g IV q24h for a mean of 11 days	364	Treatment failure, all-cause mortality, diarrhea, nausea/vomiting, allergic reactions (14 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Vogel, 1991 [123]	Germany	English	100	NR	NR	0	18	NR	61.6	61	NR	Temafloxacin 600 mg PO q12h vs Cefotaxime 2 g IV q8h for 10 days	100	Treatment failure, all-cause mortality, diarrhea, allergic reactions (10 days after EOT)
Wallace, 1981 [124]	United States	English	100	0	NR	NR	0	NR	43	74.1	NR	Ceforanide 500 mg IV q12h vs Cefazolin 1 g IV q8h for a mean of 6 days	54	Treatment failure (14 days after EOT)
Wallace, 1982 [125] [a]	United States	English	100	NR	NR	NR	NR	NR	37.9	60.6	NR	Cefonicid 1g IV/IM q24h vs cefamandole 1g IV q6h for a mean of 5.8 days	33	Treatment failure, all-cause mortality, acute kidney injury (EOT)
Wang, 2015 [126] [a]	China	Chinese	100	NR	NR	NR	NR	NR	72	58.7	NR	Cefodizime 1 g IV q12h vs Ceftriaxone 1 g IV q12h for 7 days	63	None
Watanabe, 2010 [127]	Japan	Japanese	100	NR	NR	NR	6.1	NR	61.1	75.6	NR	Piperacillin-tazobactam 4.5 g IV q8h vs Ceftazidime 2 g q12h for 3-14 days	279	Treatment failure, diarrhea, nausea/vomiting, acute kidney injury (7 days after EOT)
Weber, 1987 [128]	United States	English	100	NR	0	NR	0	NR	68.6	65.5	NR	Ampicillin 2 g IV q6h vs Cefamandole 2 g IV q6h for 10 days	107	Treatment failure, all-cause mortality, diarrhea, allergic reactions, duration of hospitalization, adverse events leading to discontinuation of treatment (EOT)
Williams, 1994 [129]	United States	English	100	NR	NR	NR	41.3	NR	73	52	NR	Ampicillin-sulbactam 1.5-3 g IV q6h vs Cefamandole 1-2 g IV q6h for a mean of 5.3 days	75	Treatment failure, all-cause mortality, diarrhea, nausea/vomiting, allergic reactions (14 days after EOT)
Wolff, 1998 [130]	Multinational	English	100	100	68.8	NR	100	NR	56.6	69	NR	Cefpirome 2 g IV q12h vs Ceftazidime 2 g IV q8h for a mean of 8.5 days	102	Treatment failure (2 days after EOT)
Xu, 2006 [131]	China	English	100	NR	0	NR	0	NR	NR	NR	NR	Moxifloxacin 400 mg IV q24h vs Cefoperazone 2 g IV q12h + Azithromycin 500 mg IV q24h for 7-14 d	40	Treatment failure, nausea/vomiting (EOT)

Yadegarynia, 2022 [132]	Iran	English	100	NR	NR	NR	0	NR	50.1	53	NR	Ceftriaxone 1g IV q24h + Azithromycin 500 mg PO q24h vs Levofloxacin 750 mg PO q24h for 5-7 days	160	Duration of hospitalization, nausea/vomiting, allergic reactions (EOT)
Yamamoto, 2013 [133]	Japan	English	100	NR	NR	NR	0	NR	78.3	53.5	NR	Piperacillin-tazobactam 4.5 g IV q8h vs Meropenem 500 mg IV q8h for a mean of 9.5 days	95	Treatment failure, all-cause mortality, diarrhea (7 days after EOT)
Yanagihara, 2006 [134]	Japan	English	100	NR	NR	NR	7.5	NR	78.4	71.6	6	Ampicillin-sulbactam 3 g IV q12h vs Imipenem 0.5 g IV twice daily for 7-14 days	71	Treatment failure (EOT)
Yang, 2007 [135] [a]	China	Chinese	100	NR	NR	NR	NR	NR	46	42.2	NR	Biapenem 300 mg IV q12h vs Meropenem 500 mg IV q12h for a mean of 9 days	127	Treatment failure (14 days after EOT)
Yang, 2009 [136]	China	Chinese	100	NR	NR	NR	NR	NR	73.1	53	NR	Moxifloxacin 400mg IV q24h vs Ceftriaxone 2 g q24h + Azithromycin 500 mg q24h for 7 days	100	Treatment failure (EOT)
Yang, 2009 [137] [a]	China	Chinese	NR	NR	NR	NR	NR	NR	46.1	52.5	NR	Moxifloxacin 400mg IV q24h vs Levofloxacin 200 mg IV q12h for 7-14 days	80	Treatment failure, nausea/vomiting, allergic reactions (7 days after EOT)
Yang, 2020 [138]	China	English	100	NR	NR	NR	NR	NR	60	50.2	NR	Imipenem 500 mg IV q6h vs Moxifloxacin 400 mg IV q24h vs Imipenem 500 mg IV q6h + Azithromycin 250 mg q12h	213	Duration of hospitalization (EOT)
Yaqub, 2005 [139]	Pakistan	English	100	0	NR	NR	0	NR	53.9	58	NR	Amoxicillin-clavulanate 1.2 g IV q8h vs Ceftriaxone 1-2 g IV q24h for a mean of 8.2 days	50	Treatment failure, all-cause mortality, diarrhea, allergic reactions, duration of hospitalization (30 days after EOT)
Zervos, 1998 [140]	United States	English	100	NR	NR	NR	3.5	NR	57.6	68.7	NR	Cefepime 2 g IV q12h vs Ceftriaxone 1 g IV q12h for a mean of 6.5 days	115	Treatment failure, all-cause mortality (EOT)
Zervos, 2004 [141]	Multinational	English	100	NR	NR	NR	9.4	NR	71.5	56.1	30.1	Ceftriaxone 1 g IV q24h + Azithromycin 500 mg IV q24h vs Levofloxacin 500 mg IV q24 h for 7-14 days	212	Treatment failure, all-cause mortality, duration of hospitalization (14 days after EOT), adverse events leading to discontinuation of treatment (EOT)
Zhong, 2014 [142]	Multinational	English	100	0	NR	NR	0	NR	66	70.5	16.3	Ceftaroline 600 mg IV q12h vs Ceftriaxone 2g IV q24h for a mean of 6.5 days	771	Treatment failure (15 days after EOT), all-cause mortality, diarrhea, nausea/vomiting, allergic reaction (35 days after EOT)
Zuck, 1990 [143] [a]	France	English	100	NR	NR	NR	100	NR	65.3	75	NR	Cefpodoxime 200 mg PO q12h vs Ceftriaxone 1 g IM q24h for a mean of 9.5 days	96	Treatment failure, all-cause mortality, diarrhea, allergic reactions (20 days after EOT), adverse events leading to discontinuation of treatment (EOT)

EOT: end of therapy; IV: intravenous; ICU: intensive care unit; NR: not reported; PO: orally

[a] The trial was excluded from the primary network meta-analysis because both arms have been classified within the same antibiotic class (intervention node).

[b] Duration of antibiotic therapy is the total duration of intravenous and oral treatment; patients who initially received intravenous antibiotics were switched to oral regimens if clinical signs and symptoms of pneumonia had improve

Supplement 5. List of antibiotics within each class (treatment node) included in the network meta-analysis

Respiratory fluoroquinolones alone	Levofloxacin Moxifloxacin Gemifloxacin Sitafloxacin Gatifloxacin Sparfloxacin Grepafloxacin Temafloxacin Trovafloxacin Clinafloxacin
Penicillins alone	Amoxicillin Ampicillin Piperacillin Penicillin G
β-Lactam/β-lactamase inhibitors alone	Amoxicillin-clavulanate Ampicillin-sulbactam Piperacillin-tazobactam Ticarcillin-clavulanate
1st generation cephalosporins alone	Cefadroxil Cefazolin
2nd generation cephalosporins alone	Cefuroxime Cefamandole Cefaclor Ceforanide
3rd generation cephalosporins alone	Ceftriaxone Ceftazidime Ceftizoxime Cefoperazone Cefotaxime Ceftibuten
3rd generation cephalosporin/β-lactamase inhibitors alone	Cefoperazone-sulbactam Ceftriaxone-sulbactam
4th generation cephalosporins alone	Cefepime Cefpirome
5th generation cephalosporins alone	Ceftaroline Ceftobiprole
Macrolides alone	Azithromycin Clarithromycin Telithromycin Erythromycin Roxithromycin Solithromycin
Tetracyclines alone	Omadacycline Tetracycline
Lefamulin	Lefamulin

Carbapenems alone	Meropenem Imipenem Ertapenem
Other fluoroquinolones alone	Ciprofloxacin Enoxacin
Tigecycline	Tigecycline
Cotrimoxazole	Cotrimoxazole
Pristinamycin	Pristinamycin
A penicillin plus an other fluoroquinolone	Penicillin G + Ofloxacin Amoxycillin + Ofloxacin
A β-lactam/β-lactamase inhibitor plus a macrolide	Amoxicillin-clavulanate + Clarithromycin Amoxicillin-clavulanate + Erythromycin Amoxicillin-clavulanate + Roxithromycin Piperacillin-tazobactam + Erythromycin
A β-lactam/β-lactamase inhibitors plus an aminoglycoside	Amoxicillin-clavulanate + Netilmicin or Gentamicin
A 2nd generation cephalosporin plus a macrolide	Cefuroxime + Azithromycin Cefuroxime + Erythromycin
A 2nd generation cephalosporin plus a tetracycline	Cefuroxime + Doxycycline
A 3rd generation cephalosporin plus a macrolide	Ceftriaxone + Azithromycin Ceftriaxone + Clarithromycin Ceftriaxone + Erythromycin or Clarithromycin Ceftriaxone + Clarithromycin or Azithromycin or Erythromycin or Roxithromycin or Spiramycin Cefoperazone + Azithromycin
A 3rd generation cephalosporin plus a respiratory fluoroquinolone	Ceftriaxone + Levofloxacin
A 3rd generation cephalosporin plus an other fluoroquinolone	Cefotaxime + Ofloxacin
A 3rd generation cephalosporin plus an aminoglycoside	Ceftazidime + Amikacin
A macrolide plus an aminoglycoside	Clarithromycin + Amikacin
A carbapenems plus a macrolide	Imipenem + Azithromycin Imipenem + Erythromycin
A respiratory fluoroquinolone plus metronidazole	Moxifloxacin + Metronidazole
Daptomycin plus Aztreonam	Daptomycin + Aztreonam
Linezolid plus Aztreonam	Linezolid + Aztreonam
Teicoplanin plus an other fluoroquinolone	Teicoplanin + Ciprofloxacin

Supplement 6. Risk of bias of included trials in the network meta-analysis

Treatment failure

	Randomization	Allocation concealment	Blinding of patients	Blinding of healthcare providers	Blinding of outcome assessors	Missing outcome data
Anzueto, 2006	Probably Low	Low	Probably Low	Probably Low	Probably Low	High
Aquino, 1994	High	High	High	High	High	Low
Aubier, 1998	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Low
Aufiero, 1997	Probably Low	Probably High	High	High	High	Low
Barrera, 2016	Low	Low	Low	Probably Low	Probably Low	Low
Bartoloni, 1999	Low	Probably High	Probably High	Probably High	Probably High	Probably High
Bergallo, 2009	Probably Low	Low	Probably Low	Probably Low	Probably Low	Probably Low
Berman, 1997	Low	Probably High	Probably High	Probably High	High	High
Bertrand, 1988	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	High
Bittner, 1986	Probably Low	Probably High	Probably High	Probably High	Probably High	High
Bonfitto, 1999	Probably Low	Probably High	High	High	High	Probably High
Brambilla, 1992	Probably Low	Probably High	High	High	High	Low
Carbon, 1992	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low
Castro, 1986	Probably Low	Probably High	High	High	High	Low
Chaudhary, 2018	Probably Low	Probably High	High	High	High	Low
Chen, 2014	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Low
Colardyn , 1996	Probably Low	Probably High	High	High	High	Probably Low
Correa, 2003	Probably Low	Probably High	High	High	High	Probably High
Covington, 2013	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Low
Dal Negro, 2001	Probably Low	Probably Low	Probably Low	Low	Probably Low	Low
Dall, 1986	Probably Low	Probably High	Probably High	Probably High	Probably High	Low
de Celis, 2002	Probably Low	Low	Probably Low	Probably Low	Probably Low	Low
Ebright, 1983	Probably Low	Probably High	Probably High	Probably High	Probably High	Low
Edelstein, 1991	Probably Low	Probably High	Probably High	Probably High	Probably High	Probably High
Fang, 2019	Probably Low	Probably High	Probably High	Probably High	Probably High	Low
Feldman, 2001	Probably Low	Probably High	High	High	High	Probably Low
File , 2019	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low
File, 1983	Low	Probably High	Probably High	Probably High	Probably High	High
File, 2011	Low	Low	Low	Low	Low	Low
File, 2016	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	High
Finch, 2002	Probably Low	Low	High	High	High	High
Fink, 1994	Low	Probably Low	Probably Low	Probably Low	Probably Low	High
Fogarty, 2004	Low	Probably High	High	High	High	High
Frank, 2002	Low	Probably High	High	High	High	Probably Low
Gaillat, 1994	Probably Low	Probably High	Probably High	Probably High	Probably High	High
Garcìa-Contreras, 2000	Probably Low	Probably High	Probably High	Probably High	Probably High	Low
Geckler, 1984	Probably Low	Probably High	Probably High	Probably High	Probably High	Probably Low
Geerts, 1971	Probably Low	Probably Low	Low	Low	Probably Low	Low

Genne, 1997	Probably Low	Probably High	High	High	High	High
Gotfried, 1997	Probably Low	Probably High	High	High	High	Low
Grieco, 1982	Probably Low	Probably High	Probably Low	Probably High	Probably High	Low
Grossman, 1999	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	High
Hirata-Dulas, 1991	Probably Low	Probably High	Probably High	Probably High	Probably High	Probably Low
Ho, 1997	Probably Low	Probably High	Probably High	Probably High	Probably High	Low
Horcajada, 2019	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Low
Huang, 2023	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Low
Ito, 2010	Probably Low	Probably High	High	High	High	Low
Izadi, 2018	Low	Probably High	Probably High	Probably High	Probably High	Low
Jardim, 2003	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	High
Kalbermatter, 2000	Probably Low	Probably High	Probably High	Probably High	Probably High	Low
Keeton, 1983	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Low
Kouno, 2003	Low	Low	Probably Low	Probably Low	Probably Low	Probably High
Kouno, 2011	Low	Low	High	High	High	Probably High
Kuzman, 2005	Probably Low	Probably High	High	High	High	Probably Low
LeFrock, 1982	Low	Probably High	Probably Low	Probably High	Probably High	Probably Low
Leophonte, 1993	Probably Low	Probably High	High	High	High	High
Leophonte, 2004	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	High
Leroy, 2005	Probably Low	Low	High	High	High	High
Leuenberger, 1983	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Probably High
Li, 2007	Probably Low	Probably High	Probably High	Probably High	Probably High	Low
Li, 2024	Low	Probably Low	Low	Low	Low	High
Lin, 2007	High	High	High	High	High	Low
Lin, 2007	Low	Probably High	Probably High	Probably High	Probably High	High
Lin, 2007	Probably Low	Probably High	High	High	High	Low
Lode, 2002	Probably Low	Probably High	High	High	High	High
López-Véjar, 2013	Probably Low	Probably High	High	High	High	Low
Low, 2011	Low	Low	Low	Low	Low	Low
McCabe, 1993	Probably Low	Probably High	Probably High	Probably Low	Probably Low	High
Miyazaki, 2019	Low	Low	Probably High	Probably High	Probably High	Probably Low
Moola, 1999	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Probably High
Mouton, 1995	Probably Low	Probably High	High	High	High	Probably High
Ni, 2012	Probably Low	Probably High	Probably High	Probably High	Probably High	Low
Nicholson, 2012	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Low
Nicolle, 1996	Probably Low	Probably Low	Probably High	Probably High	Probably High	Low
NORRBY, 1998	Probably Low	Low	High	High	High	Low
Oh, 1996	Low	Probably High	Probably High	Probably High	Probably High	Low
Oi, 2020	Probably Low	Probably High	High	High	High	Probably Low
Ortiz-Ruiz, 2002	Low	Probably Low	Probably Low	Probably Low	Probably Low	Low
Ortqvist , 1996	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	High
Paladino, 2007	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	High
Pariente, 1988	Low	Probably High	Probably High	Probably High	Probably High	High
Peng, 2006	Probably Low	Probably High	High	High	High	Low

Pertel, 2008	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	High
Petermann, 2001	Probably Low	Probably High	High	High	High	Probably High
Peterson, 1988	Low	Probably Low	Probably High	Probably High	Probably High	Low
Phillips, 1993	Low	Probably High	Probably High	Probably High	Probably High	Probably Low
Plouffe, 2000	Probably Low	Probably High	High	High	High	High
Poirier, 1991	Probably Low	Probably High	High	High	High	High
Poirier, 1999	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Low
Portier, 1996	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Low
Portier, 2005	Probably Low	Low	High	High	High	High
Rahlwes, 1988	Probably Low	Probably High	Probably High	Probably High	Probably High	Low
Rizzato , 1992	Probably Low	Probably High	Probably High	Probably High	Probably High	Low
Rizzato, 1993	Probably Low	Probably High	Probably High	Probably High	Probably High	Low
Rizzato, 1995	Probably Low	Probably High	High	High	High	Low
Rizzato, 1997	Probably Low	High	High	High	High	Probably Low
Romanelli, 2002	Probably Low	Probably High	Probably High	Probably High	Probably High	Probably High
Roson, 2001	Probably Low	Probably High	High	Probably High	Low	Low
Rossoff, 1995	Low	Probably High	Probably High	Probably High	Probably High	High
Samsonov, 2023	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Low
San Pedro, 2002	Probably Low	Probably High	High	High	High	High
Seki, 2009	Low	Low	Probably High	Probably High	Probably High	Probably High
Shao, 2008	Probably Low	Probably High	High	High	High	Probably Low
Shlaes, 1994	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	High
Sopena, 2004	Probably Low	Probably High	Probably High	Probably High	Probably High	Probably High
Speich, 1998	Low	Probably High	High	High	High	Probably Low
Stets, 2019	Low	Low	Low	Low	Probably Low	Low
Stille, 2000	Low	Low	High	High	High	Low
Sturm, 1998	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	High
Tanaseanu, 2009	Low	Low	Probably Low	Probably Low	Probably Low	Probably Low
Thadepalli, 1991	Probably Low	Probably High	Probably High	Probably High	Probably High	High
Tieying, 2014	Probably Low	Probably High	High	High	High	Low
Torres, 2008	Low	Probably Low	Low	Probably Low	Probably Low	Probably Low
Tremolieres, 1998	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	High
Vergis, 2000	Low	Probably High	High	High	High	Probably High
Vetter, 1997	Probably Low	Probably High	High	High	High	Probably Low
Vetter, 2002	Low	Probably Low	Probably Low	Probably Low	Probably Low	Probably High
Vogel, 1991	Probably Low	Probably High	High	High	High	High
Wallace, 1981	Low	Probably High	High	High	High	Low
Wallace, 1982	Probably Low	Probably High	Probably High	Probably High	Probably High	Low
Watanabe, 2010	Probably Low	Low	High	High	High	Probably High
Weber, 1987	Low	Low	Probably Low	Probably Low	Probably Low	High
Williams , 1994	Probably Low	Probably High	High	High	High	High
Wolff, 1997	Low	Low	High	High	Low	Probably High
XU, 2006	Probably Low	Probably High	Probably High	Probably High	Probably High	Low
Yamamoto, 2013	Low	Low	Probably High	Probably High	Probably High	High

Yanagihara, 2006	Probably Low	Probably High	Probably High	Probably High	Probably High	Probably Low
Yang, 2007	Probably Low	Probably High	High	High	High	Probably Low
Yang, 2009	Probably Low	Probably High	Probably High	Probably High	Probably High	Low
Yang, 2009	Probably Low	Probably High	High	High	High	Low
Yaqub, 2005	High	High	High	High	High	Low
Zervos, 1998	Probably Low	Probably High	High	High	High	Low
Zervos, 2004	Probably Low	Probably High	High	High	High	High
Zhong, 2014	Low	Low	Low	Low	Low	High
Zuck, 1990	Probably Low	Probably High	High	High	High	High

All-cause mortality

	Randomization	**Allocation concealment**	**Blinding of patients**	**Blinding of healthcare providers**	**Blinding of outcome assessors**	**Missing outcome data**
Anzueto, 2006	Probably Low	Low	Probably Low	Probably Low	Low	High
Aquino, 1994	High	High	High	High	Low	Low
Aubier, 1998	Probably Low	Probably Low	Probably Low	Probably Low	Low	Low
Barrera, 2016	Low	Low	Low	Probably Low	Low	Low
Bartoloni, 1999	Low	Probably High	Probably High	Probably High	Low	Probably High
Bergallo, 2009	Probably Low	Low	Probably Low	Probably Low	Low	Probably Low
Berman, 1997	Low	Probably High	Probably High	Probably High	Low	High
Bittner, 1986	Probably Low	Probably High	Probably High	Probably High	Low	High
Carbon, 1992	Probably Low	Probably Low	Probably Low	Probably Low	Low	Low
Castro, 1986	Probably Low	Probably High	High	High	Low	Low
Chaudhary, 2018	Probably Low	Probably High	High	High	Low	Low
Correa, 2003	Probably Low	Probably High	High	High	Low	Probably High
Covington, 2013	Probably Low	Probably Low	Probably Low	Probably Low	Low	Low
Dal Negro, 2001	Probably Low	Probably Low	Probably Low	Low	Low	Low
Dall, 1986	Probably Low	Probably High	Probably High	Probably High	Low	Low
de Celis, 2002	Probably Low	Low	Probably Low	Probably Low	Low	Low
Ebright, 1983	Probably Low	Probably High	Probably High	Probably High	Low	Low
Edelstein, 1991	Probably Low	Probably High	Probably High	Probably High	Low	Probably High
Feldman, 2001	Probably Low	Probably High	High	High	Low	Low
File, 2011	Low	Low	Low	Low	Low	Low
File, 2016	Probably Low	Probably Low	Probably Low	Probably Low	Low	High
Finch, 2002	Probably Low	Low	High	High	Low	High
Fogarty, 2004	Low	Probably High	High	High	Low	High
Forbes, 1971	Probably Low	Probably High	Probably High	Probably High	Low	High
Frank, 2002	Low	Probably High	High	High	Low	Probably Low
Gaillat, 1994	Probably Low	Probably High	Probably High	Probably High	Low	High
Garcìa-Contreras, 2000	Probably Low	Probably High	Probably High	Probably High	Low	Low
Geckler, 1984	Probably Low	Probably High	Probably High	Probably High	Low	Probably Low
Gotfried, 1997	Probably Low	Probably High	High	High	Low	Low

Grossman, 1999	Probably Low	Probably Low	Probably Low	Probably Low	Low	High
Hirata-Dulas, 1991	Probably Low	Probably High	Probably High	Probably High	Low	Probably Low
Ho, 1997	Probably Low	Probably High	Probably High	Probably High	Low	Low
Horcajada, 2019	Probably Low	Probably Low	Probably Low	Probably Low	Low	Low
Huys, 1972	Low	Low	Probably Low	Probably Low	Low	Low
Ito, 2010	Probably Low	Probably High	High	High	Low	Low
Izadi, 2018	Low	Probably High	Probably High	Probably High	Low	Low
Kalbermatter, 2000	Probably Low	Probably High	Probably High	Probably High	Low	Low
Keeton, 1983	Probably Low	Probably Low	Probably Low	Probably Low	Low	Low
Leophonte, 1993	Probably Low	Probably High	High	High	Low	High
Leophonte, 2004	Probably Low	Probably Low	Probably Low	Probably Low	Low	High
Leroy, 2005	Probably Low	Low	High	High	Low	High
Li, 2024	Low	Probably Low	Low	Low	Low	Probably High
Lode, 2002	Probably Low	Probably High	High	High	Low	High
López-Véjar, 2013	Probably Low	Probably High	High	High	Low	Low
Low, 2011	Low	Low	Low	Low	Low	Low
Macfarlane, 1983	Probably Low	Probably Low	Probably Low	Probably Low	Low	High
McCabe, 1993	Probably Low	Probably High	Probably High	Probably Low	Low	High
Moola, 1999	Probably Low	Probably Low	Probably Low	Probably Low	Low	Probably High
Morganroth, 2005	Low	Low	Low	Low	Low	Low
Ni, 2012	Probably Low	Probably High	Probably High	Probably High	Low	Low
Nicholson, 2012	Probably Low	Probably Low	Probably Low	Probably Low	Low	Low
Nicolle, 1996	Probably Low	Probably Low	Probably High	Probably High	Low	Low
NORRBY, 1998	Probably Low	Low	High	High	Low	Low
Oi, 2020	Probably Low	Probably High	High	High	Low	Probably Low
Ortqvist, 1996	Probably Low	Probably Low	Probably Low	Probably Low	Low	High
Paladino, 2007	Probably Low	Probably Low	Probably Low	Probably Low	Low	High
Pariente, 1988	Low	Probably High	Probably High	Probably High	Low	High
Pertel, 2008	Probably Low	Probably Low	Probably Low	Probably Low	Low	Low
Petermann, 2001	Probably Low	Probably High	High	High	Low	Low
Peterson, 1988	Low	Probably Low	Probably High	Probably High	Low	Low
Phillips, 1993	Low	Probably High	Probably High	Probably High	Low	Probably Low
Plouffe, 2000	Probably Low	Probably High	High	High	Low	Low
Portier, 2005	Probably Low	Low	High	High	Low	High
Rahlwes, 1988	Probably Low	Probably High	Probably High	Probably High	Low	Low
Rizzato, 1997	Probably Low	High	High	High	Low	Probably Low
Romanelli, 2002	Probably Low	Probably High	Probably High	Probably High	Low	Probably High
Roson, 2001	Probably Low	Probably High	High	Probably High	Low	Low
Rossoff, 1995	Low	Probably High	Probably High	Probably High	Low	High
Samsonov, 2023	Probably Low	Probably Low	Probably Low	Probably Low	Low	Low
San Pedro, 2002	Probably Low	Probably High	High	High	Low	Low
Shlaes, 1994	Probably Low	Probably Low	Probably Low	Probably Low	Low	High
Speich, 1998	Low	Probably High	High	High	Low	Probably Low
Stets, 2019	Low	Low	Low	Low	Low	Low

Tanaseanu, 2009	Low	Low	Probably Low	Probably Low	Low	Low
Torres, 2008	Low	Probably Low	Low	Probably Low	Low	Probably Low
Tremolieres, 1998	Probably Low	Probably Low	Probably Low	Probably Low	Low	High
Vergis, 2000	Low	Probably High	High	High	Low	Probably High
Vetter, 1997	Probably Low	Probably High	High	High	Low	Probably Low
Vetter, 2002	Low	Probably Low	Probably Low	Probably Low	Low	Probably High
Vogel, 1991	Probably Low	Probably High	High	High	Low	High
Wallace, 1982	Probably Low	Probably High	Probably High	Probably High	Low	Low
Weber, 1987	Low	Low	Probably Low	Probably Low	Low	High
Williams , 1994	Probably Low	Probably High	High	High	Low	High
Yamamoto, 2013	Low	Low	Probably High	Probably High	Low	High
Yaqub, 2005	High	High	High	High	Low	Low
Zervos, 1998	Probably Low	Probably High	High	High	Low	Low
Zervos, 2004	Probably Low	Probably High	High	High	Low	High
Zhong, 2014	Low	Low	Low	Low	Low	High
Zuck, 1990	Probably Low	Probably High	High	High	Low	High

Duration of hospitalization and need for mechanical ventilation

	Randomization	**Allocation concealment**	**Blinding of patients**	**Blinding of healthcare providers**	**Blinding of outcome assessors**	**Missing outcome data**
Anzueto, 2006	Probably Low	Low	Probably Low	Probably Low	Low	High
Bergallo, 2009	Probably Low	Low	Probably Low	Probably Low	Low	Probably Low
Finch, 2002	Probably Low	Low	High	High	Low	High
Forbes, 1971	Probably Low	Probably High	Probably High	Probably High	Low	High
Garcìa-Contreras, 2000	Probably Low	Probably High	Probably High	Probably High	Low	Low
Gotfried, 1997	Probably Low	Probably High	High	High	Low	Low
Hirata-Dulas, 1991	Probably Low	Probably High	Probably High	Probably High	Low	Probably Low
Lode, 2002	Probably Low	Probably High	High	High	Low	High
López-Véjar, 2013	Probably Low	Probably High	High	High	Low	Low
Ni, 2012	Probably Low	Probably High	Probably High	Probably High	Low	Low
NORRBY, 1998	Probably Low	Low	High	High	Low	Low
Peterson, 1988	Low	Probably Low	Probably High	Probably High	Low	Low
Rizzato, 1995	Probably Low	Probably High	High	High	Low	Low
Rizzato, 1997	Probably Low	High	High	High	Low	Probably Low
Romanelli, 2002	Probably Low	Probably High	Probably High	Probably High	Low	Probably High
Roson, 2001	Probably Low	Probably High	High	Probably High	Low	Low
Rossoff, 1995	Low	Probably High	Probably High	Probably High	Low	High
Shao, 2008	Probably Low	Probably High	High	High	Low	Probably Low
Weber, 1987	Low	Low	Probably Low	Probably Low	Low	High
Yadegarynia, 2022	Low	Probably High	Probably High	Probably High	Low	Probably Low

Yang, 2020	Probably Low	Probably High	Probably High	Probably High	Low	Low
Yaqub, 2005	High	High	High	High	Low	Low
Zervos, 2004	Probably Low	Probably High	High	High	Low	High

Adverse events outcomes

	Randomization	**Allocation concealment**	**Blinding of patients**	**Blinding of healthcare providers**	**Blinding of outcome assessors**	**Missing outcome data**
Anzueto, 2006	Probably Low	Low	Probably Low	Probably Low	Probably Low	High
Aubier, 1998	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Low
Barrera, 2016	Low	Low	Low	Probably Low	Probably Low	Low
Bartoloni, 1999	Low	Probably High	Probably High	Probably High	Probably High	Probably High
Bergallo, 2009	Probably Low	Low	Probably Low	Probably Low	Probably Low	Probably Low
Berman, 1997	Low	Probably High	Probably High	Probably High	High	High
Bertrand, 1988	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	High
Carbon, 1992	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Low
Castro, 1986	Probably Low	Probably High	High	High	High	Low
Chaudhary, 2018	Probably Low	Probably High	High	High	High	Low
Correa, 2003	Probably Low	Probably High	High	High	High	Probably High
Dal Negro, 2001	Probably Low	Probably Low	Probably Low	Low	Probably Low	Low
Dall, 1986	Probably Low	Probably High	Probably High	Probably High	Probably High	Low
de Celis, 2002	Probably Low	Low	Probably Low	Probably Low	Probably Low	Low
Edelstein, 1991	Probably Low	Probably High	Probably High	Probably High	Probably High	Probably High
File, 1983	Low	Probably High	Probably High	Probably High	Probably High	High
File, 2011	Low	Low	Low	Low	Low	Low
File, 2016	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	High
File, 2019	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low
Finch, 2002	Probably Low	Low	High	High	High	High
Fogarty, 2004	Low	Probably High	High	High	High	High
Forbes, 1971	Probably Low	Probably High	Probably High	Probably High	Probably High	High
Frank, 2002	Low	Probably High	High	High	High	Probably Low
Gaillat, 1994	Probably Low	Probably High	Probably High	Probably High	Probably High	High
Geckler, 1984	Probably Low	Probably High	Probably High	Probably High	Probably High	Probably Low
Geerts, 1971	Probably Low	Probably Low	Low	Low	Probably Low	Low
Genne, 1997	Probably Low	Probably High	High	High	High	High
Gotfried, 1997	Probably Low	Probably High	High	High	High	Low
Grieco, 1982	Probably Low	Probably High	Probably Low	Probably High	Probably High	Low
Grossman, 1999	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	High
Hirata-Dulas, 1991	Probably Low	Probably High	Probably High	Probably High	Probably High	Probably Low

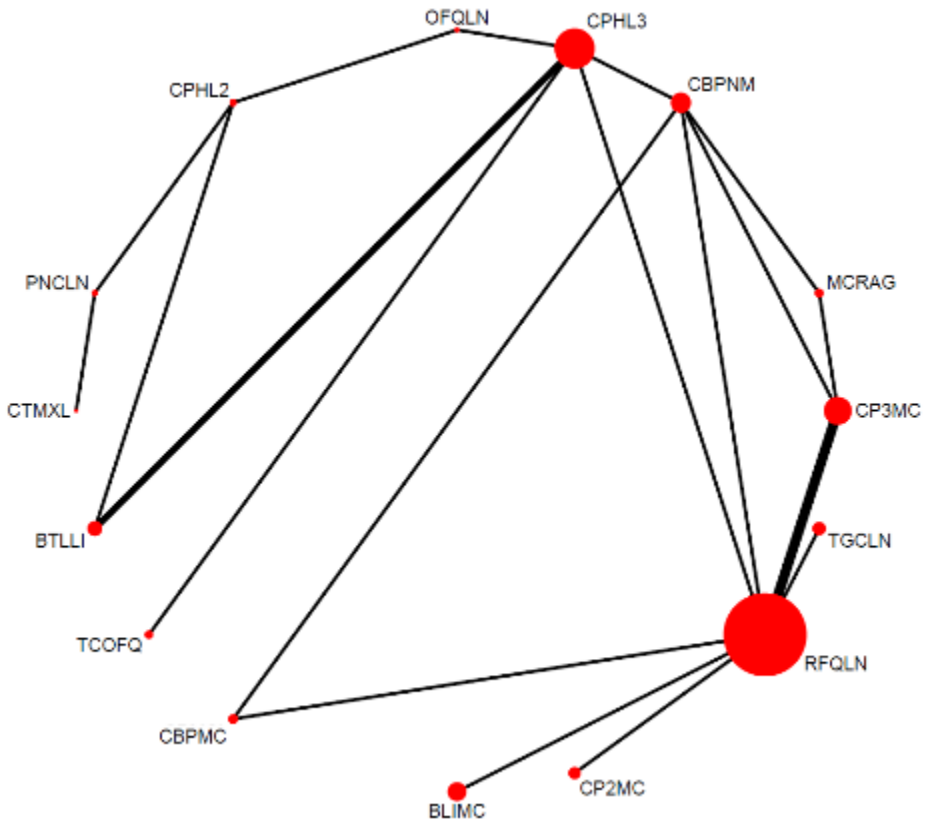
Ho, 1997	Probably Low	Probably High	Probably High	Probably High	Probably High	Low
Horcajada, 2019	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Low
Huys, 1972	Low	Low	Probably Low	Probably Low	Probably Low	Low
Ito, 2010	Probably Low	Probably High	High	High	High	Low
Izadi, 2018	Low	Probably High	Probably High	Probably High	Probably High	Low
Jardim, 2003	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	High
Kalbermatter, 2000	Probably Low	Probably High	Probably High	Probably High	Probably High	Low
Kouno, 2011	Low	Low	High	High	High	Probably High
Kuzman, 2005	Probably Low	Probably High	High	High	High	Low
LeFrock, 1982	Low	Probably High	Probably Low	Probably High	Probably High	Probably Low
Leophonte, 1993	Probably Low	Probably High	High	High	High	High
Leophonte, 2004	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	High
Leroy, 2005	Probably Low	Low	High	High	High	High
Leuenberger, 1983	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Probably High
Li, 2024	Low	Probably Low	Low	Low	Low	Probably High
Lin, 2007	Probably Low	Probably High	High	High	High	Low
Lode, 2002	Probably Low	Probably High	High	High	High	High
Low, 2011	Low	Low	Low	Low	Low	Low
Macfarlane, 1983	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	High
McCabe, 1993	Probably Low	Probably High	Probably High	Probably Low	Low	High
Moola, 1999	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Probably High
Ni, 2012	Probably Low	Probably High	Probably High	Probably High	Probably High	Low
Nicholson, 2012	Probably Low	Probably Low	Probably Low	Probably Low	Low	Low
NORRBY, 1998	Probably Low	Low	High	High	High	Low
Oh, 1996	Low	Probably High	Probably High	Probably High	Probably High	Low
Oi, 2020	Probably Low	Probably High	High	High	High	Probably Low
Ortiz-Ruiz, 2002	Low	Probably Low	Probably Low	Probably Low	Probably Low	Low
Ortqvist , 1996	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	High
Pariente, 1988	Low	Probably High	Probably High	Probably High	Probably High	High
Pertel, 2008	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Low
Petermann, 2001	Probably Low	Probably High	High	High	High	Low
Peterson, 1988	Low	Probably Low	Probably High	Probably High	Probably High	Low
Phillips, 1993	Low	Probably High	Probably High	Probably High	Probably High	Probably Low
Plouffe, 2000	Probably Low	Probably High	High	High	High	Low
Poirier, 1991	Probably Low	Probably High	High	High	High	Probably Low
Poirier, 1999	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Low
Portier, 1996	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Low
Portier, 2005	Probably Low	Low	High	High	High	High
Rahlwes, 1988	Probably Low	Probably High	Probably High	Probably High	Probably High	Low

Rizzato, 1997	Probably Low	High	High	High	High	Probably Low
Romanelli, 2002	Probably Low	Probably High	Probably High	Probably High	Probably High	Probably High
Roson, 2001	Probably Low	Probably High	High	Probably High	Low	Low
Rossoff, 1995	Low	Probably High	Probably High	Probably High	Probably High	High
Samsonov, 2023	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Low
San Pedro, 2002	Probably Low	Probably High	High	High	High	Low
Shao, 2008	Probably Low	Probably High	High	High	High	Probably Low
Shlaes, 1994	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	High
Speich, 1998	Low	Probably High	High	High	High	Probably Low
Stets, 2019	Low	Low	Low	Low	Probably Low	Low
Stille, 2000	Low	Low	High	High	High	Low
Tanaseanu, 2009	Low	Low	Probably Low	Probably Low	Probably Low	Low
Thadepalli, 1991	Probably Low	Probably High	Probably High	Probably High	Probably High	High
Tieying, 2014	Probably Low	Probably High	High	High	High	Low
Torres, 2008	Low	Probably Low	Low	Probably Low	Probably Low	Probably Low
Tremolieres, 1998	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Low
Vergis, 2000	Low	Probably High	High	High	High	Probably High
Vetter, 1997	Probably Low	Probably High	High	High	High	Probably Low
Vetter, 2002	Low	Probably Low	Probably Low	Probably Low	Probably Low	Probably High
Vogel, 1991	Probably Low	Probably High	High	High	High	High
Wallace, 1982	Probably Low	Probably High	Probably High	Probably High	Probably High	Low
Watanabe, 2010	Probably Low	Low	High	High	High	Probably High
Weber, 1987	Low	Low	Probably Low	Probably Low	Probably Low	High
Williams, 1994	Probably Low	Probably High	High	High	High	High
XU, 2006	Probably Low	Probably High	Probably High	Probably High	Probably High	Low
Yadegarynia, 2022	Low	Probably High	Probably High	Probably High	Probably High	Probably Low
Yamamoto, 2013	Low	Low	Probably High	Probably High	Probably High	High
Yang, 2009	Probably Low	Probably High	High	High	High	Low
Yaqub, 2005	High	High	High	High	High	Low
Zervos, 2004	Probably Low	Probably High	High	High	High	High
Zhong, 2014	Low	Low	Low	Low	Low	High
Zuck, 1990	Probably Low	Probably High	High	High	High	High

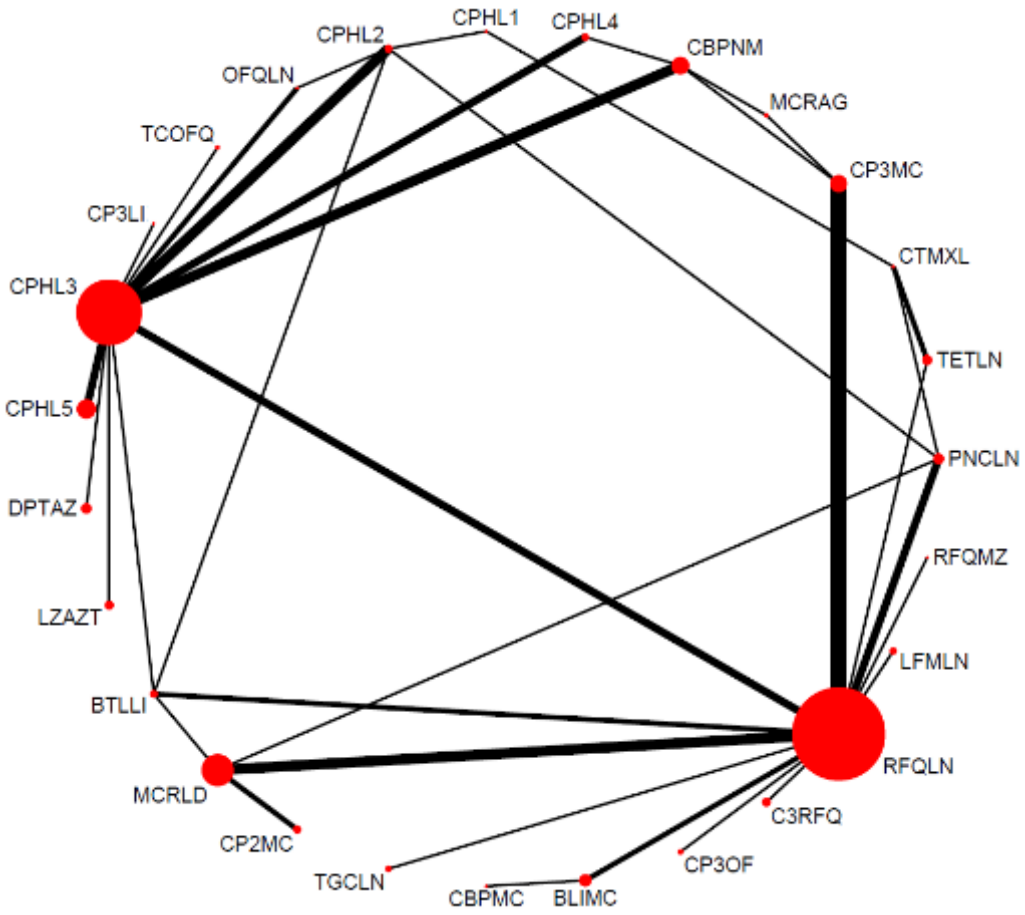
Supplement 7. Network plots

The size of the nodes is proportional to the number of participants randomized to each antibiotic regimen and the lines link nodes are weighted according to the number of trials informed a specific direct comparison. BTLLI: β-lactam/β-lactamase inhibitors alone; BLIMC: A β-lactam/β-lactamase inhibitor plus a macrolide; BTLAG: A β-lactam/β-lactamase inhibitor plus an aminoglycoside; CBPMC: a carbapenem plus a macrolide; CP3AG: a 3rd generation cephalosporin plus an aminoglycoside; CBPNM: carbapenems alone; CP3MC: a 3rd generation cephalosporin plus a macrolide; CPHL3: 3rd generation cephalosporins alone; CP3LI: 3rd generation cephalosporin/β-lactamase inhibitors alone; CPHL4: 4th generation cephalosporins alone; CPHL5: 5th generation cephalosporins alone; CPHL2: 2nd generation cephalosporins alone; CPHL1: 1st generation cephalosporins alone; CTMXL: cotrimoxazole; DPTAZ: daptomycin plus aztreonam; LZAZT: linezolid plus aztreonam; MCRAG: a macrolide plus an aminoglycoside; MCRLD: macrolides lone; CP2TT: a 2nd generation cephalosporin plus a tetracycline; OFQLN: other fluoroquinolones alone; PENOF: a penicillin plus an other fluoroquinolone; PNCLN: penicillins alone; PRSMN: pristinamycin; RFQLN: respiratory fluoroquinolones alone; C3RFQ: a 3rd generation cephalosporin plus a respiratory fluoroquinolone; LFMLN: lefamulin; CP2MC: a 2nd generation cephalosporin plus a macrolide; CP3OF: a 3rd generation cephalosporin plus an other fluoroquinolone; RFQMZ: a respiratory fluoroquinolone plus a metronidazole; TCOFQ: teicoplanin plus an other fluoroquinolone; TETLN: tetracyclines alone; TGCLN: tigecycline.

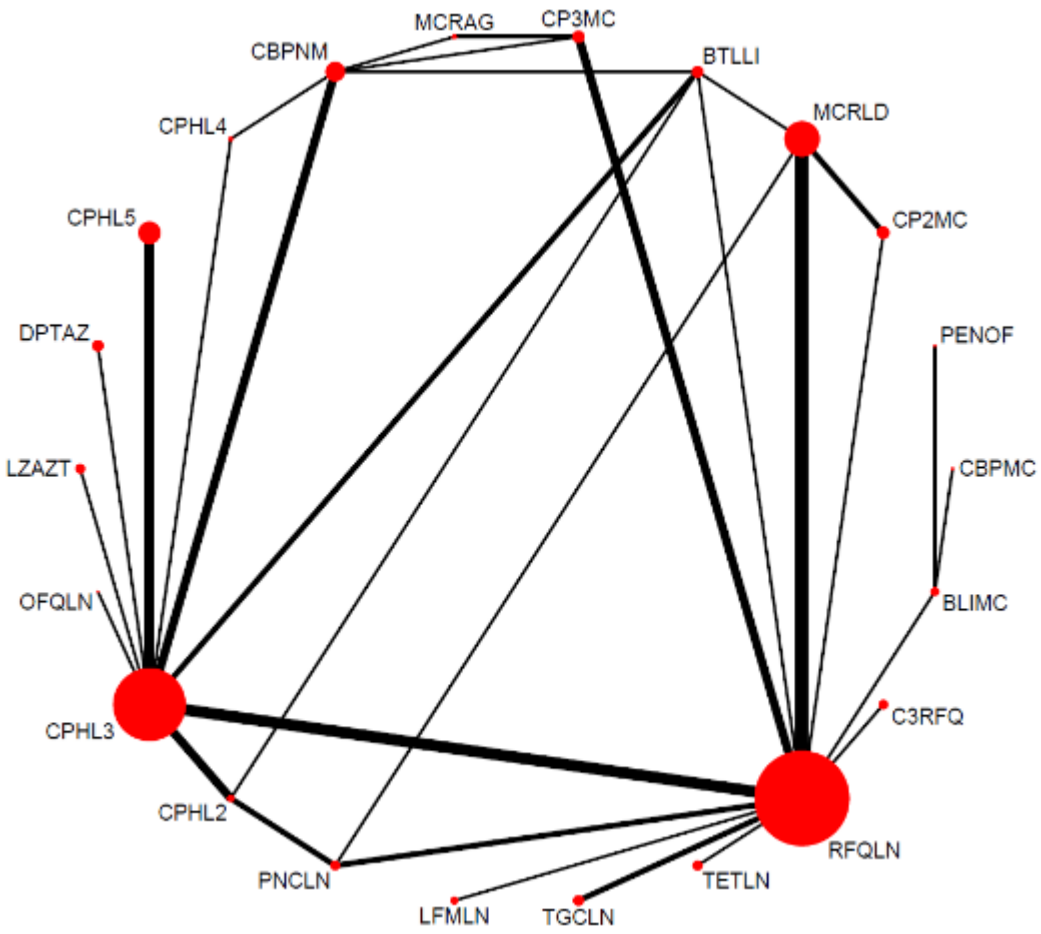
Duration of hospitalization



Discontinuation due to adverse events



Diarrhea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MCRLD
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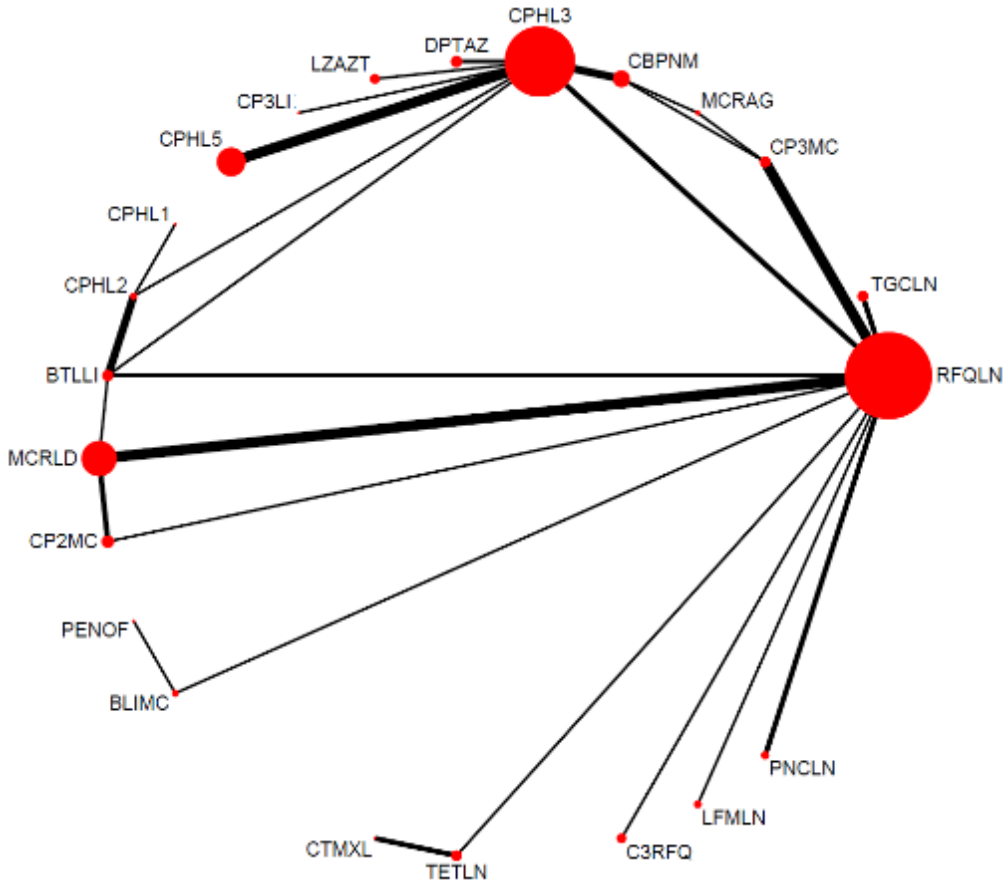
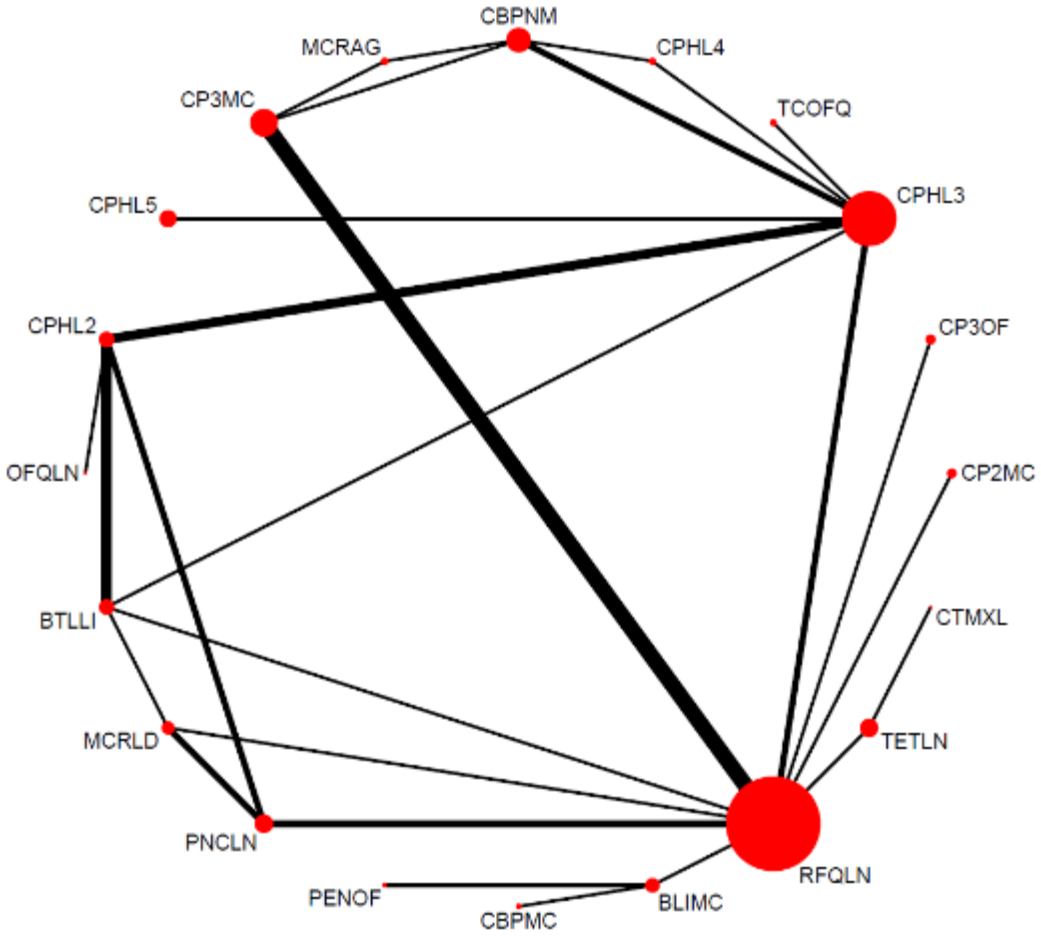
DPTAZ
PENOF
LZAZT
CBPMC
OFQLN
BLIMC
C3RFQ
CPHL3
CPHL2
RFQLN
PNCLN
TETLN
LFMLN
TGCLN

Nausea and/or vomiting



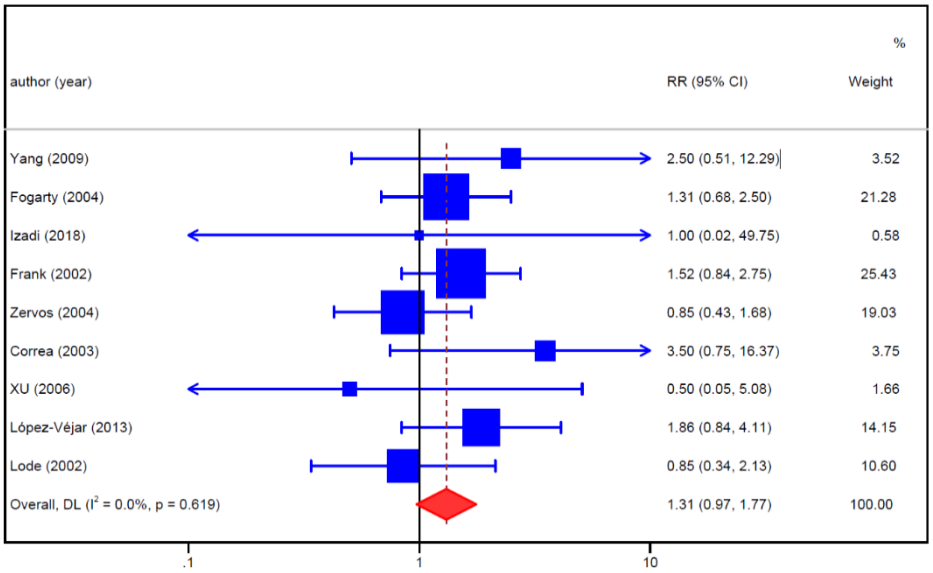
Any allergic reactions



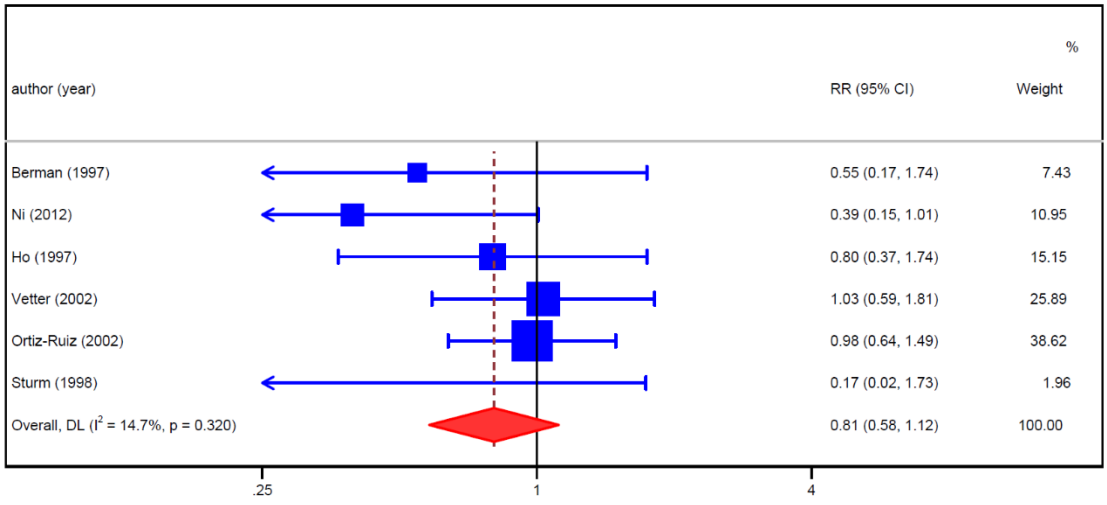
Supplement 8. Forest plots for direct comparisons

Treatment failure

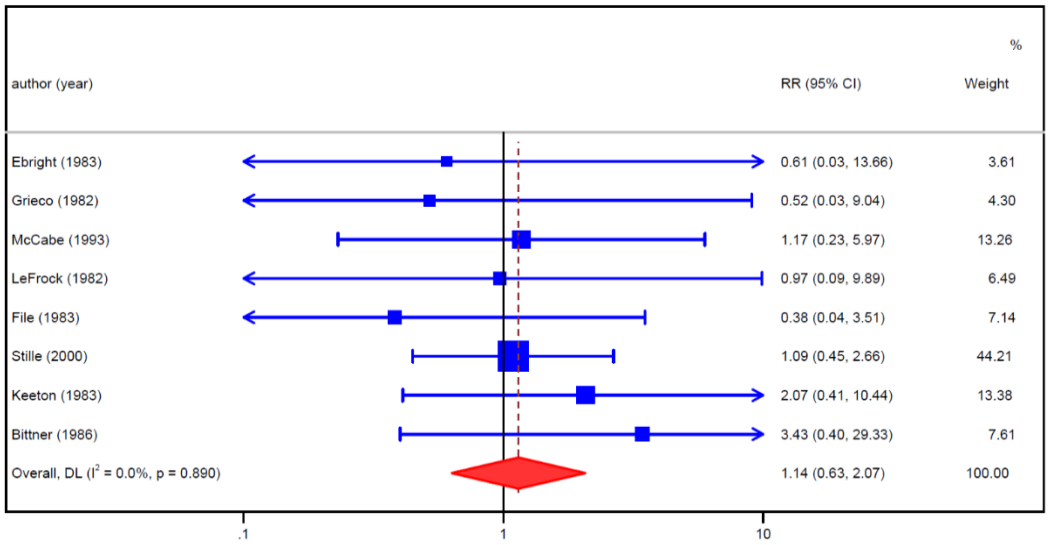
A 3rd generation cephalosporin + a macrolide vs Respiratory fluoroquinolones



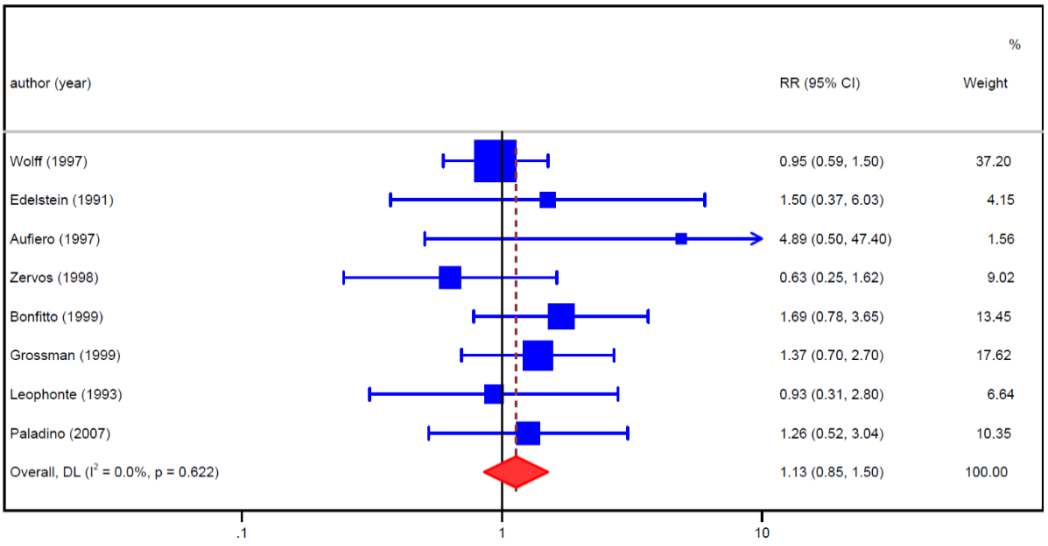
Carbapenems vs 3rd generation cephalosporins



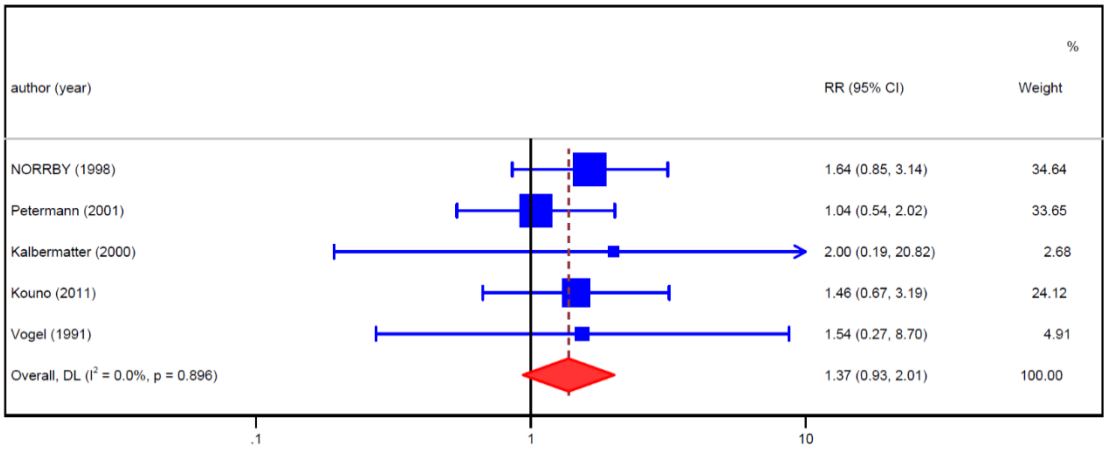
2nd generation cephalosporin vs 3rd generation cephalosporins



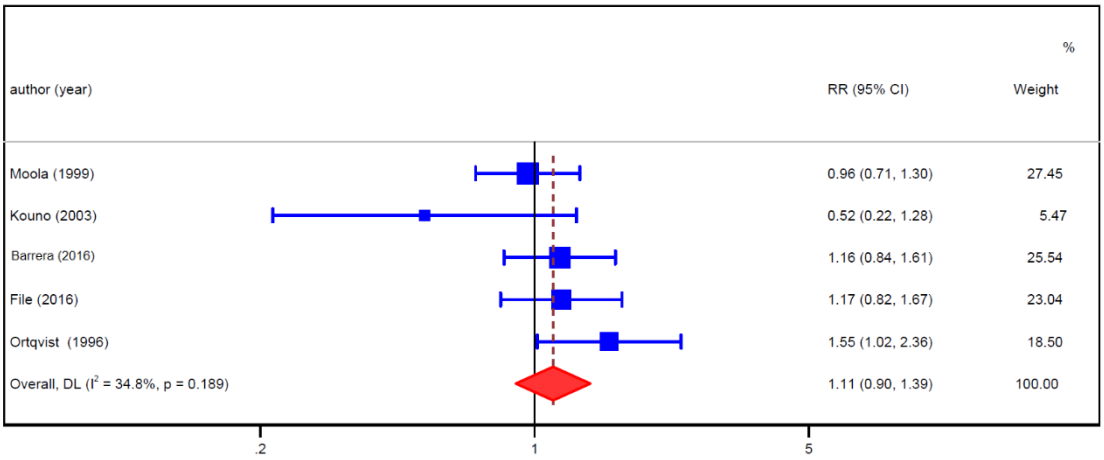
3rd generation cephalosporins vs 4th generation cephalosporins



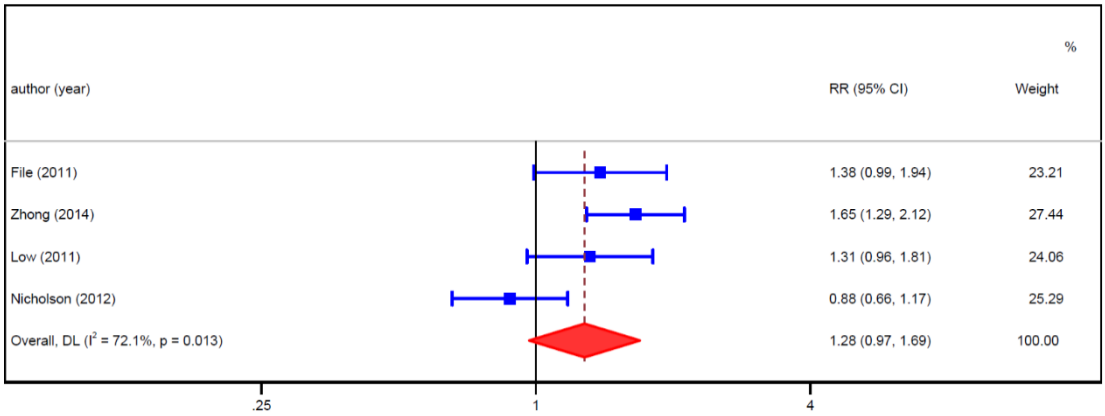
3rd generation cephalosporins vs Respiratory fluoroquinolones



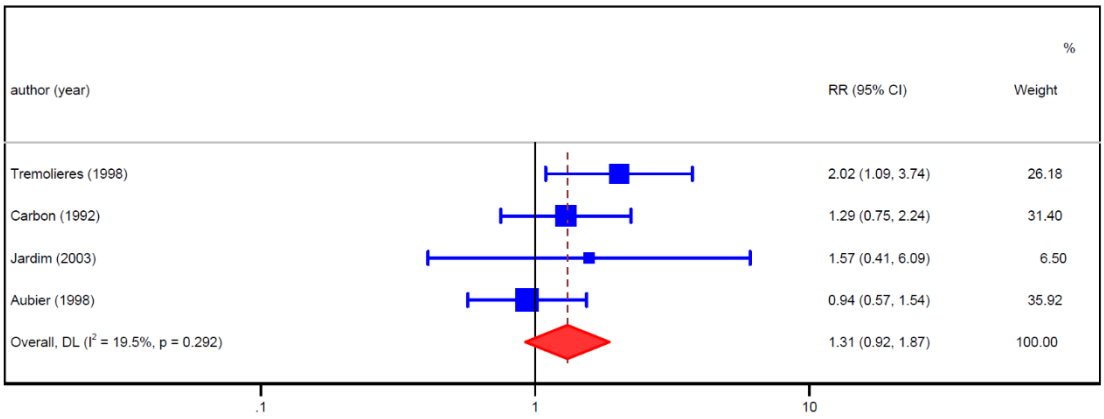
Macrolides vs Respiratory fluoroquinolones



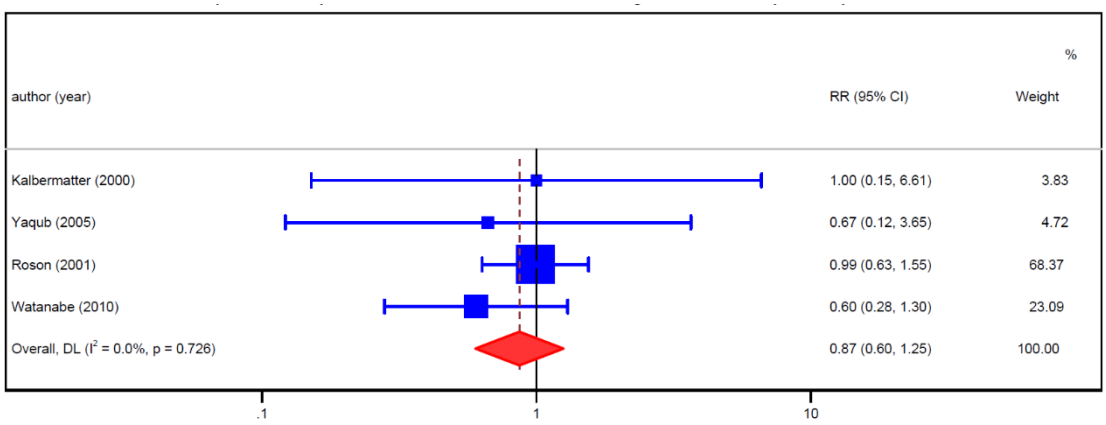
3rd generation cephalosporins vs 5th generation cephalosporins



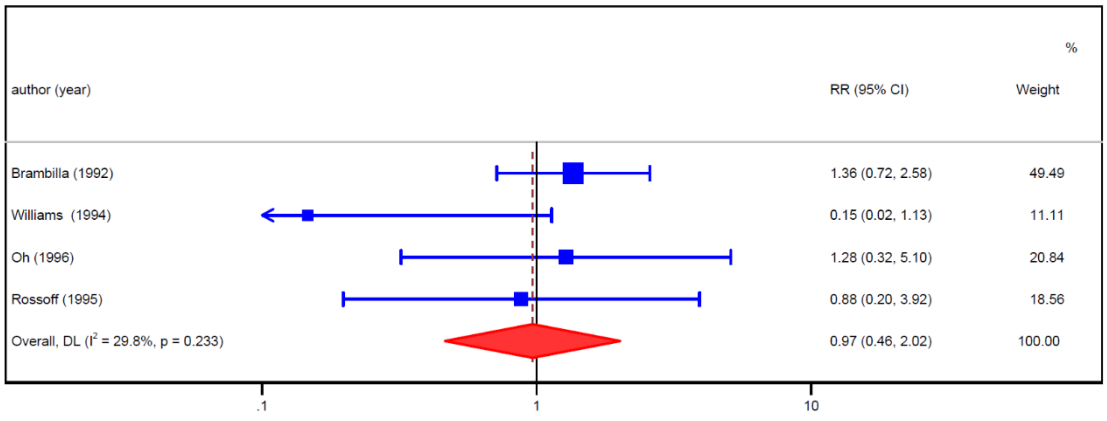
Penicillins vs Respiratory fluoroquinolones



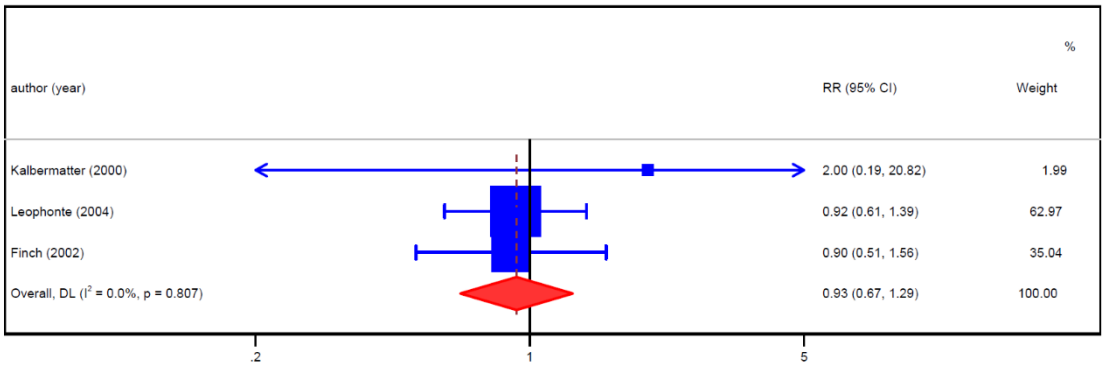
β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporins



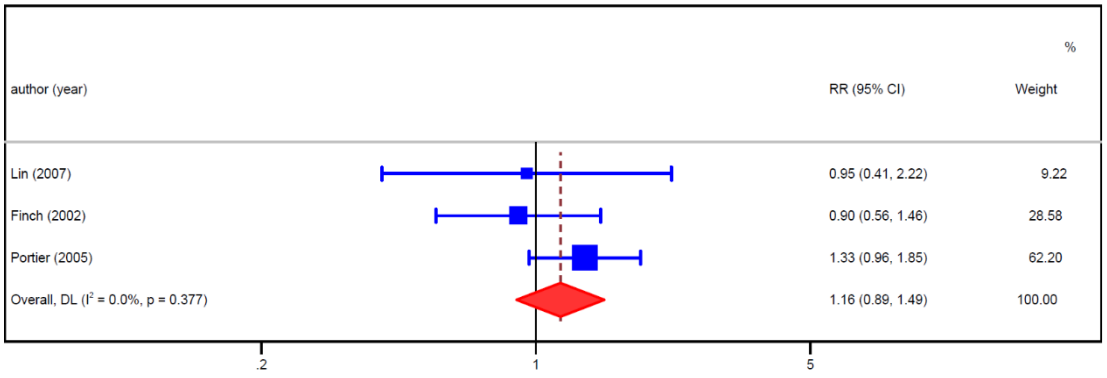
β-Lactam/β-lactamase inhibitors vs 2nd generation cephalosporins



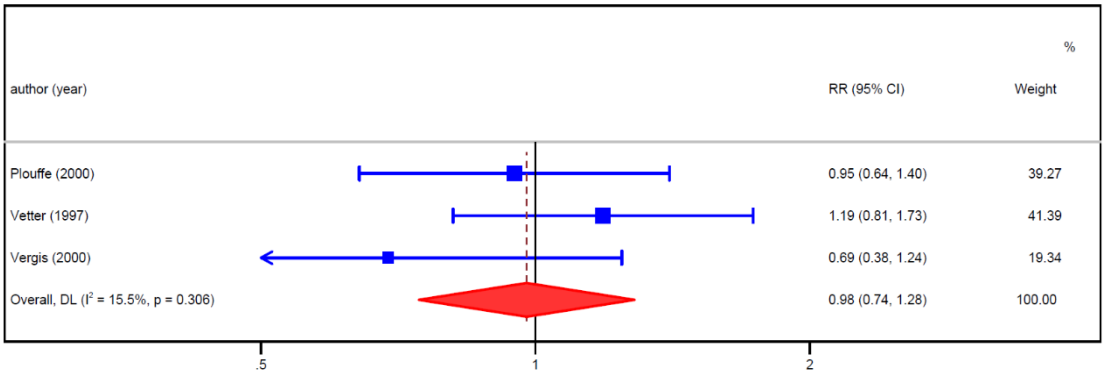
β-Lactam/β-lactamase inhibitors vs Respiratory fluoroquinolones



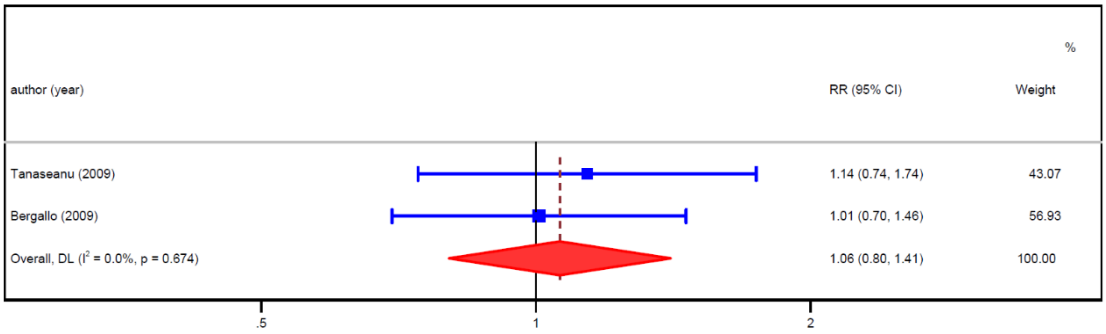
A β-lactam/β-lactamase inhibitor + a macrolide vs Respiratory fluoroquinolones



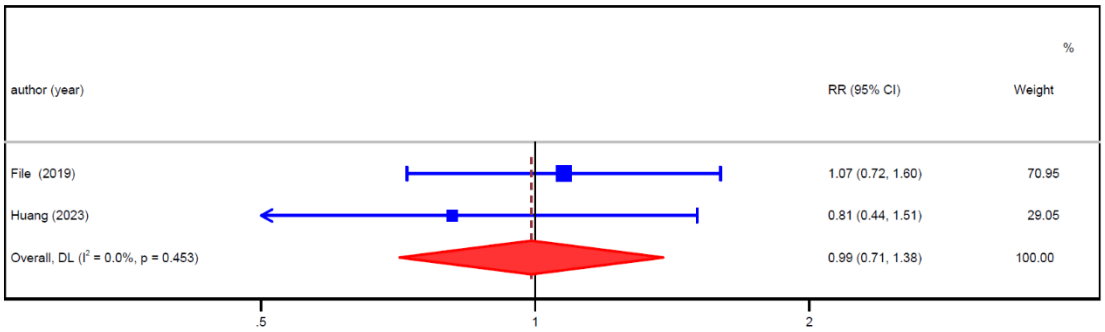
A 2nd generation cephalosporin + a macrolide vs Macrolide alone



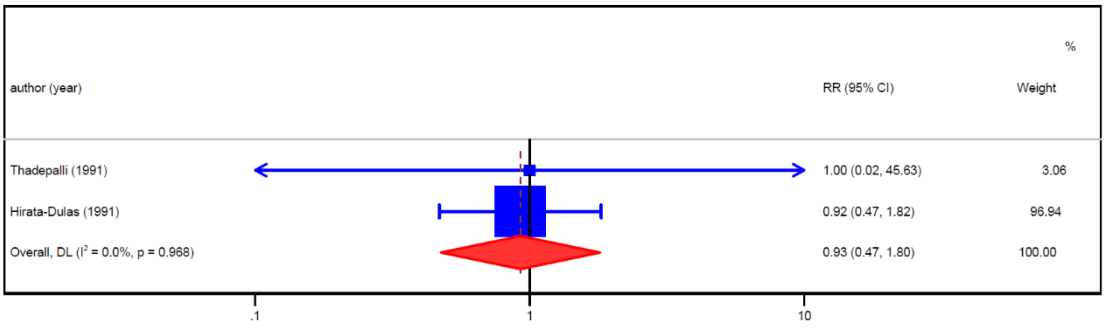
Respiratory fluoroquinolones vs Tigecycline



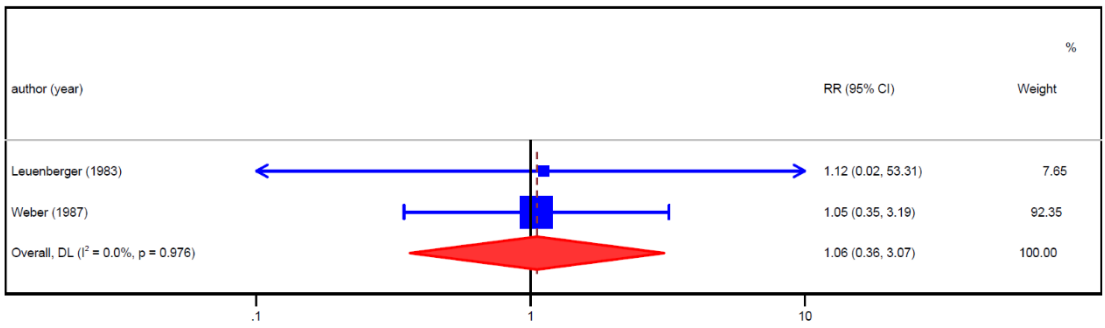
Lefamulin vs Respiratory fluoroquinolones



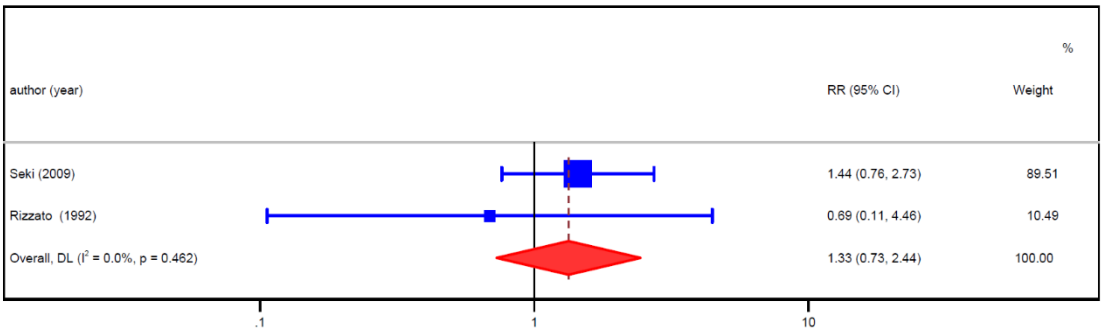
3rd generation cephalosporins vs other fluoroquinolones



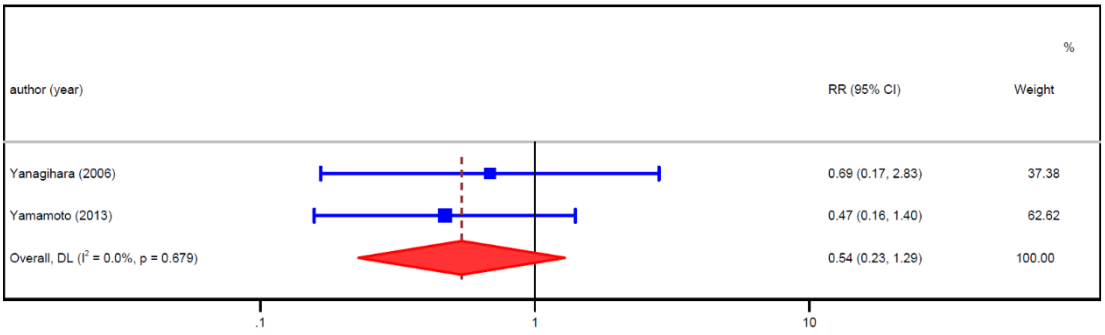
2nd generation cephalosporins vs Penicillins



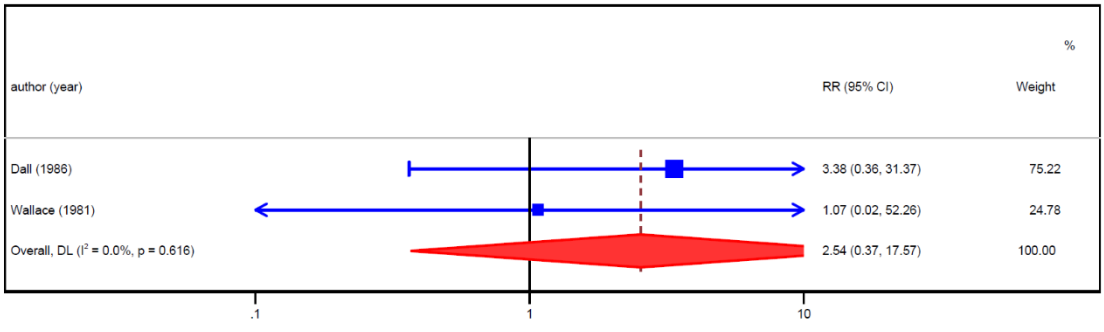
β-Lactam/β-lactamase inhibitors vs Penicillins



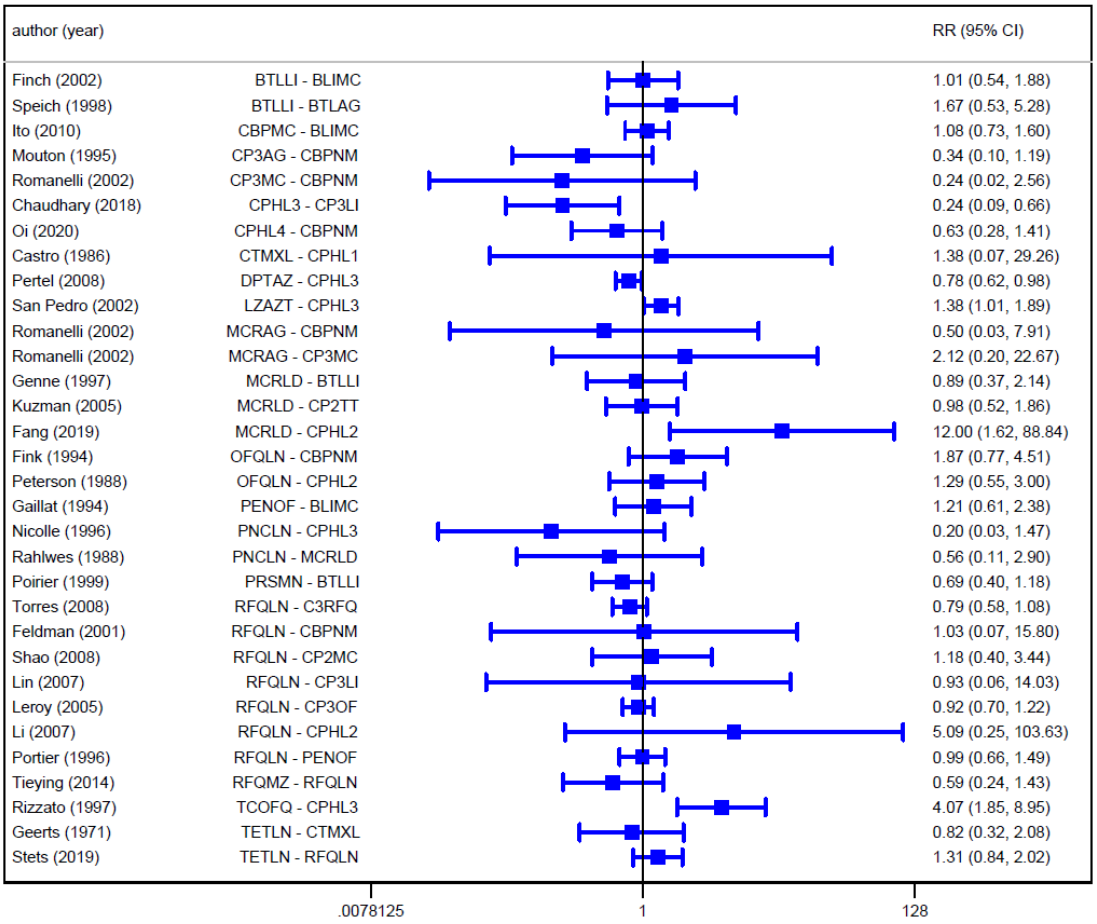
β-Lactam/β-lactamase inhibitors vs Carbapenems



1st generation cephalosporins vs 2nd generation cephalosporins



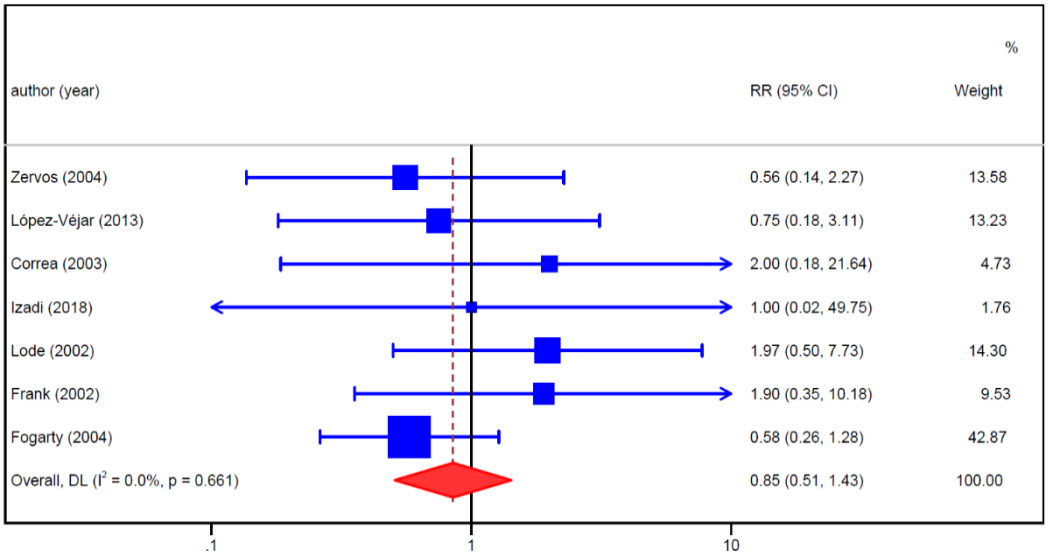
Direct comparisons informed by one trial



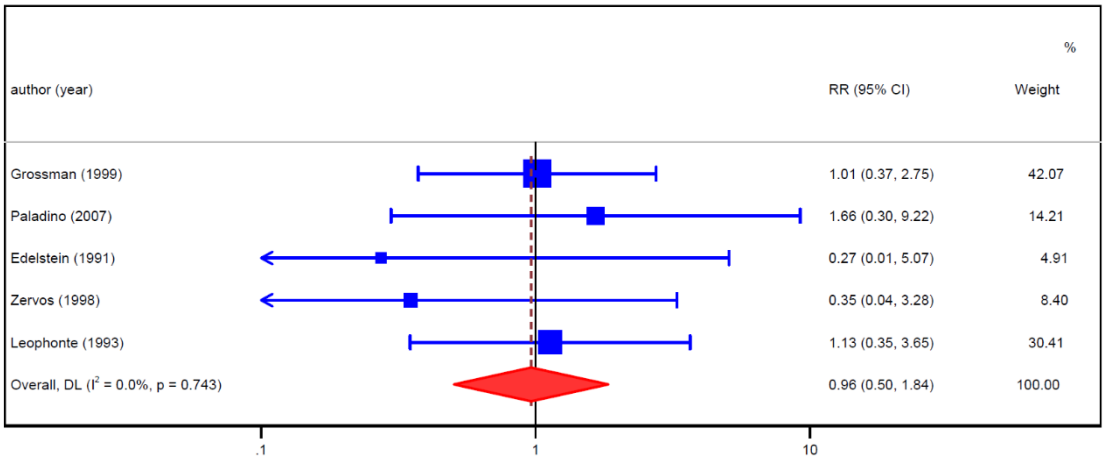
The effect is the comparison of second treatment versus the first treatment (e.g., BTLLI -BLIMC: BLIMC versus BTLLI). BTLLI: β-lactam/β-lactamase inhibitor; BLIMC: A β-lactam/β-lactamase inhibitor plus a macrolide; BTLAG: A β-lactam/β-lactamase inhibitor plus an aminoglycoside; CBPMC: a carbapenem plus a macrolide; CP3AG: a 3rd generation cephalosporin plus an aminoglycoside; CBPNM: carbapenem; CP3MC: a 3rd generation cephalosporin plus a macrolide; CPHL3: 3rd generation cephalosporin; CP3LI: 3rd generation cephalosporin/β-lactamase inhibitor; CPHL4: 4th generation cephalosporin; CTMXL: cotrimoxazole; CPHL1: 1st generation cephalosporin; DPTAZ: daptomycin plus aztreonam; LZAZT: linezolid plus aztreonam; MCRAG: a macrolide plus an aminoglycoside; MCRLD: macrolide; CP2TT: a 2nd generation cephalosporin plus a tetracycline; CPHL2: 2nd generation cephalosporin; OFQLN: other fluoroquinolone; PENOF: a penicillin plus an other fluoroquinolone; PNCLN: penicillin; PRSMN: pristinamycin; RFQLN: respiratory fluoroquinolone; C3RFQ: a 3rd generation cephalosporin plus a respiratory fluoroquinolone; CP2MC: a 2nd generation cephalosporin plus a macrolide; CP3OF: a 3rd generation cephalosporin plus an other fluoroquinolone; RFQMZ: a respiratory fluoroquinolone plus a metronidazole; TCOFQ: teicoplanin plus an other fluoroquinolone; TETLN: tetracycline.

All-cause mortality

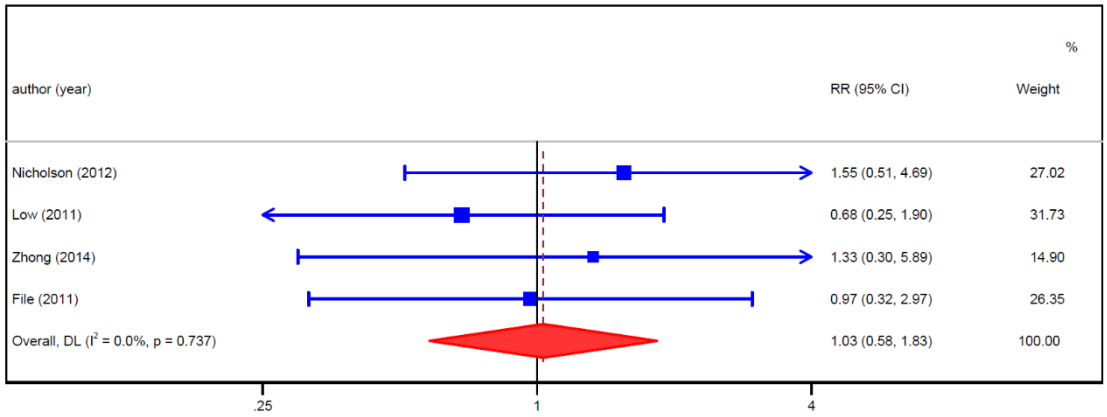
A 3rd generation cephalosporin + a macrolide vs Respiratory fluoroquinolones



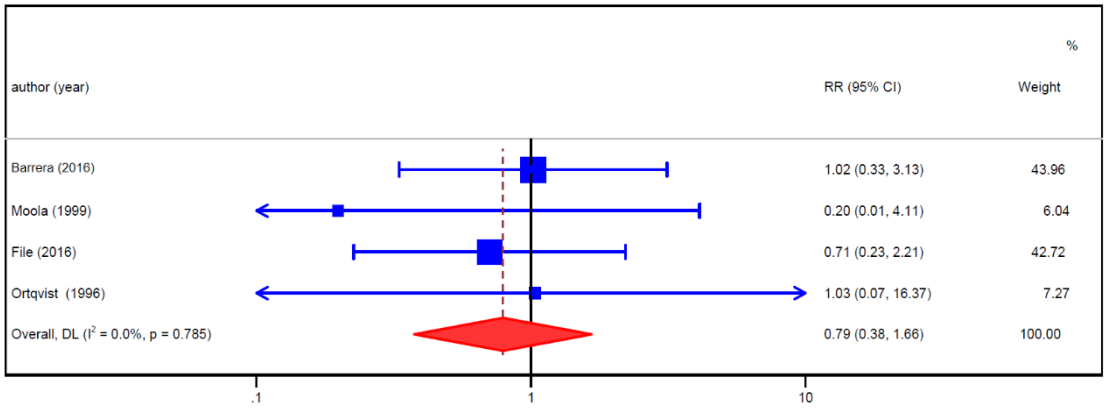
3rd generation cephalosporins vs 4th generation cephalosporins



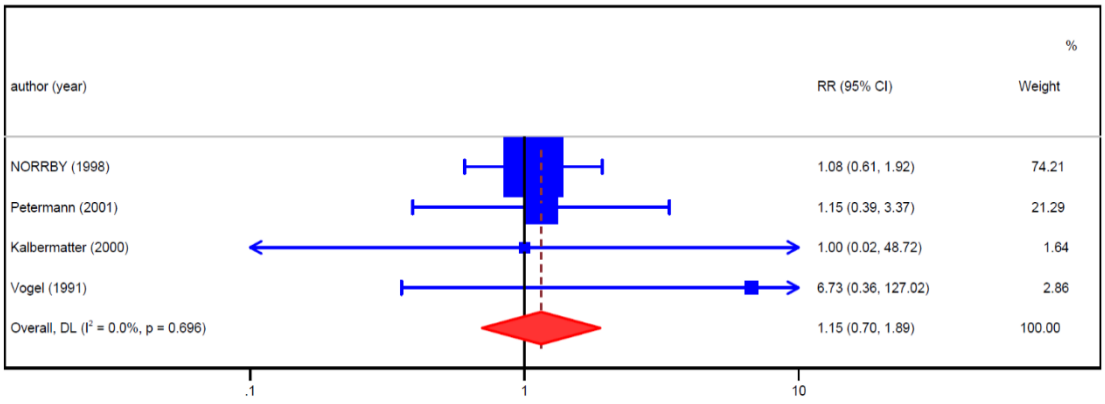
3rd generation cephalosporins vs 5th generation cephalosporins



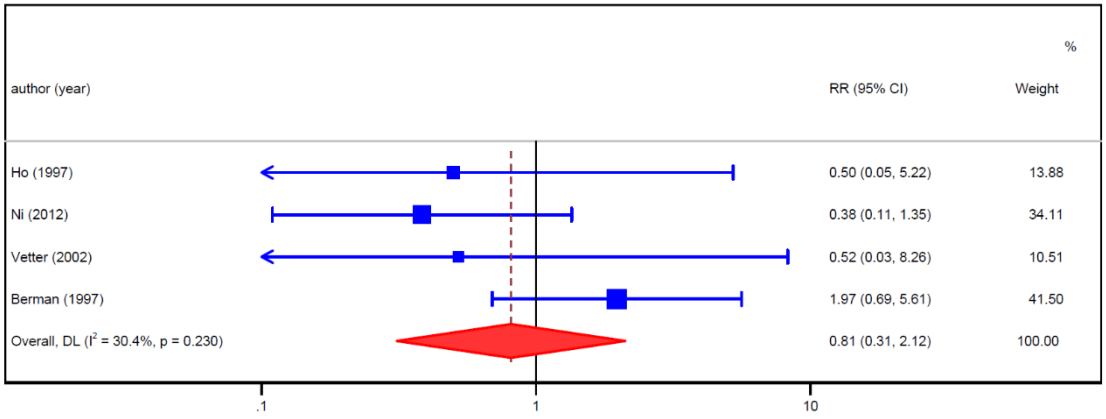
Macrolides vs Respiratory fluoroquinolones



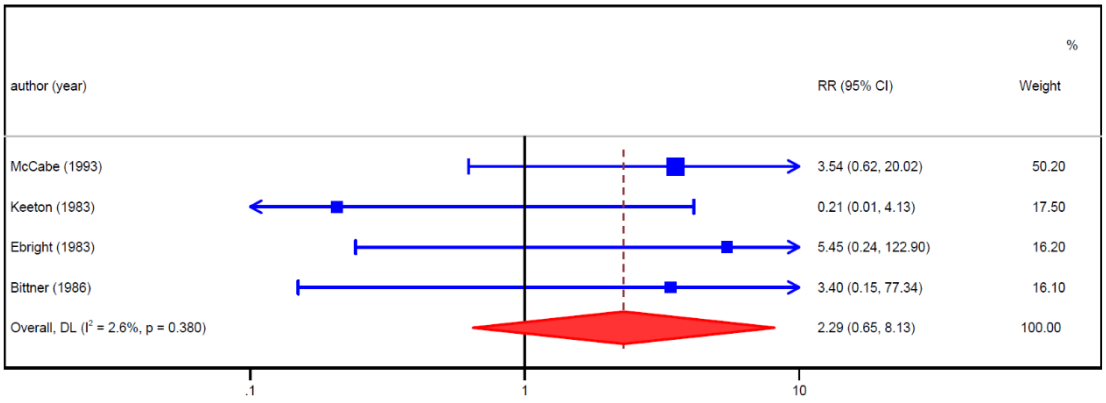
3rd generation cephalosporins vs Respiratory fluoroquinolones



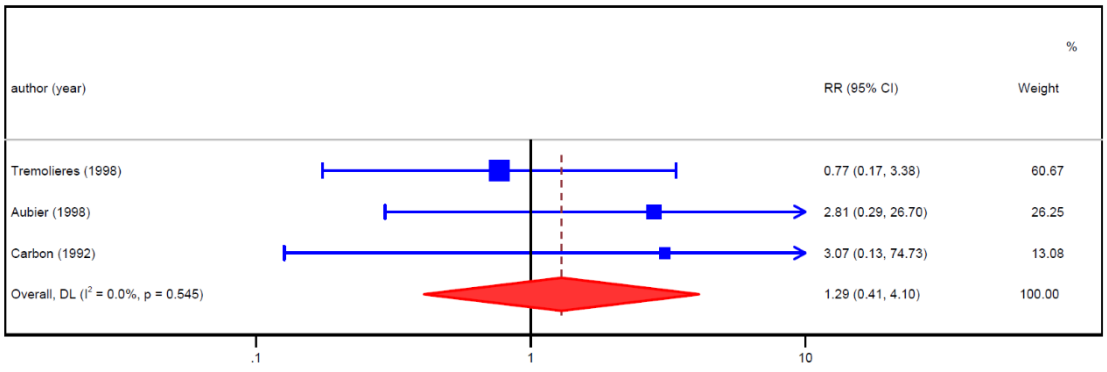
Carbapenems vs 3rd generation cephalosporins



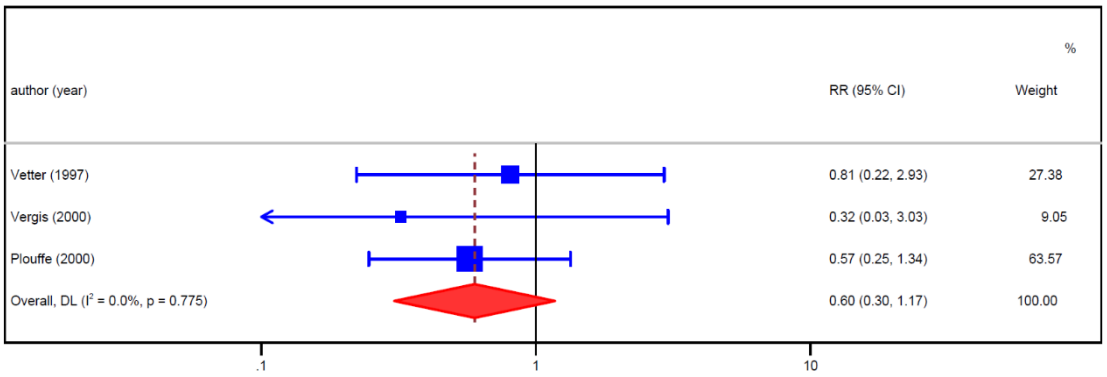
2nd generation cephalosporins vs 3rd generation cephalosporins



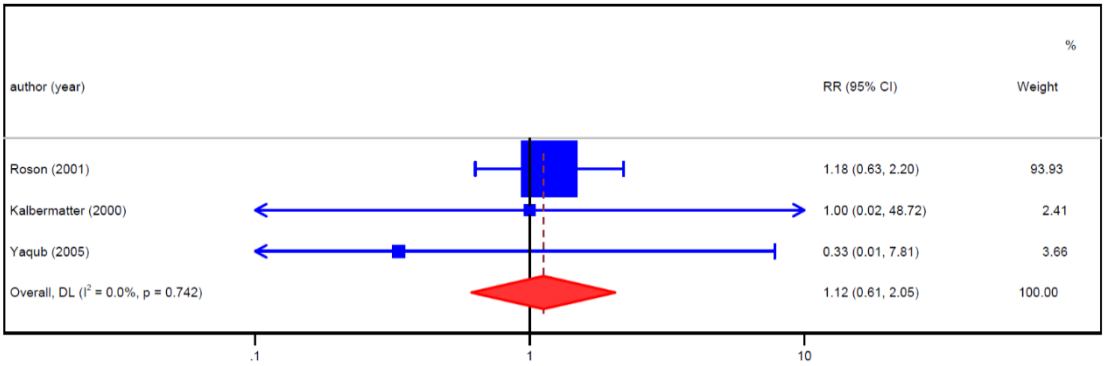
Penicillins vs Respiratory fluoroquinolones



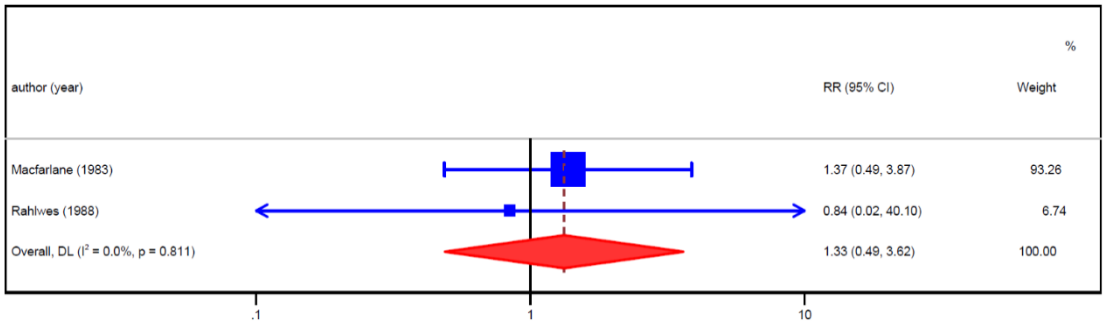
A 2nd generation cephalosporin + a macrolide vs Macrolide alone



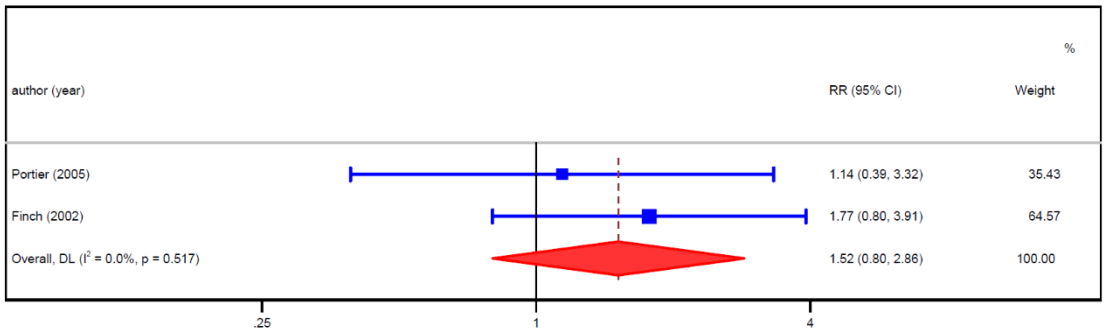
β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporins



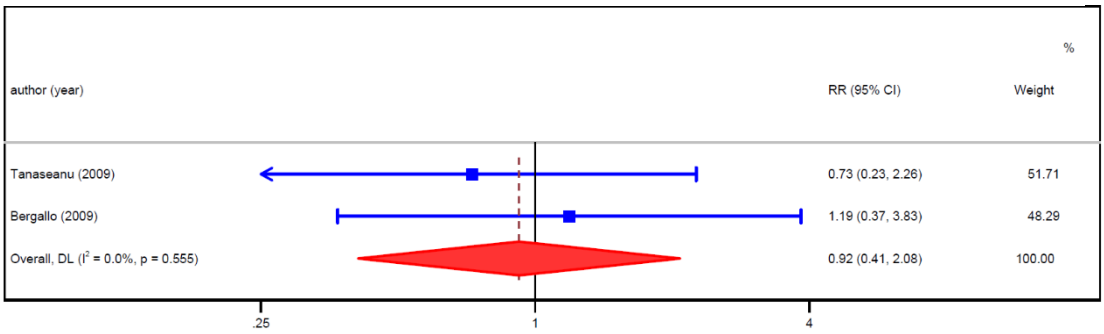
Macrolides vs Penicillins



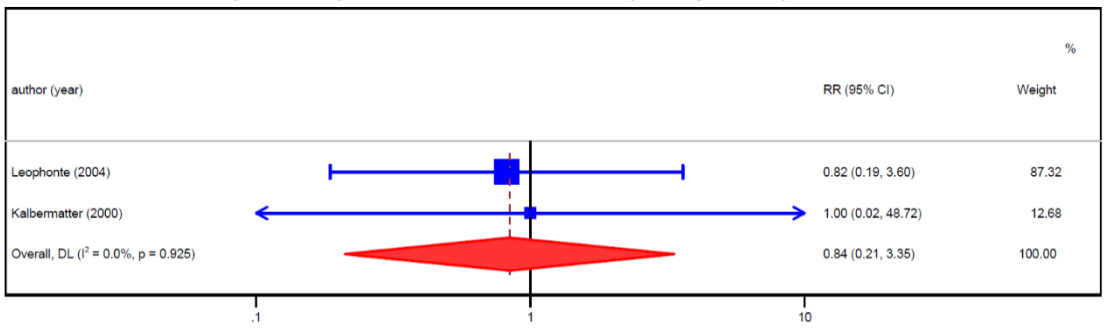
A β-lactam/β-lactamase inhibitor + a macrolide vs Respiratory fluoroquinolones



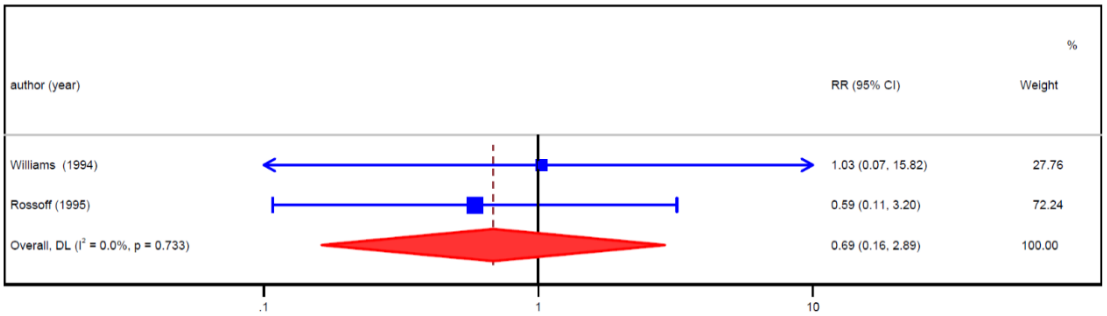
Respiratory fluoroquinolones vs Tigecycline



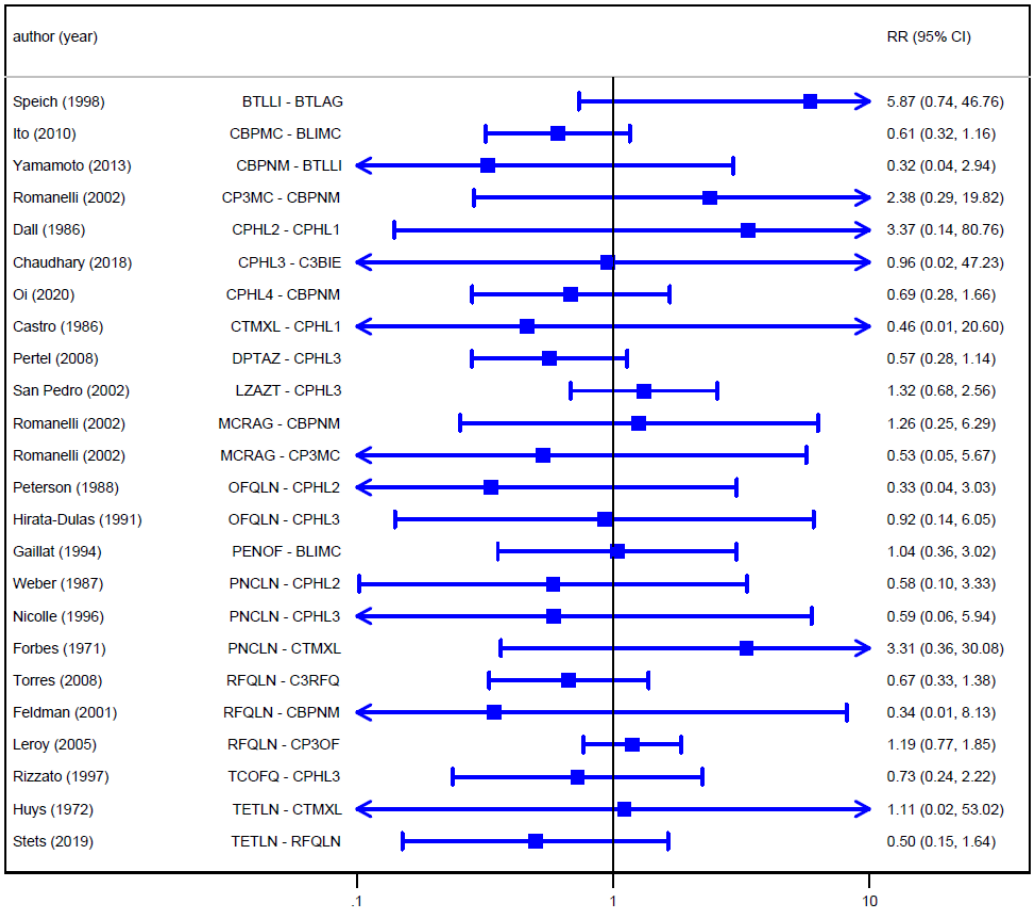
β-Lactam/β-lactamase inhibitors vs Respiratory fluoroquinolones



β-Lactam/β-lactamase inhibitors vs 2nd generation cephalosporins



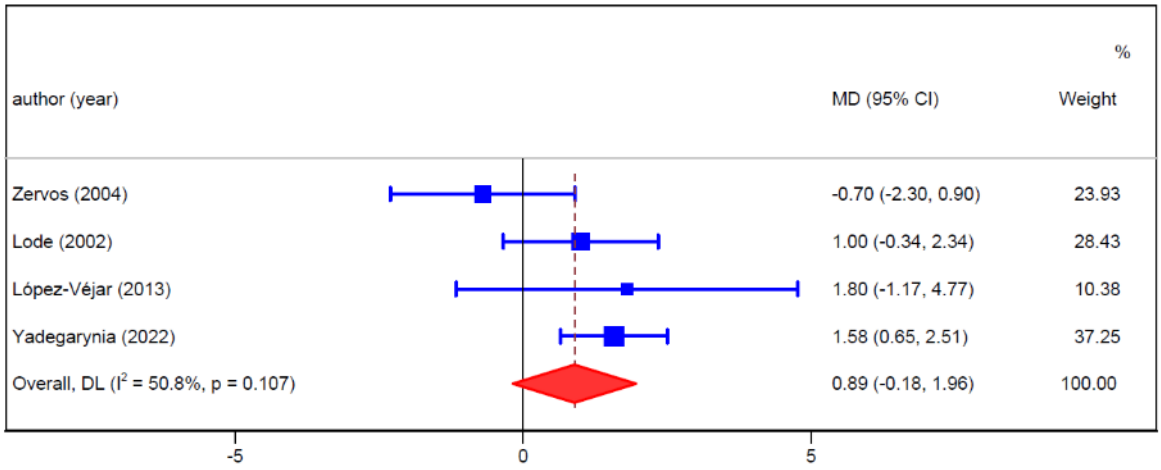
Direct comparisons informed by one trial



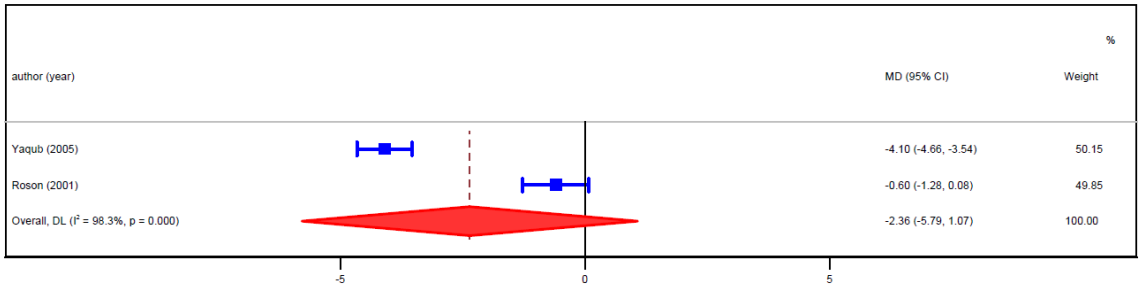
The effect is the comparison of second treatment versus the first treatment (e.g., BTLLI -BTLAG: BTLAG versus BTLLI). BTLLI: β-lactam/β-lactamase inhibitor; BLIMC: A β-lactam/β-lactamase inhibitor plus a macrolide; BTLAG: A β-lactam/β-lactamase inhibitor plus an aminoglycoside; CBPMC: a carbapenem plus a macrolide; CBPNM: carbapenem; CP3MC: a 3rd generation cephalosporin plus a macrolide; CPHL3: 3rd generation cephalosporin; C3BIE: 3rd generation cephalosporin/β-lactamase inhibitor; CPHL4: 4th generation cephalosporin; CTMXL: cotrimoxazole; CPHL1: 1st generation cephalosporin; DPTAZ: daptomycin plus aztreonam; LZAZT: linezolid plus aztreonam; MCRAG: a macrolide plus an aminoglycoside; MCRLD: macrolide; CP2TT: a 2nd generation cephalosporin plus a tetracycline; CPHL2: 2nd generation cephalosporin; OFQLN: other fluoroquinolone; PENOF: a penicillin plus an other fluoroquinolone; PNCLN: penicillin; RFQLN: respiratory fluoroquinolone; C3RFQ: a 3rd generation cephalosporin plus a respiratory fluoroquinolone; CP3OF: a 3rd generation cephalosporin plus an other fluoroquinolone; TCOFQ: teicoplanin plus an other fluoroquinolone; TETLN: tetracycline.

Duration of hospitalization

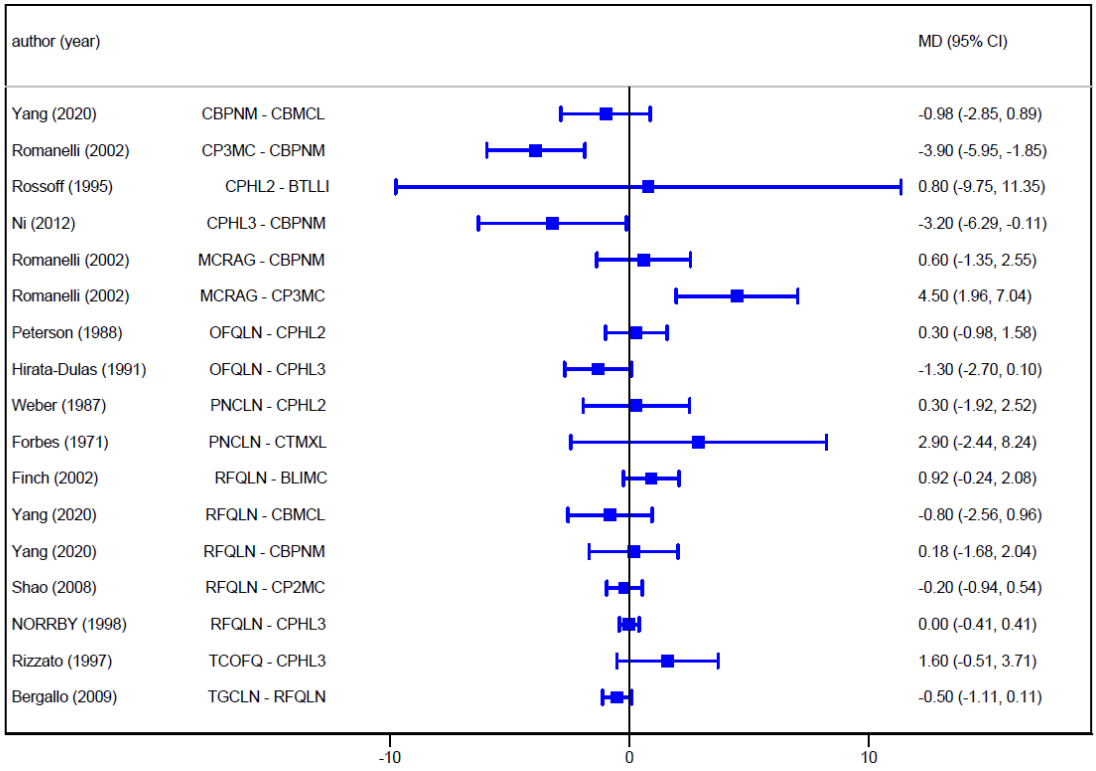
A 3rd generation cephalosporin + a macrolide vs Respiratory fluoroquinolones



β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporins



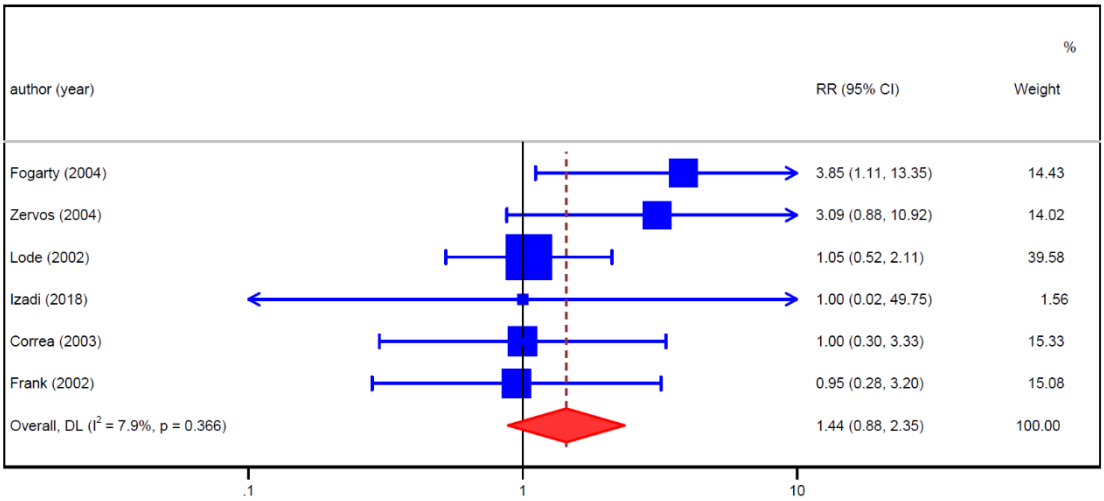
Direct comparisons informed by one trial



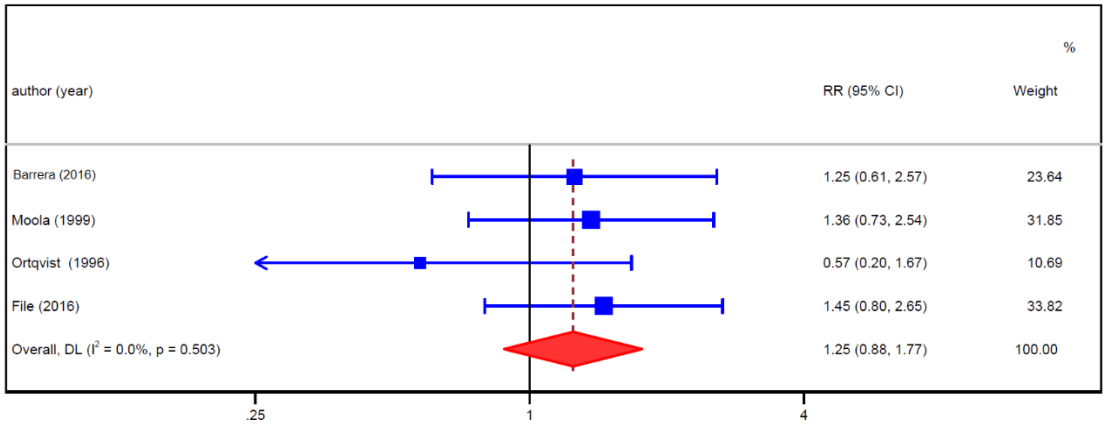
The effect is the comparison of second treatment versus the first treatment (e.g., CBPNM -CBMCL: CBMCL versus CBPNM). BTLLI: β-lactam/β-lactamase inhibitor; BLIMC: A β-lactam/β-lactamase inhibitor plus a macrolide; CBMCL: a carbapenem plus a macrolide; CBPNM: carbapenem; CP3MC: a 3rd generation cephalosporin plus a macrolide; CPHL3: 3rd generation cephalosporin; CTMXL: cotrimoxazole; MCRAG: a macrolide plus an aminoglycoside; CPHL2: 2nd generation cephalosporin; OFQLN: other fluoroquinolone; PNCLN: penicillin; RFQLN: respiratory fluoroquinolone; CP2MC: a 2nd generation cephalosporin plus a macrolide; TCOFQ: teicoplanin plus an other fluoroquinolone; TGCLN: tigecycline.

Discontinuation due to adverse events

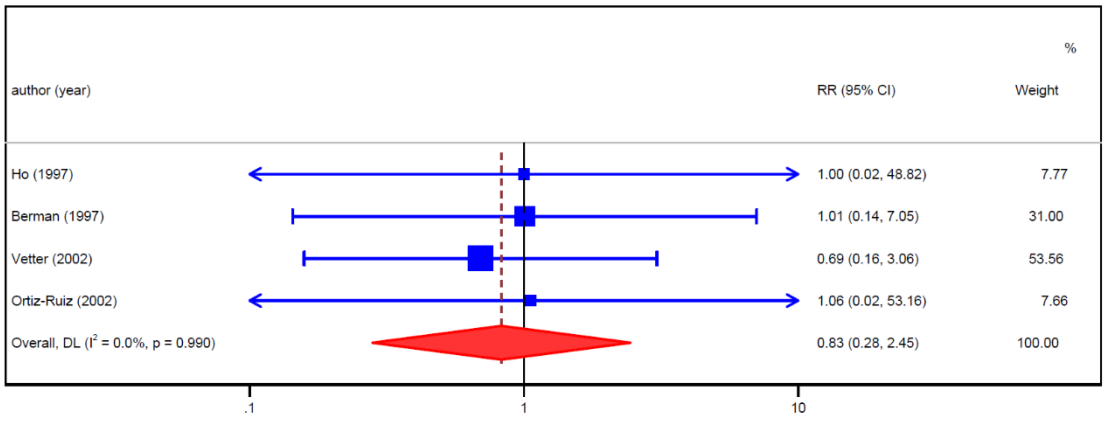
A 3rd generation cephalosporin + a macrolide vs Respiratory fluoroquinolones



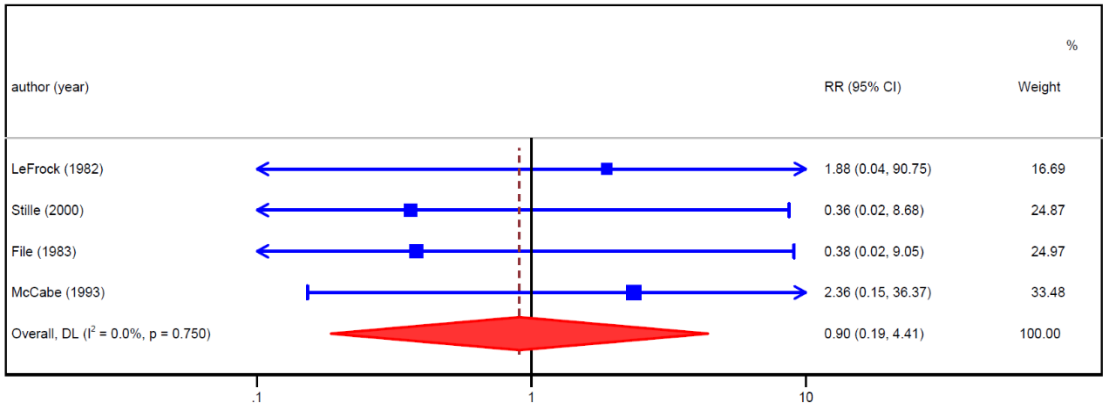
Macrolides vs Respiratory fluoroquinolones



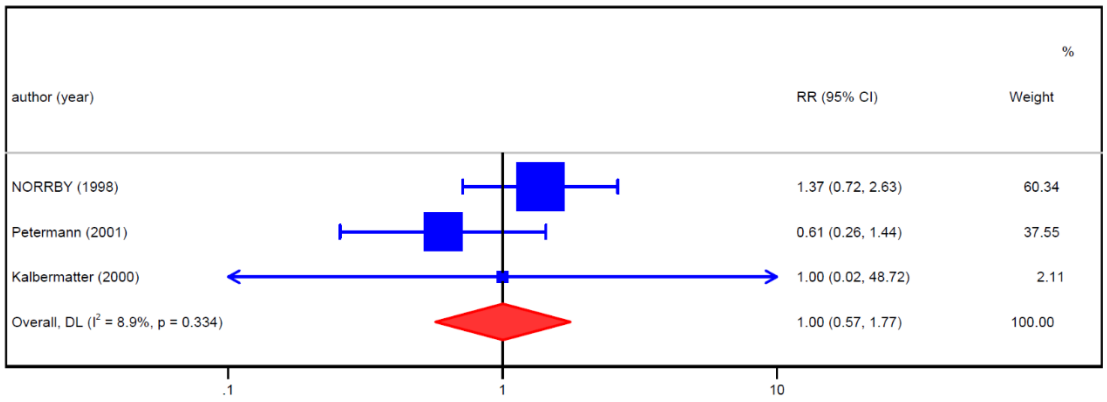
Carbapenems vs 3rd generation cephalosporins



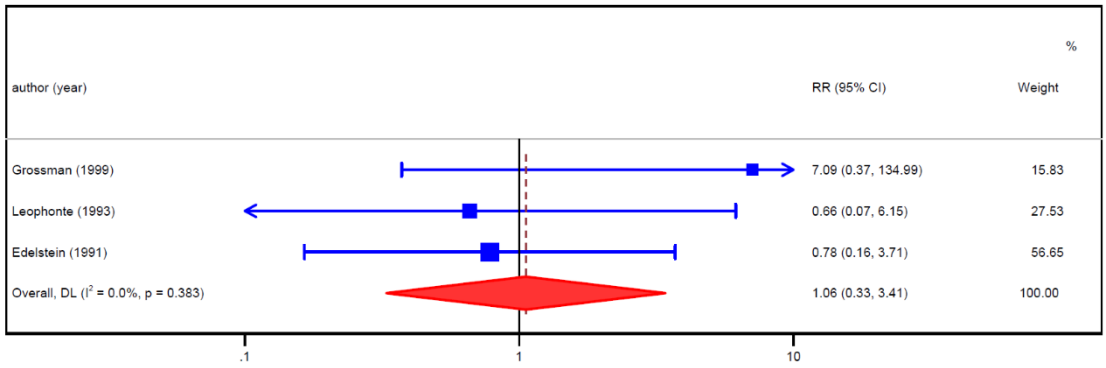
2nd generation cephalosporins vs 3rd generation cephalosporins



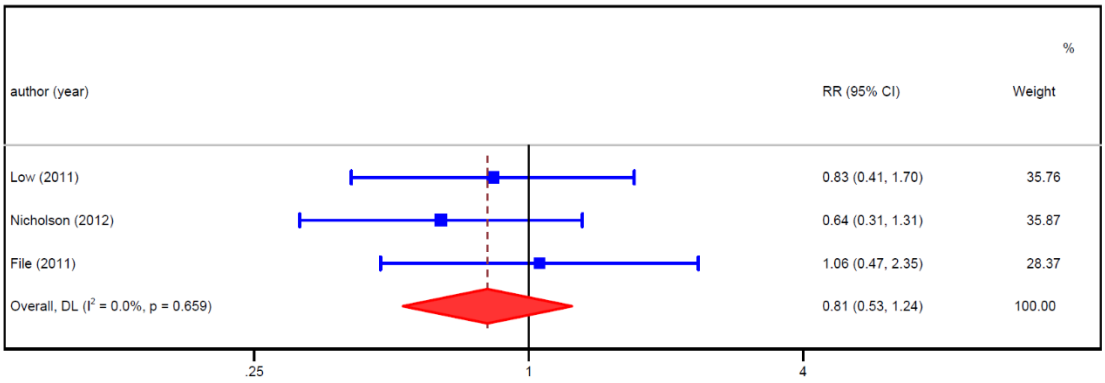
3rd generation cephalosporins vs Respiratory fluoroquinolones



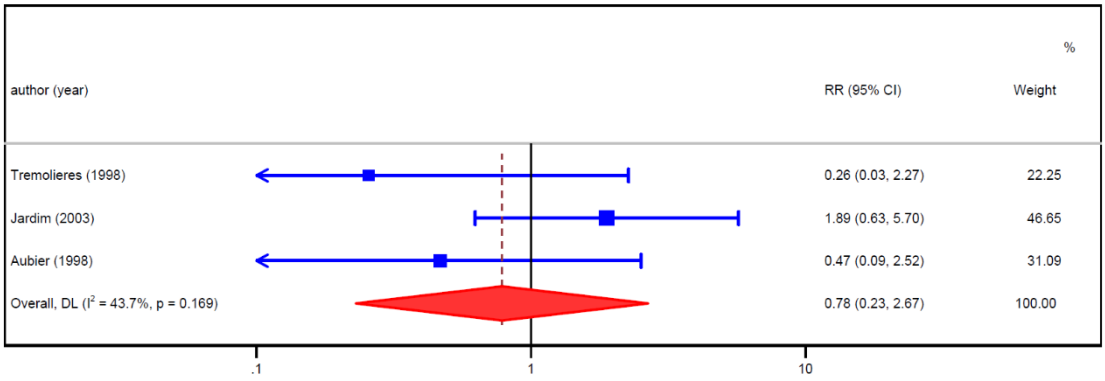
3rd generation cephalosporins vs 4th generation cephalosporins



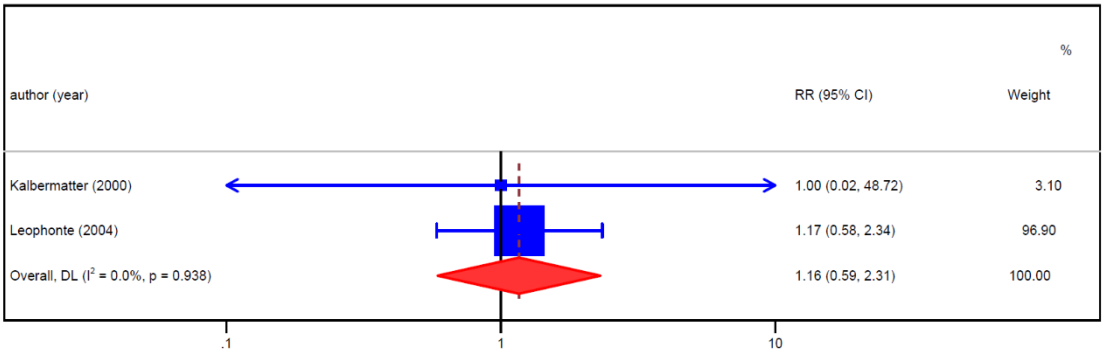
3rd generation cephalosporins vs 5th generation cephalosporins



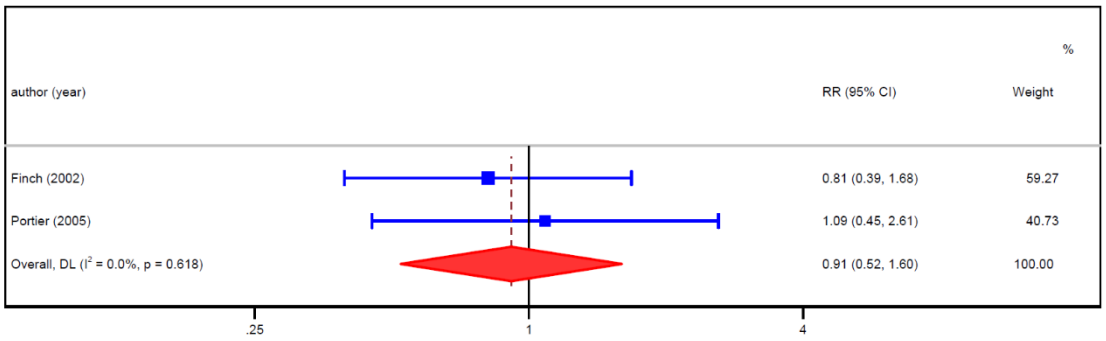
Penicillin vs Respiratory fluoroquinolone



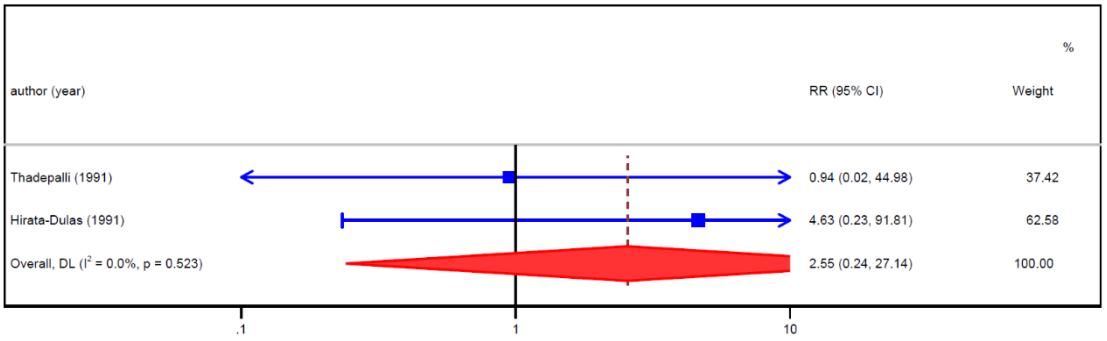
β-Lactam/β-lactamase inhibitors vs Respiratory fluoroquinolones



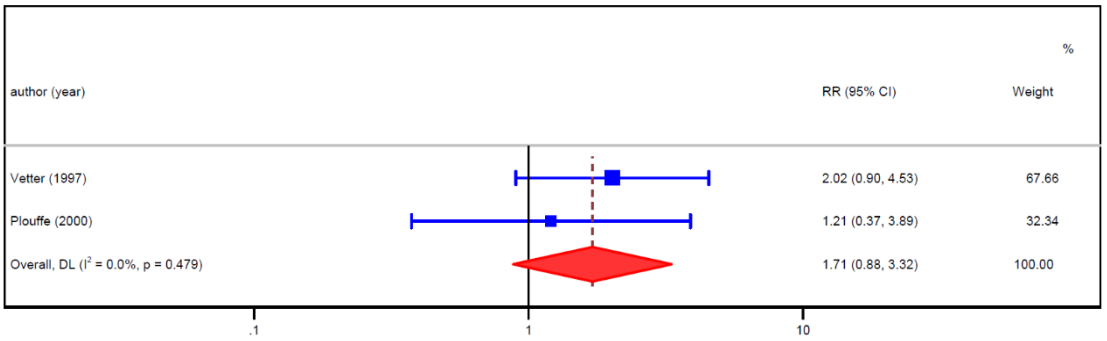
A β-lactam/β-lactamase inhibitor + a macrolide vs Respiratory fluoroquinolones



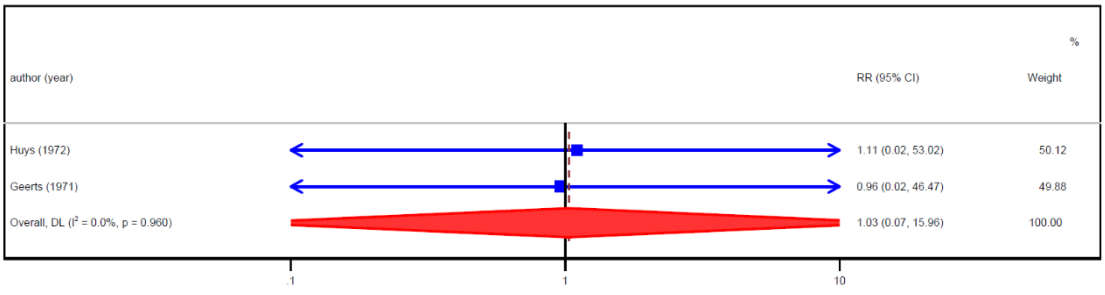
3rd generation cephalosporins vs Other fluoroquinolones



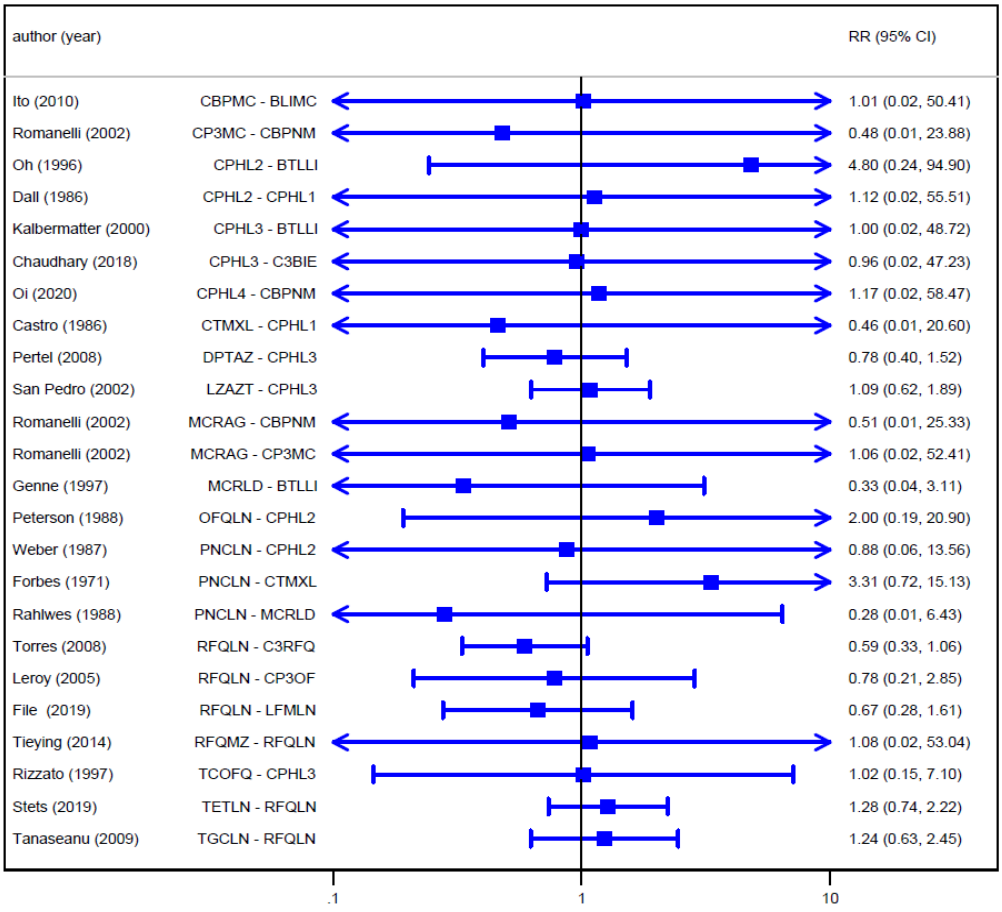
A 2nd generation cephalosporin + a macrolide vs Macrolide alone



Cotrimoxazole vs Tetracycline



Direct comparisons informed by one trial



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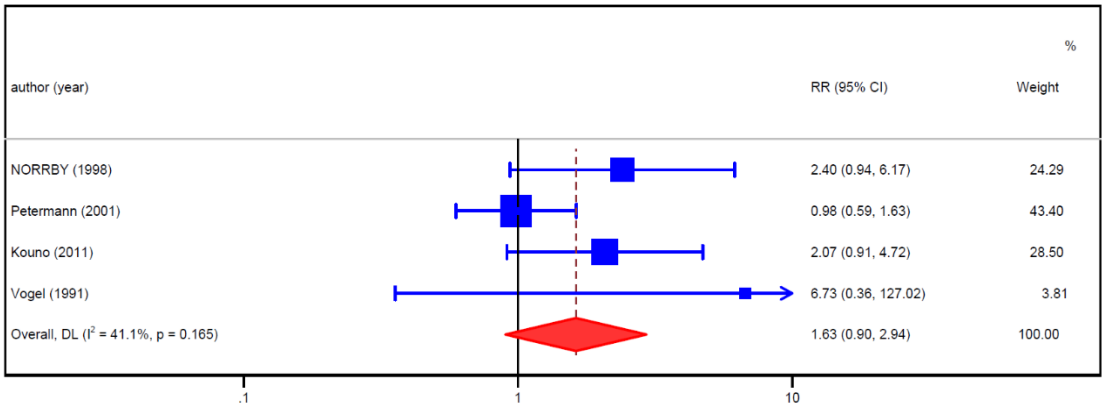
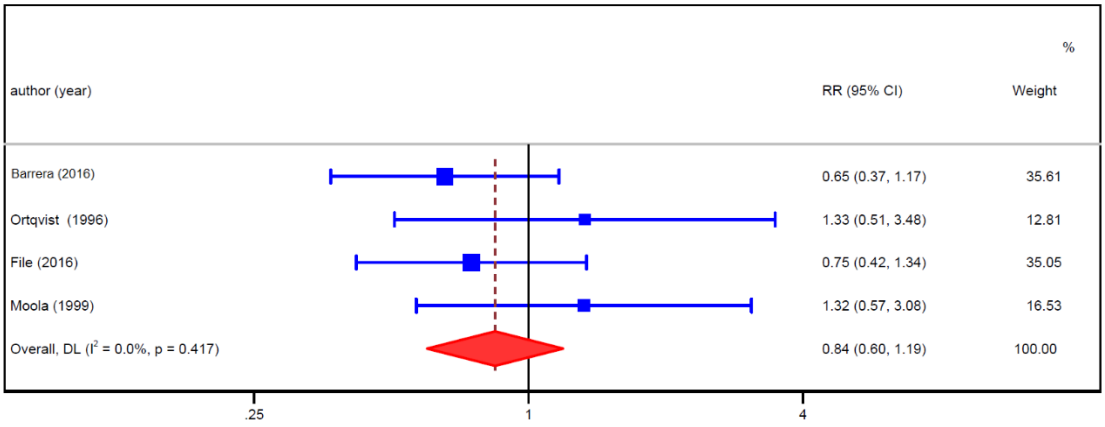
Diarrhea

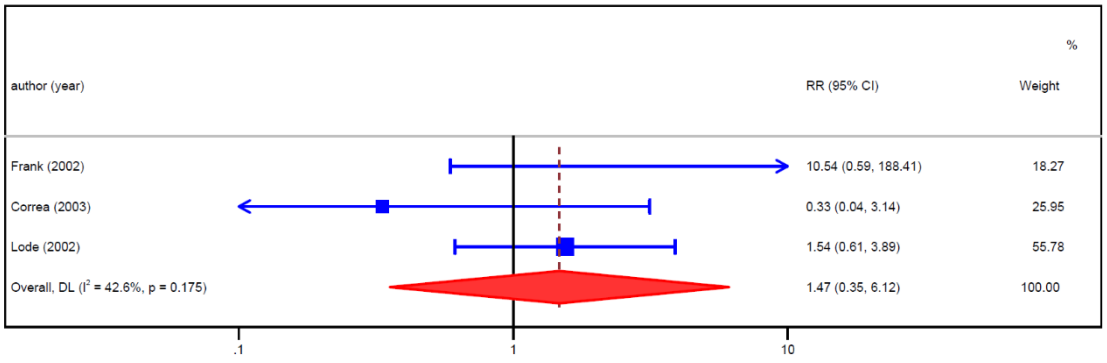
3rd generation cephalosporins vs Respiratory fluoroquinolones



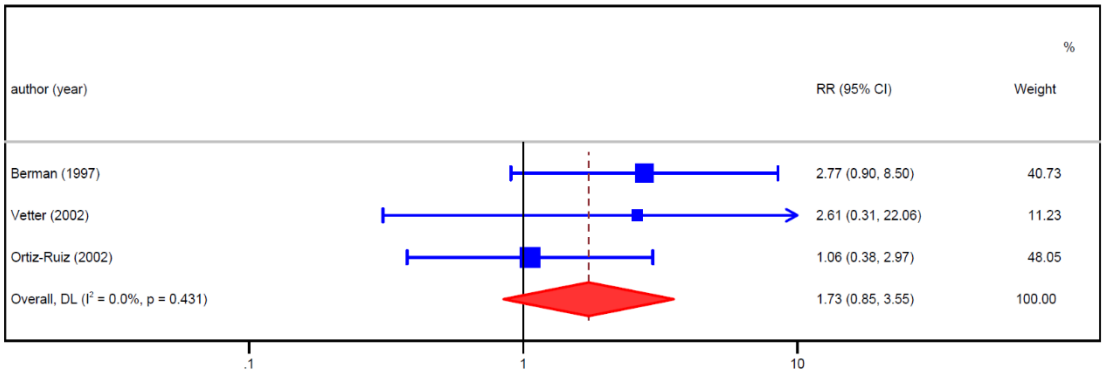
Macrolides vs Respiratory fluoroquinolones



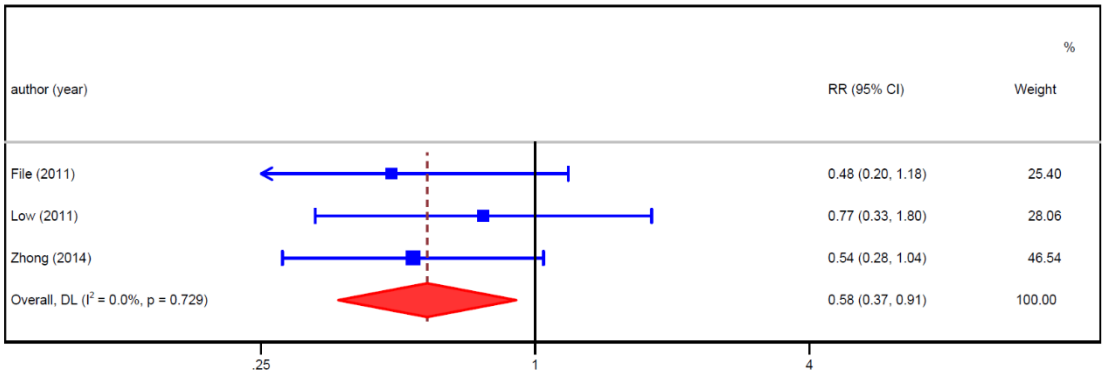
A 3rd generation cephalosporin + a macrolide vs Respiratory fluoroquinolones



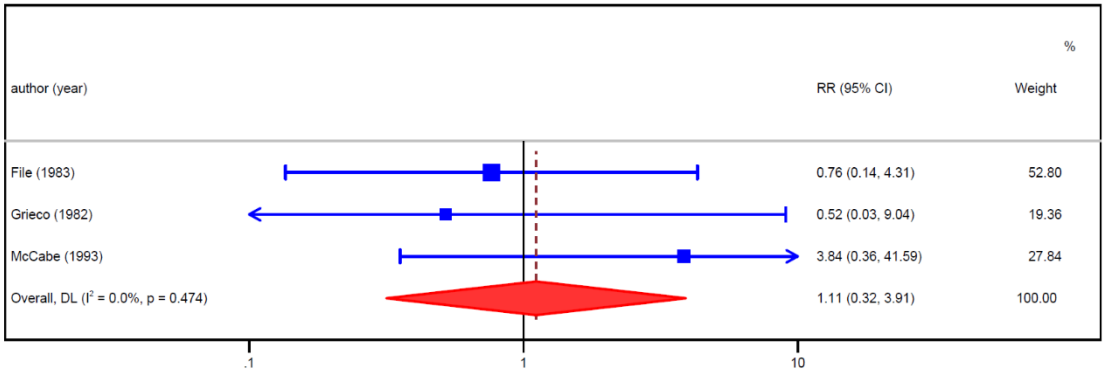
Carbapenems vs 3rd generation cephalosporins



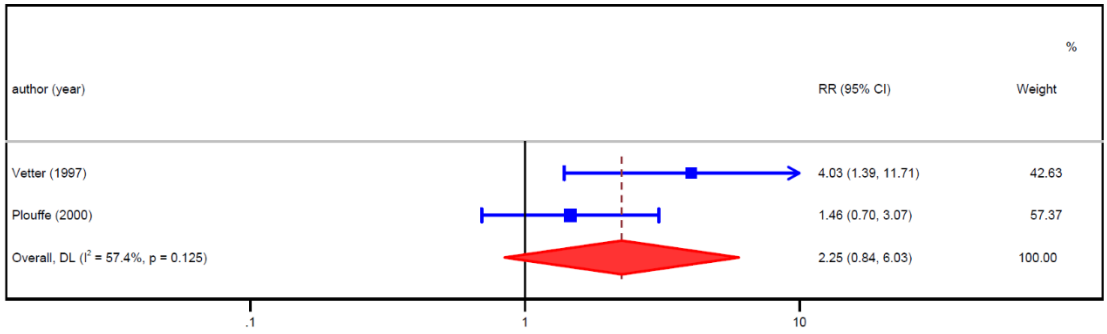
3rd generation cephalosporins vs 5th generation cephalosporins



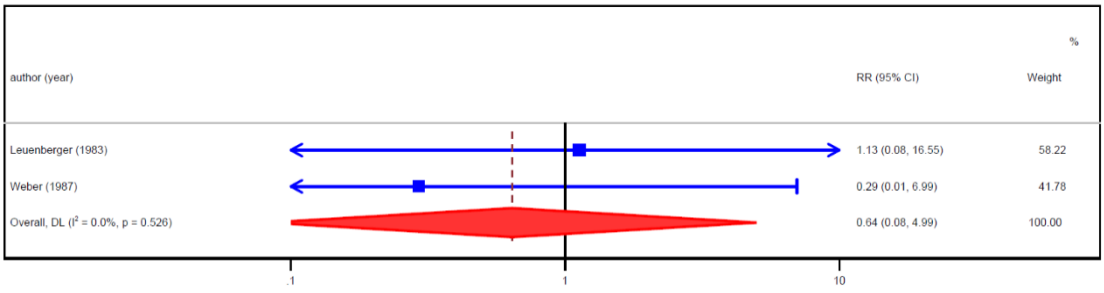
2nd generation cephalosporins vs 3rd generation cephalosporins



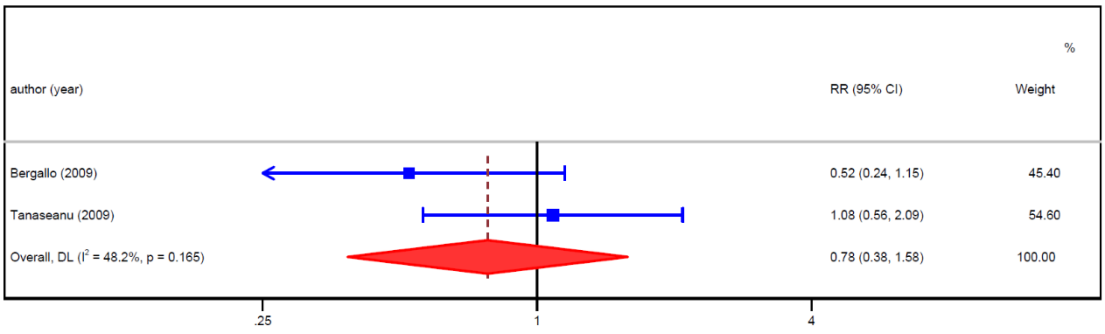
A 2nd generation cephalosporin + a macrolide vs Macrolide alone



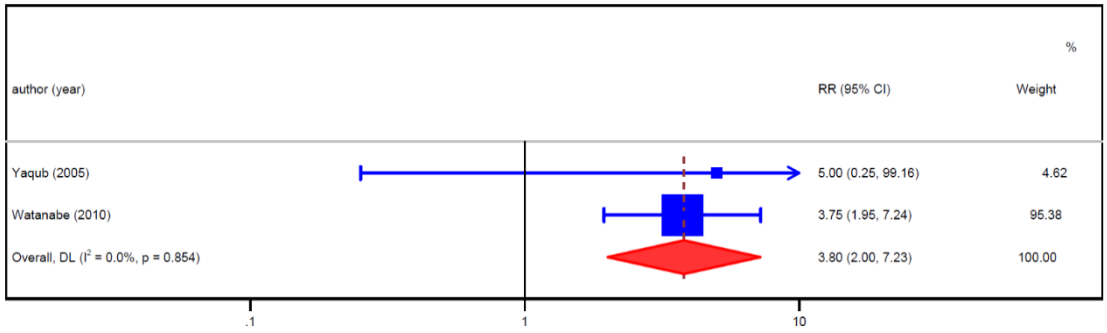
2nd generation cephalosporins vs Penicillins



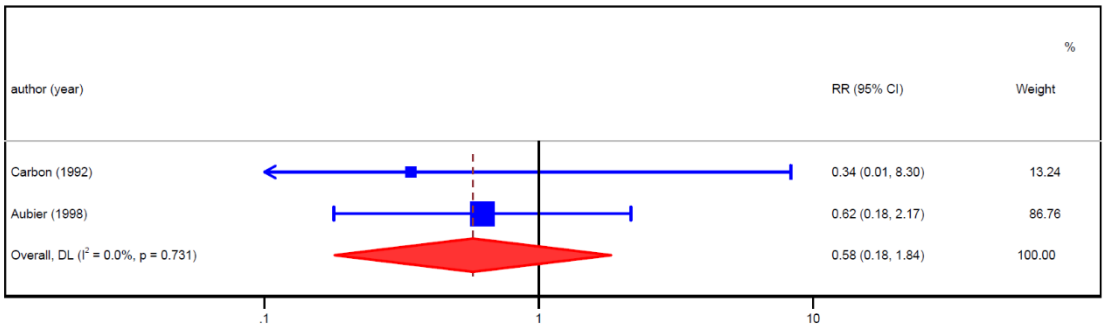
Respiratory fluoroquinolones vs Tigecycline



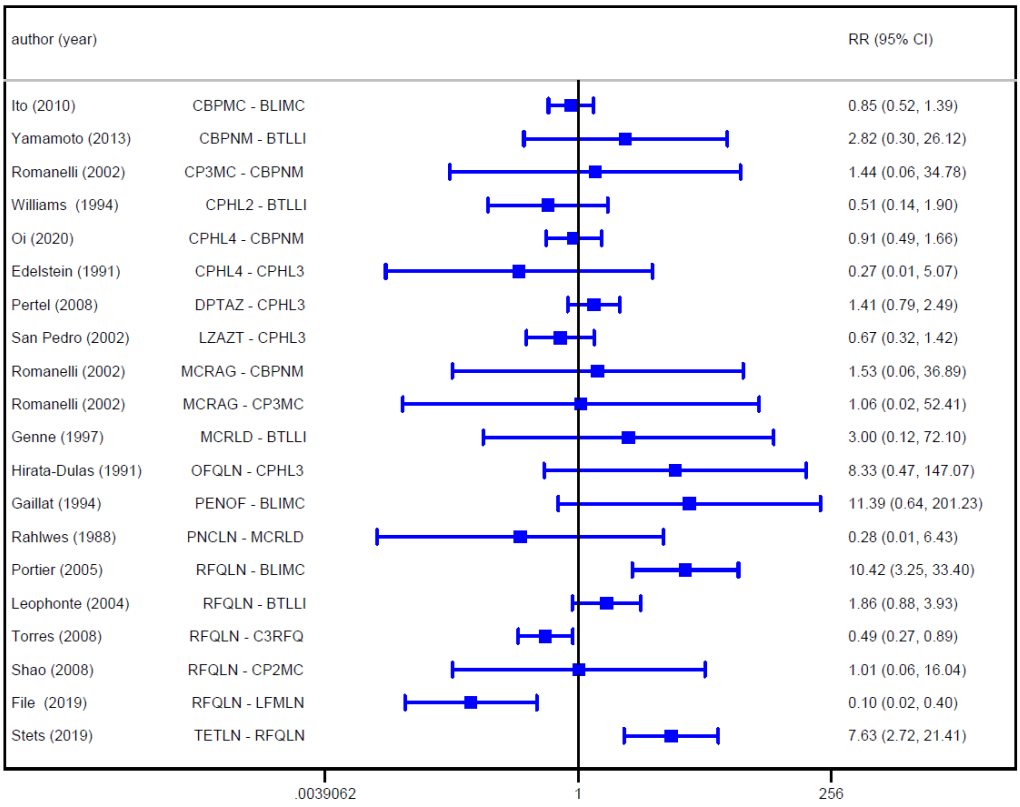
β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporins



Penicillins vs Respiratory fluoroquinolones



Direct comparisons informed by one trial



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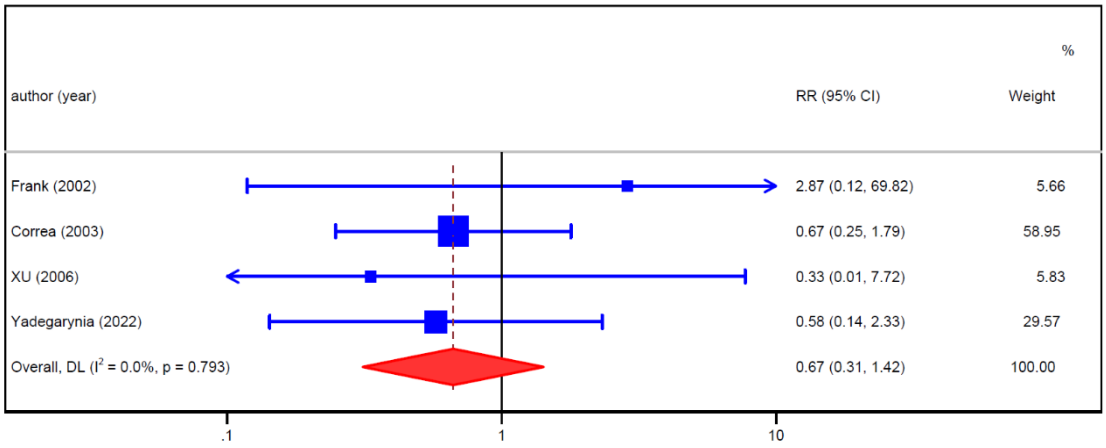
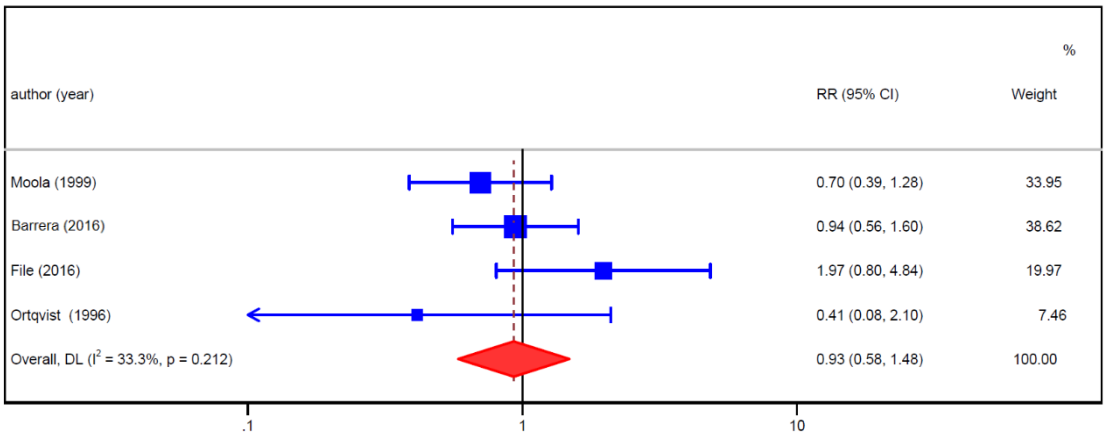
Nausea and/or vomiting

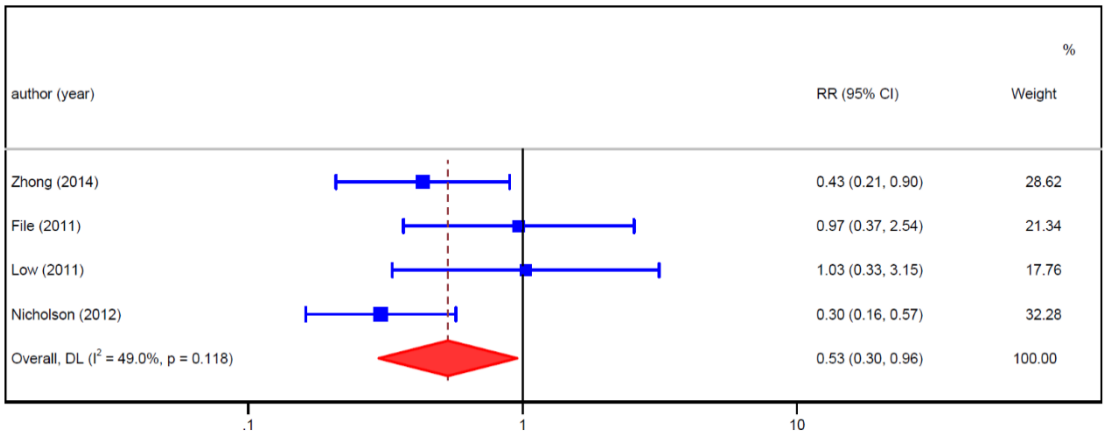
A 3rd generation cephalosporin + a macrolide vs Respiratory fluoroquinolones



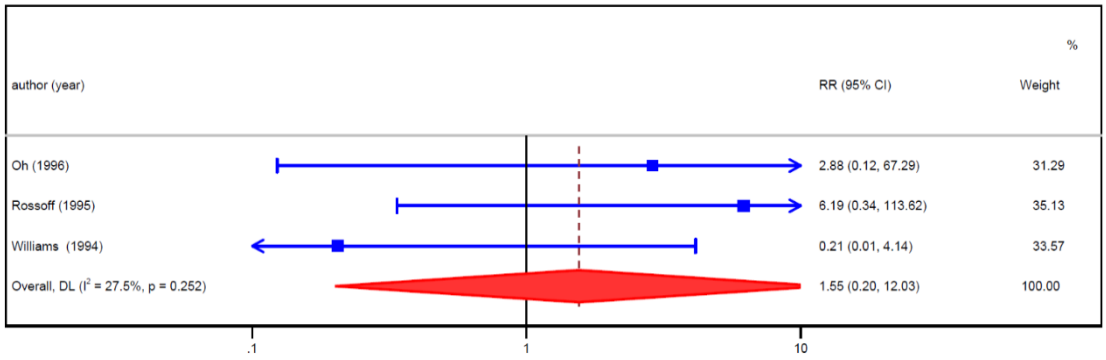
Macrolides vs Respiratory fluoroquinolones



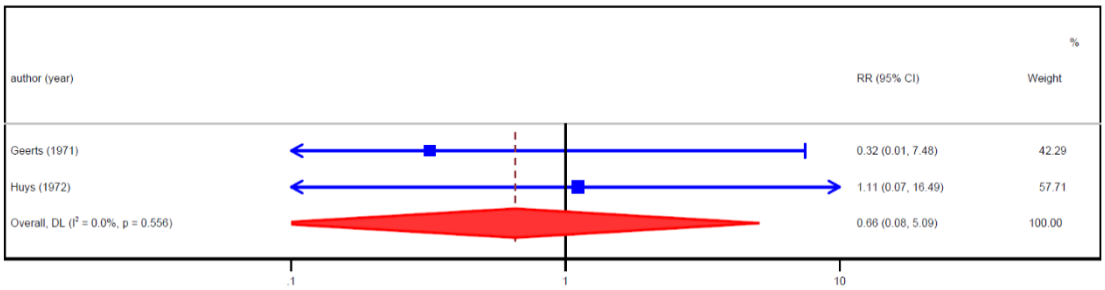
3rd generation cephalosporins vs 5th generation cephalosporins



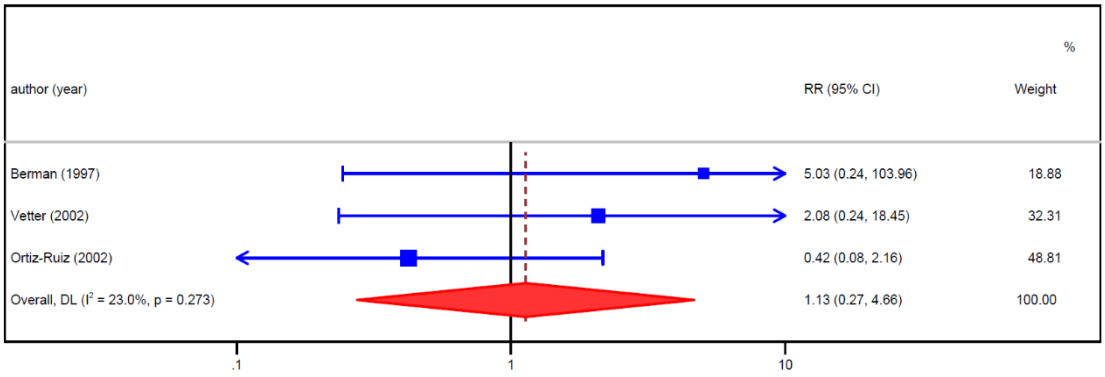
β-Lactam/β-lactamase inhibitors vs 2nd generation cephalosporins



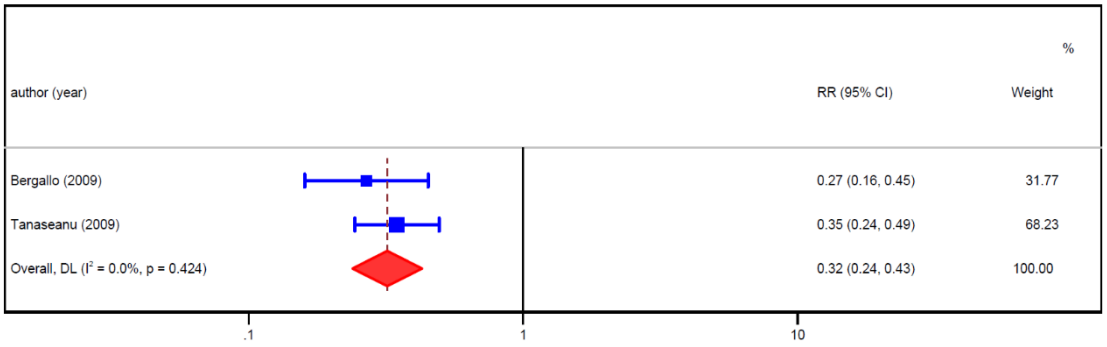
Cotrimoxazole vs Tetracycline



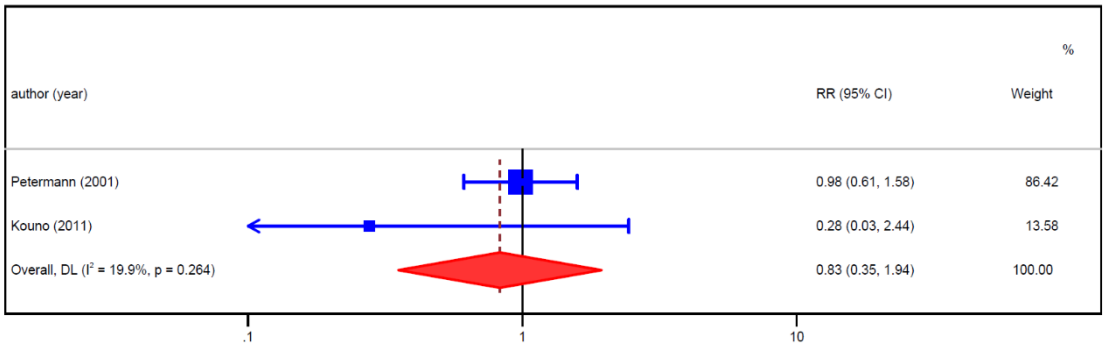
Carbapenems vs 3rd generation cephalosporins



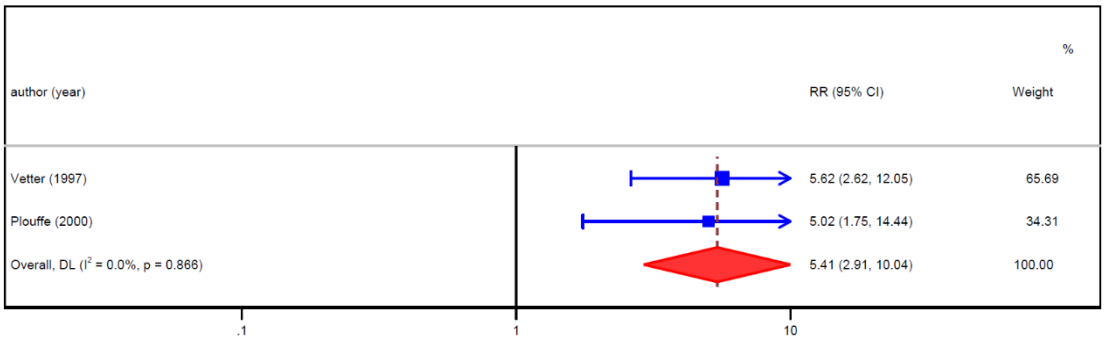
Respiratory fluoroquinolone vs Tigecycline



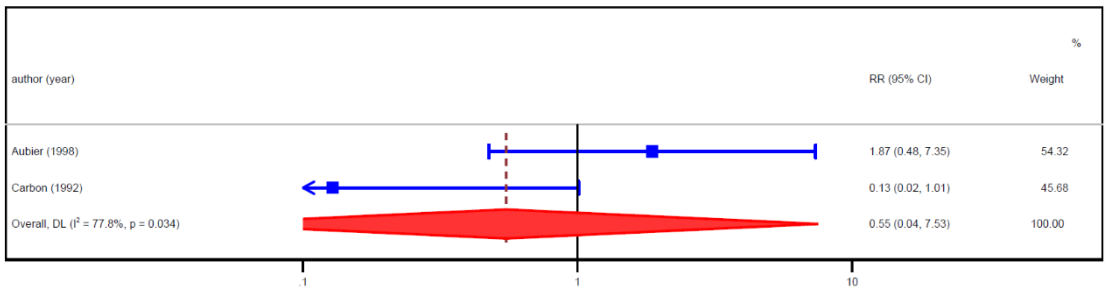
3rd generation cephalosporins vs Respiratory fluoroquinolones

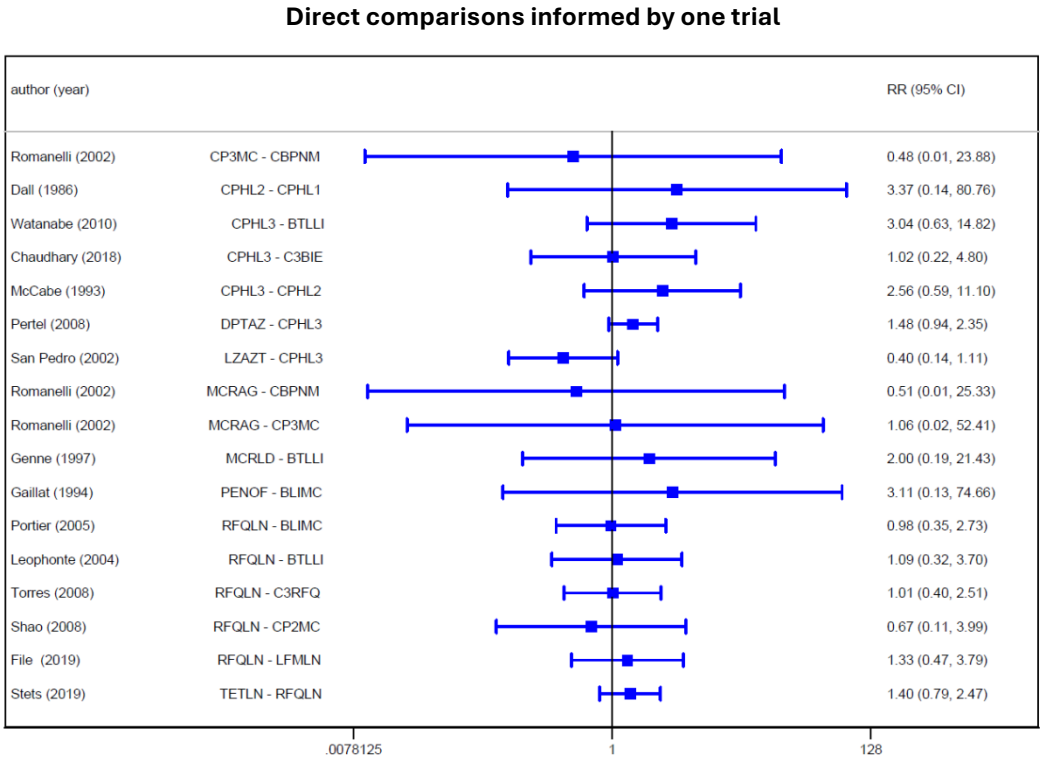


A 2nd generation cephalosporin + a macrolide vs Macrolide alone



Penicillins vs Respiratory fluoroquinolones





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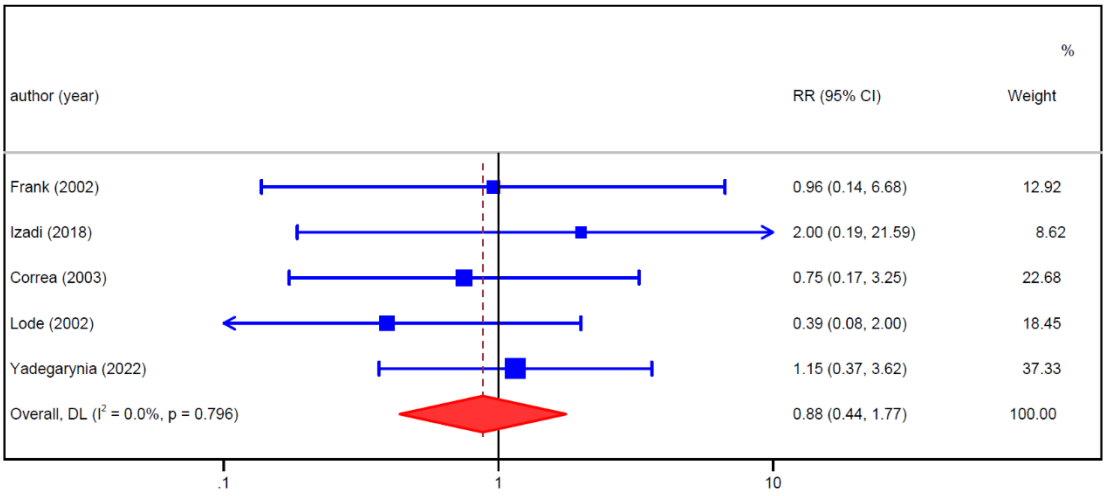
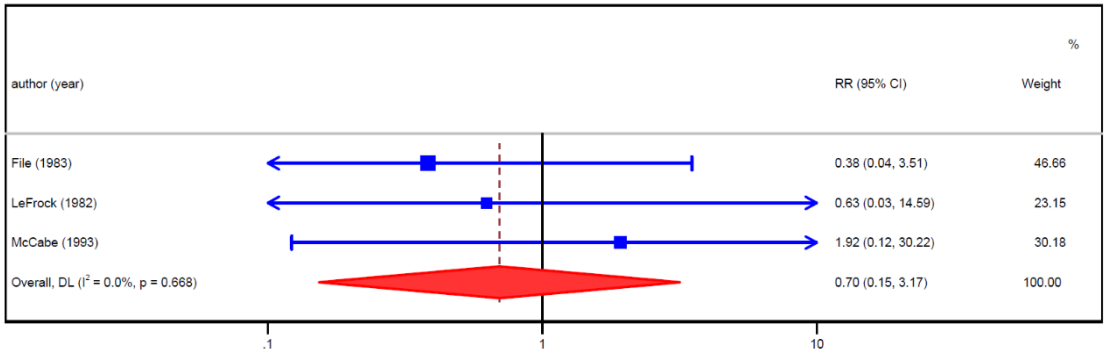
Any allergic reactions

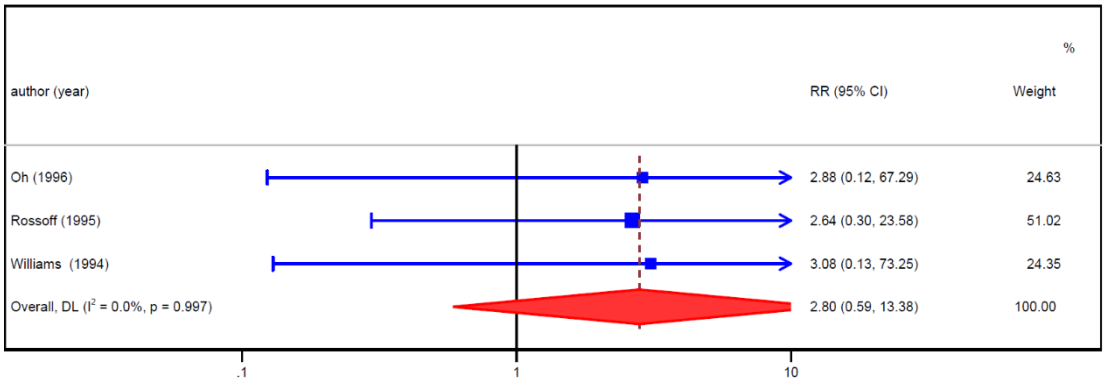
A 3rd generation cephalosporin + a macrolide vs Respiratory fluoroquinolones



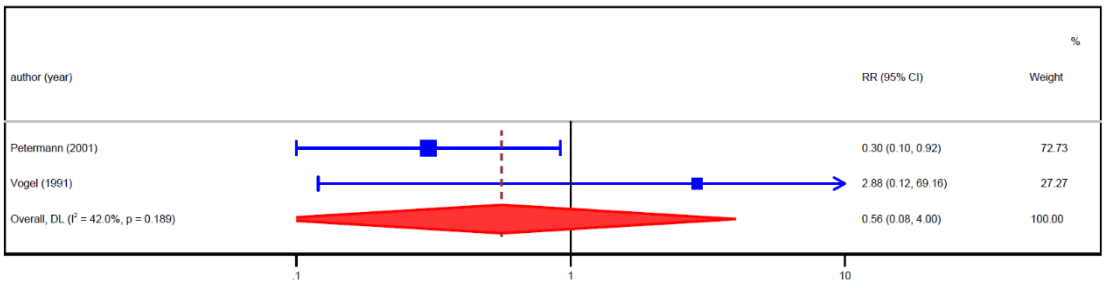
2nd generation cephalosporins vs 3rd generation cephalosporins



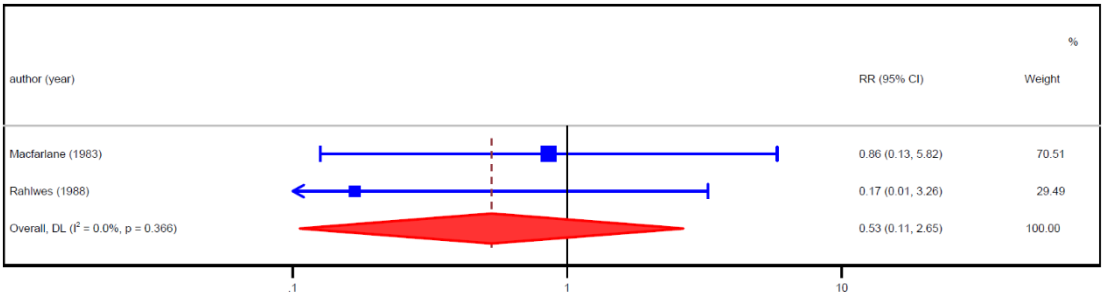
β-Lactam/β-lactamase inhibitors vs 2nd generation cephalosporins



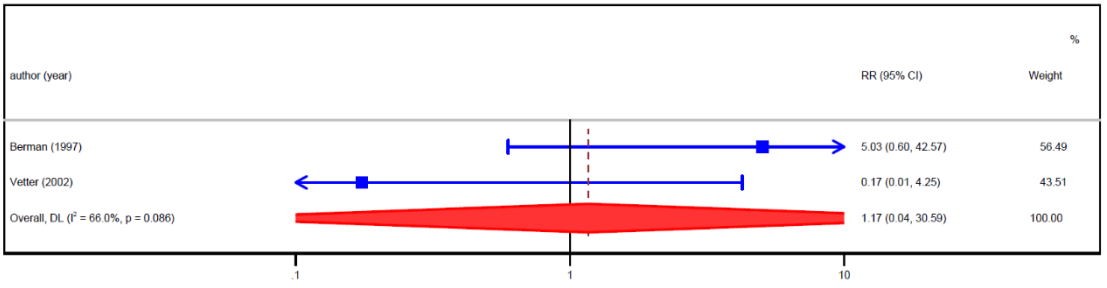
3rd generation cephalosporins vs Respiratory fluoroquinolones



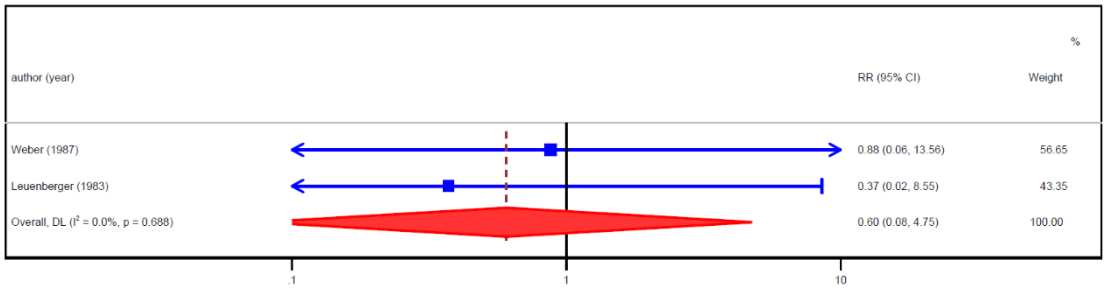
Macrolides vs Penicillins



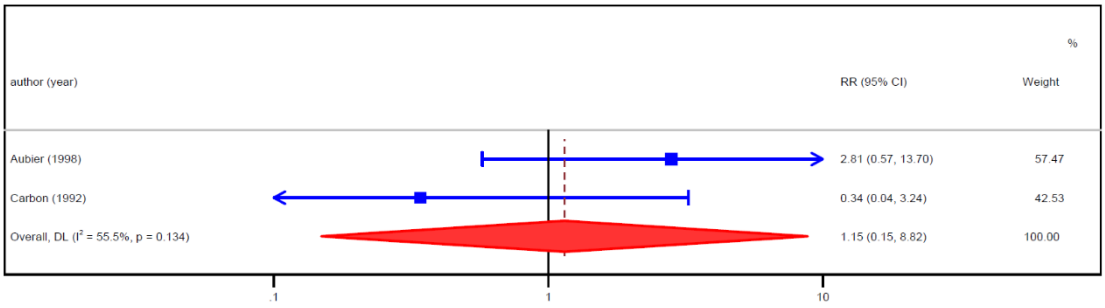
Carbapenems vs 3rd generation cephalosporins

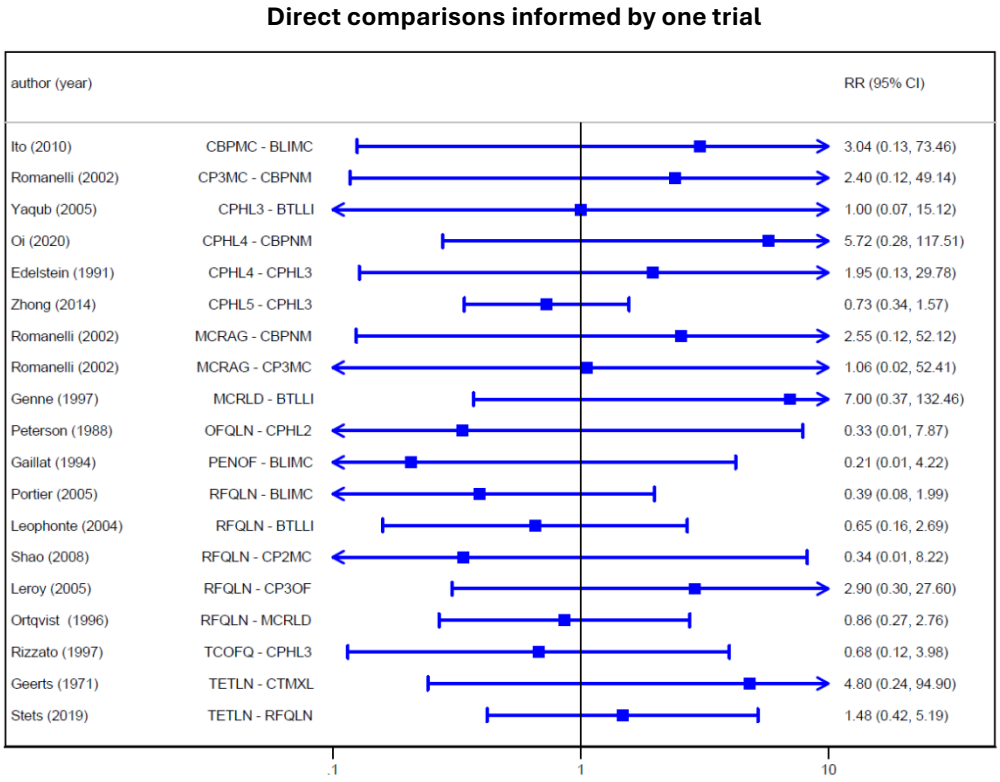


2nd generation cephalosporins vs Penicillins



Penicillin vs Respiratory fluoroquinolone





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Supplement 9. Direct, indirect, and network estimates and certainty of evidence for treatment failure

Minimal important difference	20 per 1000 patients												
Large effect threshold	60 per 1000 patients												
Baseline risk [1]	132 per 1000 patients												
	Direct evidence		**Indirect evidence**	**Network evidence**							**Best estimate**	**Final certainty rating if the best estimate is not NMA**	**Reason for downgrading the certainty**
Comparison	**RR (95% CI)**	**RD** [2] **(95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RD** [2] **(95% CI)**	**Starting evidence**	**Starting certainty rating**	**Incoherence**	**Imprecision**	**Final certainty rating**			
Penicillins vs Respiratory fluoroquinolones	1.31 (0.92, 1.87)	41 (-11, 115)	1.1 (0.62, 1.95)	1.25 (0.93, 1.67)	33 (-9, 88)	Direct	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Penicillin + Other fluoroquinolone vs Respiratory fluoroquinolones	0.99 (0.66, 1.49)	-1 (-45, 65)	0.95 (0.43, 2.07)	0.98 (0.65, 1.47)	-3 (-46, 62)	Direct	HIGH	Not serious	Serious	MODERATE	NMA	NA	Imprecision
β-Lactam/β-lactamase inhibitors vs Respiratory fluoroquinolones	0.93 (0.67, 1.29)	-9 (-44, 38)	1.32 (0.92, 1.88)	1.1 (0.85, 1.44)	13 (-20, 58)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
β-Lactam/β-lactamase inhibitor + Macrolide vs Respiratory fluoroquinolones	1.16 (0.89, 1.49)	21 (-15, 65)	1.3 (0.63, 2.67)	1.15 (0.87, 1.53)	20 (-17, 70)	Direct	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs Respiratory fluoroquinolones	NA	NA	1.84 (0.55, 6.15)	1.84 (0.55, 6.15)	111 (-59, 680)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
1st generation cephalosporins vs Respiratory fluoroquinolones	NA	NA	2.38 (0.44, 12.94)	2.38 (0.44, 12.94)	182 (-74, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
2nd generation cephalosporins vs Respiratory fluoroquinolones	5.09 (0.25, 103.63)	540 (-99, 1000)	1.31 (0.87, 1.98)	1.34 (0.89, 2.02)	45 (-15, 135)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
3rd generation cephalosporins vs Respiratory fluoroquinolones	1.37 (0.93, 2.01)	49 (-9, 133)	1.27 (0.83, 1.94)	1.32 (0.99, 1.77)	42 (-1, 102)	Direct	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
4th generation cephalosporins vs Respiratory fluoroquinolones	NA	NA	1.22 (0.81, 1.83)	1.22 (0.81, 1.83)	29 (-25, 110)	Indirect	MODERATE	Not serious	Vey Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
5th generation cephalosporins vs Respiratory fluoroquinolones	NA	NA	1.03 (0.72, 1.46)	1.03 (0.72, 1.46)	4 (-37, 61)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
3rd generation cephalosporin/β-lactamase inhibitors vs Respiratory fluoroquinolones	0.93 (0.06, 14.03)	-9 (-124, 1000)	0.31 (0.11, 0.92)	0.36 (0.13, 0.99)	-84 (-115, -1)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Respiratory fluoroquinolones	1.18 (0.4, 3.44)	24 (-79, 322)	1.05 (0.74, 1.51)	1.07 (0.76, 1.49)	9 (-32, 65)	Indirect	LOW	Not serious	Serious	VERY LOW	NMA	NA	RoBx2, Imprecision
3rd generation cephalosporin + Macrolide vs Respiratory fluoroquinolones	1.31 (0.97, 1.77)	41 (-4, 102)	4.95 (0.44, 55.56)	1.34 (0.98, 1.84)	45 (-3, 111)	Direct	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision

3rd generation cephalosporin + Respiratory fluoroquinolone vs Respiratory fluoroquinolones	0.79 (0.58, 1.08)	-28 (-55, 11)	NA	0.79 (0.54, 1.17)	-28 (-61, 22)	Direct	LOW	Not serious	Very Serious	VERY LOW	NMA	VERY LOW	Imprecision, Publication bias, Indirectness [3]
3rd generation cephalosporin+ Other fluoroquinolone vs Respiratory fluoroquinolones	0.92 (0.7, 1.22)	-11 (-40, 29)	NA	0.92 (0.64, 1.33)	-11 (-48, 44)	Direct	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
2nd generation cephalosporin +Tetracycline vs Respiratory fluoroquinolones	NA	NA	1.07 (0.53, 2.17)	1.07 (0.53, 2.17)	9 (-62, 154)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin + Aminoglycoside vs Respiratory fluoroquinolones	NA	NA	3.35 (0.88, 12.7)	3.35 (0.88, 12.7)	310 (-16, 1000)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Macrolides vs Respiratory fluoroquinolones	1.11 (0.90, 1.39)	12 (-24, 59)	0.89 (0.47, 1.7)	1.09 (0.89, 1.33)	12 (-15, 44)	Direct	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Macrolide + Aminoglycoside vs Respiratory fluoroquinolones	NA	NA	0.96 (0.1, 9.22)	0.96 (0.1, 9.22)	-5 (-119, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Tetracyclines vs Respiratory fluoroquinolones	0.76 (0.5, 1.19)	-32 (-66, 25)	3.04 (0.07, 132.38)	0.78 (0.48, 1.29)	-29 (-69, 38)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	Imprecisionx2 , Publications bias
Lefamulin vs Respiratory fluoroquinolones	0.99 (0.71, 1.38)	-1 (-38, 50)	NA	0.98 (0.67, 1.43)	-3 (-44, 57)	Direct	HIGH	Not serious	Serious	MODERATE	NMA	NA	Imprecision
Carbapenems vs Respiratory fluoroquinolones	1.03 (0.07, 15.8)	4 (-123, 1000)	1.14 (0.78, 1.68)	1.14 (0.78, 1.66)	18 (-29, 87)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Carbapenem + Macrolide vs Respiratory fluoroquinolones	NA	NA	1.06 (0.62, 1.83)	1.06 (0.62, 1.83)	8 (-50, 110)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Respiratory fluoroquinolone + metronidazole vs Respiratory fluoroquinolones	1.69 (0.7, 4.17)	91 (-40, 418)	NA	1.7 (0.68, 4.26)	92 (-42, 430)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Other fluoroquinolones vs Respiratory fluoroquinolones	NA	NA	1.04 (0.6, 1.81)	1.04 (0.6, 1.81)	5 (-53, 107)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Tigecycline vs Respiratory fluoroquinolones	0.94 (0.71, 1.25)	-8 (-38, 33)	NA	0.94 (0.68, 1.3)	-8 (-42, 40)	Direct	HIGH	Not serious	Serious	MODERATE	NMA	NA	Imprecision
Cotrimoxazole vs Respiratory fluoroquinolones	NA	NA	0.7 (0.25, 1.98)	0.7 (0.25, 1.98)	-40 (-99, 129)	Indirect	HIGH	Not serious	Extremely serious	VERY LOW	NMA	NA	Imprecisionx3
Daptomycin + Aztreonam vs Respiratory fluoroquinolones	NA	NA	1.7 (1.09, 2.65)	1.7 (1.09, 2.65)	92 (12, 218)	Indirect	MODERATE	Not serious	Not Serious	MODERATE	NMA	NA	RoB
Linezolid + Aztreonam vs Respiratory fluoroquinolones	NA	NA	0.95 (0.58, 1.56)	0.95 (0.58, 1.56)	-7 (-55, 74)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Pristinamycin vs Respiratory fluoroquinolones	NA	NA	1.6 (0.84, 3.04)	1.6 (0.84, 3.04)	79 (-21, 269)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
Teicoplanin + Other fluoroquinolone vs Respiratory fluoroquinolones	NA	NA	0.32 (0.14, 0.78)	0.32 (0.14, 0.78)	-90 (-114, -29)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
Penicillins vs Penicillin + Other fluoroquinolone	NA	NA	1.27 (0.78, 2.09)	1.27 (0.78, 2.09)	36 (-29, 144)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2

Penicillins vs β-Lactam/β-lactamase inhibitors	0.75 (0.41, 1.37)	-33 (-78, 49)	1.33 (0.88, 1.99)	1.13 (0.8, 1.59)	17 (-26, 78)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Penicillins vs β-Lactam/β-lactamase inhibitor + Macrolide	NA	NA	1.09 (0.73, 1.63)	1.09 (0.73, 1.63)	12 (-36, 83)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Penicillins vs β-Lactam/β-lactamase inhibitor + Aminoglycoside	NA	NA	0.68 (0.2, 2.31)	0.68 (0.2, 2.31)	-42 (-106, 173)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Penicillins vs 1st generation cephalosporins	NA	NA	0.53 (0.1, 2.9)	0.53 (0.1, 2.9)	-62 (-119, 251)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Penicillins vs 2nd generation cephalosporins	0.94 (0.33, 2.78)	-8 (-88, 235)	0.93 (0.56, 1.53)	0.93 (0.59, 1.47)	-9 (-54, 62)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Penicillins vs 3rd generation cephalosporins	5 (0.68, 33.33)	528 (-42, 1000)	0.89 (0.61, 1.31)	0.94 (0.65, 1.38)	-8 (-46, 50)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Penicillins vs 4th generation cephalosporins	NA	NA	1.03 (0.64, 1.65)	1.03 (0.64, 1.65)	4 (-48, 86)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Penicillins vs 5th generation cephalosporins	NA	NA	1.22 (0.8, 1.86)	1.22 (0.8, 1.86)	29 (-26, 114)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillins vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	3.45 (1.22, 9.72)	3.45 (1.22, 9.72)	323 (29, 1000)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoBx2, Imprecisionx2
Penicillins vs 2nd generation cephalosporin + Macrolide	NA	NA	1.17 (0.75, 1.82)	1.17 (0.75, 1.82)	22 (-33, 108)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
Penicillins vs 3rd generation cephalosporin + Macrolide	NA	NA	0.93 (0.61, 1.42)	0.93 (0.61, 1.42)	-9 (-51, 55)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Penicillins vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	1.57 (0.97, 2.56)	1.57 (0.97, 2.56)	75 (-4, 206)	Indirect	LOW	Not serious	Serious	VERY LOW	NMA	NA	RoB, Imprecision, Indirectness
Penicillins vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	1.35 (0.85, 2.16)	1.35 (0.85, 2.16)	46 (-20, 153)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
Penicillins vs 2nd generation cephalosporin +Tetracycline	NA	NA	1.17 (0.54, 2.51)	1.17 (0.54, 2.51)	22 (-61, 199)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillins vs 3rd generation cephalosporin + Aminoglycoside	NA	NA	0.37 (0.1, 1.44)	0.37 (0.1, 1.44)	-83 (-119, 58)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillins vs Macrolides	1.79 (0.34, 9.09)	104 (-87, 1000)	1.13 (0.79, 1.6)	1.15 (0.81, 1.62)	20 (-25, 82)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Penicillins vs Macrolide + Aminoglycoside	NA	NA	1.3 (0.13, 12.69)	1.3 (0.13, 12.69)	40 (-115, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Penicillins vs Tetracyclines	NA	NA	1.59 (0.9, 2.82)	1.59 (0.9, 2.82)	78 (-13, 240)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
Penicillins vs Lefamulin	NA	NA	1.27 (0.79, 2.06)	1.27 (0.79, 2.06)	36 (-28, 140)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillins vs Carbapenems	NA	NA	1.09 (0.7, 1.72)	1.09 (0.7, 1.72)	12 (-40, 95)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Penicillins vs Carbapenem + Macrolide	NA	NA	1.17 (0.64, 2.16)	1.17 (0.64, 2.16)	22 (-48, 153)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillins vs Respiratory fluoroquinolone + metronidazole	NA	NA	0.74 (0.28, 1.93)	0.74 (0.28, 1.93)	-34 (-95, 123)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3

Penicillins vs Other fluoroquinolones	NA	NA	1.2 (0.66, 2.19)	1.2 (0.66, 2.19)	26 (-45, 157)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillins vs Tigecycline	NA	NA	1.33 (0.86, 2.06)	1.33 (0.86, 2.06)	44 (-18, 140)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Penicillins vs Cotrimoxazole	NA	NA	1.78 (0.61, 5.2)	1.78 (0.61, 5.2)	103 (-51, 554)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillins vs Daptomycin + Aztreonam	NA	NA	0.73 (0.44, 1.22)	0.73 (0.44, 1.22)	-36 (-74, 29)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillins vs Linezolid + Aztreonam	NA	NA	1.31 (0.76, 2.26)	1.31 (0.76, 2.26)	41 (-32, 166)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillins vs Pristinamycin	NA	NA	0.78 (0.4, 1.54)	0.78 (0.4, 1.54)	-29 (-79, 71)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillins vs Teicoplanin + Other fluoroquinolone	NA	NA	3.84 (1.55, 9.52)	3.84 (1.55, 9.52)	375 (73, 1000)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
Penicillin + Other fluoroquinolone vs β-Lactam/β-lactamase inhibitors	NA	NA	0.89 (0.55, 1.43)	0.89 (0.55, 1.43)	-15 (-59, 57)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Penicillin + Other fluoroquinolone vs β-Lactam/β-lactamase inhibitor + Macrolide	0.83 (0.42, 1.64)	-22 (-77, 84)	0.87 (0.49, 1.53)	0.85 (0.55, 1.33)	-20 (-59, 44)	Direct	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Penicillin + Other fluoroquinolone vs β-Lactam/β-lactamase inhibitor + Aminoglycoside	NA	NA	0.53 (0.15, 1.89)	0.53 (0.15, 1.89)	-62 (-112, 117)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs 1st generation cephalosporins	NA	NA	0.41 (0.07, 2.35)	0.41 (0.07, 2.35)	-78 (-123, 178)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs 2nd generation cephalosporins	NA	NA	0.73 (0.41, 1.3)	0.73 (0.41, 1.3)	-36 (-78, 40)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillin + Other fluoroquinolone vs 3rd generation cephalosporins	NA	NA	0.74 (0.45, 1.22)	0.74 (0.45, 1.22)	-34 (-73, 29)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillin + Other fluoroquinolone vs 4th generation cephalosporins	NA	NA	0.81 (0.45, 1.43)	0.81 (0.45, 1.43)	-25 (-73, 57)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillin + Other fluoroquinolone vs 5th generation cephalosporins	NA	NA	0.95 (0.56, 1.63)	0.95 (0.56, 1.63)	-7 (-58, 83)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Penicillin + Other fluoroquinolone vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	2.71 (0.91, 8)	2.71 (0.91, 8)	226 (-12, 924)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoBx2, Imprecisionx2
Penicillin + Other fluoroquinolone vs 2nd generation cephalosporin + Macrolide	NA	NA	0.92 (0.54, 1.55)	0.92 (0.54, 1.55)	-11 (-61, 73)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Penicillin + Other fluoroquinolone vs 3rd generation cephalosporin + Macrolide	NA	NA	0.73 (0.44, 1.22)	0.73 (0.44, 1.22)	-36 (-74, 29)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillin + Other fluoroquinolone vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	1.24 (0.7, 2.17)	1.24 (0.7, 2.17)	32 (-40, 154)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	Imprecisionx2, Publication bias, Indirectness

Penicillin + Other fluoroquinolone vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	1.06 (0.62, 1.84)	1.06 (0.62, 1.84)	8 (-50, 111)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillin + Other fluoroquinolone vs 2nd generation cephalosporin +Tetracycline	NA	NA	0.92 (0.41, 2.08)	0.92 (0.41, 2.08)	-11 (-78, 143)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillin + Other fluoroquinolone vs 3rd generation cephalosporin + Aminoglycoside	NA	NA	0.29 (0.07, 1.18)	0.29 (0.07, 1.18)	-94 (-123, 24)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecision x2
Penicillin + Other fluoroquinolone vs Macrolides	NA	NA	0.9 (0.57, 1.41)	0.9 (0.57, 1.41)	-13 (-57, 54)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Penicillin + Other fluoroquinolone vs Macrolide + Aminoglycoside	NA	NA	1.02 (0.1, 10.16)	1.02 (0.1, 10.16)	3 (-119, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Tetracyclines	NA	NA	1.25 (0.66, 2.37)	1.25 (0.66, 2.37)	33 (-45, 181)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	Imprecisionx3 Publications bias
Penicillin + Other fluoroquinolone vs Lefamulin	NA	NA	1 (0.57, 1.74)	1 (0.57, 1.74)	0 (-57, 98)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	NA	Imprecisionx2
Penicillin + Other fluoroquinolone vs Carbapenems	NA	NA	0.86 (0.5, 1.49)	0.86 (0.5, 1.49)	-18 (-66, 65)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillin + Other fluoroquinolone vs Carbapenem + Macrolide	NA	NA	0.92 (0.49, 1.74)	0.92 (0.49, 1.74)	-11 (-67, 98)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillin + Other fluoroquinolone vs Respiratory fluoroquinolone + metronidazole	NA	NA	0.58 (0.21, 1.58)	0.58 (0.21, 1.58)	-55 (-104, 77)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Other fluoroquinolones	NA	NA	0.94 (0.48, 1.87)	0.94 (0.48, 1.87)	-8 (-69, 115)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillin + Other fluoroquinolone vs Tigecycline	NA	NA	1.04 (0.62, 1.76)	1.04 (0.62, 1.76)	5 (-50, 100)	Indirect	HIGH	Not serious	Serious	MODERATE	NMA	NA	Imprecision
Penicillin + Other fluoroquinolone vs Cotrimoxazole	NA	NA	1.39 (0.46, 4.24)	1.39 (0.46, 4.24)	51 (-71, 428)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	NA	Imprecisionx2
Penicillin + Other fluoroquinolone vs Daptomycin + Aztreonam	NA	NA	0.58 (0.32, 1.05)	0.58 (0.32, 1.05)	-55 (-90, 7)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecision x2
Penicillin + Other fluoroquinolone vs Linezolid + Aztreonam	NA	NA	1.03 (0.54, 1.94)	1.03 (0.54, 1.94)	4 (-61, 124)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillin + Other fluoroquinolone vs Pristinamycin	NA	NA	0.61 (0.29, 1.31)	0.61 (0.29, 1.31)	-51 (-94, 41)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	NA	Imprecisionx2
Penicillin + Other fluoroquinolone vs Teicoplanin + Other fluoroquinolone	NA	NA	3.02 (1.15, 7.9)	3.02 (1.15, 7.9)	267 (20, 911)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs β-Lactam/β-lactamase inhibitor + Macrolide	0.99 (0.53, 1.85)	-1 (-62, 112)	0.93 (0.59, 1.46)	0.96 (0.66, 1.39)	-5 (-45, 51)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
β-Lactam/β-lactamase inhibitors vs β-Lactam/β-lactamase inhibitor + Aminoglycoside	0.6 (0.19, 1.89)	-53 (-107, 117)	NA	0.6 (0.18, 1.94)	-53 (-108, 124)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3

β-Lactam/β-lactamase inhibitors vs 1st generation cephalosporins	NA	NA	0.46 (0.09, 2.53)	0.46 (0.09, 2.53)	-71 (-120, 202)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs 2nd generation cephalosporins	0.97 (0.46, 2.02)	-4 (-71, 135)	0.64 (0.38, 1.08)	0.82 (0.56, 1.2)	-24 (-58, 26)	Direct	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporins	0.87 (0.6, 1.25)	-17 (-53, 33)	0.82 (0.56, 1.2)	0.84 (0.63, 1.1)	-21 (-49, 13)	Direct	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
β-Lactam/β-lactamase inhibitors vs 4th generation cephalosporins	NA	NA	0.91 (0.61, 1.35)	0.91 (0.61, 1.35)	-12 (-51, 46)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
β-Lactam/β-lactamase inhibitors vs 5th generation cephalosporins	NA	NA	1.08 (0.77, 1.51)	1.08 (0.77, 1.51)	11 (-30, 67)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	3.05 (1.11, 8.36)	3.05 (1.11, 8.36)	271 (15, 972)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoBx2, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs 2nd generation cephalosporin + Macrolide	NA	NA	1.04 (0.68, 1.57)	1.04 (0.68, 1.57)	5 (-42, 75)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporin + Macrolide	NA	NA	0.82 (0.55, 1.24)	0.82 (0.55, 1.24)	-24 (-59, 32)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	1.39 (0.87, 2.23)	1.39 (0.87, 2.23)	51 (-17, 162)	Indirect	LOW	Not serious	Serious	VERY LOW	NMA	NA	RoB, Imprecision, Indirectness
β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	1.2 (0.76, 1.88)	1.2 (0.76, 1.88)	26 (-32, 116)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs 2nd generation cephalosporin +Tetracycline	NA	NA	1.03 (0.49, 2.19)	1.03 (0.49, 2.19)	4 (-67, 157)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporin + Aminoglycoside	NA	NA	0.33 (0.09, 1.24)	0.33 (0.09, 1.24)	-88 (-120, 32)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Macrolides	0.89 (0.37, 2.14)	-15 (-83, 150)	1.04 (0.74, 1.46)	1.02 (0.74, 1.4)	3 (-34, 53)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
β-Lactam/β-lactamase inhibitors vs Macrolide + Aminoglycoside	NA	NA	1.15 (0.12, 11.14)	1.15 (0.12, 11.14)	20 (-116, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs Tetracyclines	NA	NA	1.41 (0.81, 2.46)	1.41 (0.81, 2.46)	54 (-25, 193)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
β-Lactam/β-lactamase inhibitors vs Lefamulin	NA	NA	1.13 (0.71, 1.79)	1.13 (0.71, 1.79)	17 (-38, 104)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
β-Lactam/β-lactamase inhibitors vs Carbapenems	0.54 (0.23, 1.29)	-61 (-102, 38)	1.09 (0.73, 1.63)	0.97 (0.67, 1.39)	-4 (-44, 51)	Direct	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
β-Lactam/β-lactamase inhibitors vs Carbapenem + Macrolide	NA	NA	1.04 (0.57, 1.87)	1.04 (0.57, 1.87)	5 (-57, 115)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Respiratory fluoroquinolone + metronidazole	NA	NA	0.65 (0.25, 1.7)	0.65 (0.25, 1.7)	-46 (-99, 92)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs Other fluoroquinolones	NA	NA	1.06 (0.62, 1.82)	1.06 (0.62, 1.82)	8 (-50, 108)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision

β-Lactam/β-lactamase inhibitors vs Tigecycline	NA	NA	1.18 (0.77, 1.79)	1.18 (0.77, 1.79)	24 (-30, 104)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
β-Lactam/β-lactamase inhibitors vs Cotrimoxazole	NA	NA	1.57 (0.54, 4.56)	1.57 (0.54, 4.56)	75 (-61, 470)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Daptomycin + Aztreonam	NA	NA	0.65 (0.42, 1)	0.65 (0.42, 1)	-46 (-77, 0)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
β-Lactam/β-lactamase inhibitors vs Linezolid + Aztreonam	NA	NA	1.16 (0.71, 1.88)	1.16 (0.71, 1.88)	21 (-38, 116)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
β-Lactam/β-lactamase inhibitors vs Pristinamycin	0.69 (0.4, 1.18)	-41 (-79, 24)	NA	0.69 (0.38, 1.25)	-41 (-82, 33)	Direct	HIGH	Not serious	Very serious	LOW	NMA	NA	Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Teicoplanin + Other fluoroquinolone	NA	NA	3.4 (1.42, 8.12)	3.4 (1.42, 8.12)	317 (55, 940)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs β-Lactam/β-lactamase inhibitor + Aminoglycoside	NA	NA	0.62 (0.18, 2.14)	0.62 (0.18, 2.14)	-50 (-108, 150)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs 1st generation cephalosporins	NA	NA	0.48 (0.09, 2.69)	0.48 (0.09, 2.69)	-69 (-120, 223)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs 2nd generation cephalosporins	NA	NA	0.86 (0.52, 1.4)	0.86 (0.52, 1.4)	-18 (-63, 53)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
β-Lactam/β-lactamase inhibitor + Macrolide vs 3rd generation cephalosporins	NA	NA	0.87 (0.58, 1.3)	0.87 (0.58, 1.3)	-17 (-55, 40)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
β-Lactam/β-lactamase inhibitor + Macrolide vs 4th generation cephalosporins	NA	NA	0.94 (0.58, 1.54)	0.94 (0.58, 1.54)	-8 (-55, 71)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
β-Lactam/β-lactamase inhibitor + Macrolide vs 5th generation cephalosporins	NA	NA	1.12 (0.72, 1.75)	1.12 (0.72, 1.75)	16 (-37, 99)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
β-Lactam/β-lactamase inhibitor + Macrolide vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	3.17 (1.12, 9.02)	3.17 (1.12, 9.02)	286 (16, 1000)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoBx2, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs 2nd generation cephalosporin + Macrolide	NA	NA	1.08 (0.7, 1.67)	1.08 (0.7, 1.67)	11 (-40, 88)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
β-Lactam/β-lactamase inhibitor + Macrolide vs 3rd generation cephalosporin + Macrolide	NA	NA	0.86 (0.56, 1.31)	0.86 (0.56, 1.31)	-18 (-58, 41)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
β-Lactam/β-lactamase inhibitor + Macrolide vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	1.45 (0.89, 2.35)	1.45 (0.89, 2.35)	59 (-15, 178)	Indirect	LOW	Not serious	Serious	VERY LOW	NMA	NA	RoB, Imprecision, Indirectness

β-Lactam/β-lactamase inhibitor + Macrolide vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	1.25 (0.78, 1.99)	1.25 (0.78, 1.99)	33 (-29, 131)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs 2nd generation cephalosporin +Tetracycline	NA	NA	1.08 (0.5, 2.31)	1.08 (0.5, 2.31)	11 (-66, 173)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs 3rd generation cephalosporin + Aminoglycoside	NA	NA	0.34 (0.09, 1.34)	0.34 (0.09, 1.34)	-87 (-120, 45)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Macrolides	NA	NA	1.06 (0.75, 1.49)	1.06 (0.75, 1.49)	8 (-33, 65)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
β-Lactam/β-lactamase inhibitor + Macrolide vs Macrolide + Aminoglycoside	NA	NA	1.2 (0.12, 11.7)	1.2 (0.12, 11.7)	26 (-116, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs Tetracyclines	NA	NA	1.47 (0.83, 2.6)	1.47 (0.83, 2.6)	62 (-22, 211)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
β-Lactam/β-lactamase inhibitor + Macrolide vs Lefamulin	NA	NA	1.17 (0.73, 1.89)	1.17 (0.73, 1.89)	22 (-36, 117)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
β-Lactam/β-lactamase inhibitor + Macrolide vs Carbapenems	NA	NA	1.01 (0.63, 1.61)	1.01 (0.63, 1.61)	1 (-49, 81)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
β-Lactam/β-lactamase inhibitor + Macrolide vs Carbapenem + Macrolide	1.08 (0.73, 1.6)	11 (-36, 79)	NA	1.08 (0.68, 1.71)	11 (-42, 94)	Direct	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
β-Lactam/β-lactamase inhibitor + Macrolide vs Respiratory fluoroquinolone + metronidazole	NA	NA	0.68 (0.26, 1.78)	0.68 (0.26, 1.78)	-42 (-98, 103)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs Other fluoroquinolones	NA	NA	1.11 (0.6, 2.05)	1.11 (0.6, 2.05)	15 (-53, 139)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Tigecycline	NA	NA	1.22 (0.79, 1.89)	1.22 (0.79, 1.89)	29 (-28, 117)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Cotrimoxazole	NA	NA	1.64 (0.56, 4.79)	1.64 (0.56, 4.79)	84 (-58, 500)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Daptomycin + Aztreonam	NA	NA	0.68 (0.4, 1.14)	0.68 (0.4, 1.14)	-42 (-79, 18)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
β-Lactam/β-lactamase inhibitor + Macrolide vs Linezolid + Aztreonam	NA	NA	1.2 (0.69, 2.11)	1.2 (0.69, 2.11)	26 (-41, 147)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Pristinamycin	NA	NA	0.72 (0.36, 1.44)	0.72 (0.36, 1.44)	-37 (-84, 58)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Teicoplanin + Other fluoroquinolone	NA	NA	3.54 (1.42, 8.86)	3.54 (1.42, 8.86)	335 (55, 1000)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs 1st generation cephalosporins	NA	NA	0.78 (0.1, 6.1)	0.78 (0.1, 6.1)	-29 (-119, 673)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs 2nd generation cephalosporins	NA	NA	1.37 (0.4, 4.73)	1.37 (0.4, 4.73)	49 (-79, 492)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3

β-Lactam/β-lactamase inhibitor + Aminoglycoside vs 3rd generation cephalosporins	NA	NA	1.4 (0.42, 4.67)	1.4 (0.42, 4.67)	53 (-77, 484)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs 4th generation cephalosporins	NA	NA	1.51 (0.44, 5.24)	1.51 (0.44, 5.24)	67 (-74, 560)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs 5th generation cephalosporins	NA	NA	1.79 (0.53, 6.1)	1.79 (0.53, 6.1)	104 (-62, 673)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	5.09 (1.08, 23.96)	5.09 (1.08, 23.96)	540 (11, 1000)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs 2nd generation cephalosporin + Macrolide	NA	NA	1.73 (0.5, 6.02)	1.73 (0.5, 6.02)	96 (-66, 663)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs 3rd generation cephalosporin + Macrolide	NA	NA	1.37 (0.4, 4.77)	1.37 (0.4, 4.77)	49 (-79, 498)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	2.32 (0.65, 8.26)	2.32 (0.65, 8.26)	174 (-46, 958)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2, Indirectness
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	2 (0.57, 7.05)	2 (0.57, 7.05)	132 (-57, 799)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs 2nd generation cephalosporin +Tetracycline	NA	NA	1.72 (0.43, 6.97)	1.72 (0.43, 6.97)	95 (-75, 788)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs 3rd generation cephalosporin + Aminoglycoside	NA	NA	0.55 (0.09, 3.24)	0.55 (0.09, 3.24)	-59 (-120, 296)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs Macrolides	NA	NA	1.69 (0.5, 5.73)	1.69 (0.5, 5.73)	91 (-66, 624)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs Macrolide + Aminoglycoside	NA	NA	1.92 (0.15, 24.77)	1.92 (0.15, 24.77)	121 (-112, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs Tetracyclines	NA	NA	2.35 (0.64, 8.65)	2.35 (0.64, 8.65)	178 (-48, 1000)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs Lefamulin	NA	NA	1.88 (0.53, 6.66)	1.88 (0.53, 6.66)	116 (-62, 747)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs Carbapenems	NA	NA	1.62 (0.47, 5.54)	1.62 (0.47, 5.54)	82 (-70, 599)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs Carbapenem + Macrolide	NA	NA	1.73 (0.46, 6.46)	1.73 (0.46, 6.46)	96 (-71, 721)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs Respiratory fluoroquinolone + metronidazole	NA	NA	1.09 (0.24, 4.95)	1.09 (0.24, 4.95)	12 (-100, 521)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2

β-Lactam/β-lactamase inhibitor + Aminoglycoside vs Other fluoroquinolones	NA	NA	1.77 (0.49, 6.47)	1.77 (0.49, 6.47)	102 (-67, 722)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs Tigecycline	NA	NA	1.96 (0.56, 6.85)	1.96 (0.56, 6.85)	127 (-58, 772)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs Cotrimoxazole	NA	NA	2.62 (0.54, 12.83)	2.62 (0.54, 12.83)	214 (-61, 1000)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs Daptomycin + Aztreonam	NA	NA	1.08 (0.31, 3.8)	1.08 (0.31, 3.8)	11 (-91, 370)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs Linezolid + Aztreonam	NA	NA	1.93 (0.54, 6.89)	1.93 (0.54, 6.89)	123 (-61, 777)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs Pristinamycin	NA	NA	1.15 (0.31, 4.3)	1.15 (0.31, 4.3)	20 (-91, 436)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs Teicoplanin + Other fluoroquinolone	NA	NA	5.67 (1.31, 24.52)	5.67 (1.31, 24.52)	616 (41, 1000)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
1st generation cephalosporins vs 2nd generation cephalosporins	2.54 (0.37, 17.57)	203 (-83, 1000)	0.64 (0.02, 16.95)	1.77 (0.33, 9.41)	102 (-88, 1000)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs 3rd generation cephalosporins	NA	NA	1.8 (0.33, 9.8)	1.8 (0.33, 9.8)	106 (-88, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs 4th generation cephalosporins	NA	NA	1.95 (0.35, 10.9)	1.95 (0.35, 10.9)	125 (-86, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs 5th generation cephalosporins	NA	NA	2.31 (0.42, 12.74)	2.31 (0.42, 12.74)	173 (-77, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	6.56 (0.93, 46.24)	6.56 (0.93, 46.24)	734 (-9, 1000)	Indirect	LOW	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx3
1st generation cephalosporins vs 2nd generation cephalosporin + Macrolide	NA	NA	2.23 (0.4, 12.52)	2.23 (0.4, 12.52)	162 (-79, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs 3rd generation cephalosporin + Macrolide	NA	NA	1.77 (0.32, 9.91)	1.77 (0.32, 9.91)	102 (-90, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	3 (0.53, 17.06)	3 (0.53, 17.06)	264 (-62, 1000)	Indirect	LOW	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3, Indirectness
1st generation cephalosporins vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	2.58 (0.46, 14.6)	2.58 (0.46, 14.6)	209 (-71, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs 2nd generation cephalosporin +Tetracycline	NA	NA	2.22 (0.35, 13.94)	2.22 (0.35, 13.94)	161 (-86, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx3
1st generation cephalosporins vs 3rd generation cephalosporin + Aminoglycoside	NA	NA	0.71 (0.08, 6)	0.71 (0.08, 6)	-38 (-121, 660)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3

1st generation cephalosporins vs Macrolides	NA	NA	2.18 (0.4, 12.02)	2.18 (0.4, 12.02)	156 (-79, 1000)	Indirect	LOW	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx3
1st generation cephalosporins vs Macrolide + Aminoglycoside	NA	NA	2.47 (0.15, 41.56)	2.47 (0.15, 41.56)	194 (-112, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs Tetracyclines	NA	NA	3.03 (0.54, 17.03)	3.03 (0.54, 17.03)	268 (-61, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs Lefamulin	NA	NA	2.42 (0.43, 13.77)	2.42 (0.43, 13.77)	187 (-75, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs Carbapenems	NA	NA	2.08 (0.38, 11.55)	2.08 (0.38, 11.55)	143 (-82, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs Carbapenem + Macrolide	NA	NA	2.23 (0.38, 13.2)	2.23 (0.38, 13.2)	162 (-82, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs Respiratory fluoroquinolone + metronidazole	NA	NA	1.4 (0.2, 9.64)	1.4 (0.2, 9.64)	53 (-106, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs Other fluoroquinolones	NA	NA	2.29 (0.4, 13.1)	2.29 (0.4, 13.1)	170 (-79, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs Tigecycline	NA	NA	2.53 (0.45, 14.21)	2.53 (0.45, 14.21)	202 (-73, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs Cotrimoxazole	1.38 (0.07, 29.26)	50 (-123, 1000)	5.49 (0.57, 52.63)	3.38 (0.55, 20.83)	314 (-59, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs Daptomycin + Aztreonam	NA	NA	1.4 (0.25, 7.87)	1.4 (0.25, 7.87)	53 (-99, 907)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs Linezolid + Aztreonam	NA	NA	2.49 (0.44, 14.2)	2.49 (0.44, 14.2)	197 (-74, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs Pristinamycin	NA	NA	1.49 (0.25, 8.94)	1.49 (0.25, 8.94)	65 (-99, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs Teicoplanin + Other fluoroquinolone	NA	NA	7.32 (1.11, 48.22)	7.32 (1.11, 48.22)	834 (15, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
2nd generation cephalosporins vs 3rd generation cephalosporins	1.14 (0.63, 2.07)	18 (-49, 141)	0.94 (0.58, 1.53)	1.02 (0.7, 1.48)	3 (-40, 63)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
2nd generation cephalosporins vs 4th generation cephalosporins	NA	NA	1.1 (0.69, 1.77)	1.1 (0.69, 1.77)	13 (-41, 102)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
2nd generation cephalosporins vs 5th generation cephalosporins	NA	NA	1.31 (0.86, 2)	1.31 (0.86, 2)	41 (-18, 132)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
2nd generation cephalosporins vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	3.7 (1.31, 10.5)	3.7 (1.31, 10.5)	356 (41, 1000)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
2nd generation cephalosporins vs 2nd generation cephalosporin + Macrolide	NA	NA	1.26 (0.74, 2.13)	1.26 (0.74, 2.13)	34 (-34, 149)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporins vs 3rd generation cephalosporin + Macrolide	NA	NA	1 (0.6, 1.67)	1 (0.6, 1.67)	0 (-53, 88)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
2nd generation cephalosporins vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	1.69 (0.96, 2.98)	1.69 (0.96, 2.98)	91 (-5, 261)	Indirect	LOW	Not serious	Serious	VERY LOW	NMA	NA	RoB, Imprecision, Indirectness

2nd generation cephalosporins vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	1.46 (0.84, 2.53)	1.46 (0.84, 2.53)	61 (-21, 202)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
2nd generation cephalosporins vs 2nd generation cephalosporin +Tetracycline	NA	NA	1.26 (0.56, 2.84)	1.26 (0.56, 2.84)	34 (-58, 243)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporins vs 3rd generation cephalosporin + Aminoglycoside	NA	NA	0.4 (0.1, 1.55)	0.4 (0.1, 1.55)	-79 (-119, 73)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporins vs Macrolides	12 (1.62, 88.84)	1452 (82, 1000)	1.1 (0.7, 1.73)	1.23 (0.79, 1.93)	30 (-28, 123)	Indirect	MODERATE	Serious	Very serious	VERY LOW	Indirect	LOW	RoB, Imprecisionx2 , Incoherence
2nd generation cephalosporins vs Macrolide + Aminoglycoside	NA	NA	1.4 (0.14, 13.81)	1.4 (0.14, 13.81)	53 (-114, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
2nd generation cephalosporins vs Tetracyclines	NA	NA	1.71 (0.9, 3.24)	1.71 (0.9, 3.24)	94 (-13, 296)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecision x2
2nd generation cephalosporins vs Lefamulin	NA	NA	1.37 (0.78, 2.4)	1.37 (0.78, 2.4)	49 (-29, 185)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporins vs Carbapenems	NA	NA	1.18 (0.75, 1.84)	1.18 (0.75, 1.84)	24 (-33, 111)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
2nd generation cephalosporins vs Carbapenem + Macrolide	NA	NA	1.26 (0.64, 2.47)	1.26 (0.64, 2.47)	34 (-48, 194)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporins vs Respiratory fluoroquinolone + metronidazole	NA	NA	0.79 (0.29, 2.17)	0.79 (0.29, 2.17)	-28 (-94, 154)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
2nd generation cephalosporins vs Other fluoroquinolones	1.29 (0.55, 3)	38 (-59, 264)	1.3 (0.64, 2.6)	1.29 (0.75, 2.23)	38 (-33, 162)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporins vs Tigecycline	NA	NA	1.43 (0.84, 2.42)	1.43 (0.84, 2.42)	57 (-21, 187)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
2nd generation cephalosporins vs Cotrimoxazole	NA	NA	1.91 (0.63, 5.75)	1.91 (0.63, 5.75)	120 (-49, 627)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporins vs Daptomycin + Aztreonam	NA	NA	0.79 (0.48, 1.31)	0.79 (0.48, 1.31)	-28 (-69, 41)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporins vs Linezolid + Aztreonam	NA	NA	1.41 (0.81, 2.43)	1.41 (0.81, 2.43)	54 (-25, 189)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
2nd generation cephalosporins vs Pristinamycin	NA	NA	0.84 (0.42, 1.69)	0.84 (0.42, 1.69)	-21 (-77, 91)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporins vs Teicoplanin + Other fluoroquinolone	NA	NA	4.13 (1.67, 10.24)	4.13 (1.67, 10.24)	413 (88, 1000)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
3rd generation cephalosporins vs 4th generation cephalosporins	1.13 (0.85, 1.5)	17 (-20, 66)	0.69 (0.29, 1.69)	1.09 (0.81, 1.45)	12 (-25, 59)	Direct	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
3rd generation cephalosporins vs 5th generation cephalosporins	1.28 (0.97, 1.69)	37 (-4, 91)	NA	1.29 (1.06, 1.56)	38 (8, 74)	Direct	MODERATE	Not serious	Not Serious	MODERATE	NMA	NA	RoB

3rd generation cephalosporins vs 3rd generation cephalosporin/β-lactamase inhibitors	4.17 (1.52, 11.11)	418 (69, 1000)	1.41 (0.09, 21.96)	3.65 (1.38, 9.67)	350 (50, 1000)	Direct	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
3rd generation cephalosporins vs 2nd generation cephalosporin + Macrolide	NA	NA	1.24 (0.8, 1.93)	1.24 (0.8, 1.93)	32 (-26, 123)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporins vs 3rd generation cephalosporin + Macrolide	NA	NA	0.98 (0.64, 1.5)	0.98 (0.64, 1.5)	-3 (-48, 66)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
3rd generation cephalosporins vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	1.67 (1.02, 2.72)	1.67 (1.02, 2.72)	88 (3, 227)	Indirect	LOW	Not serious	Not Serious	LOW	NMA	NA	RoB, Indirectness
3rd generation cephalosporins vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	1.43 (0.9, 2.29)	1.43 (0.9, 2.29)	57 (-13, 170)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
3rd generation cephalosporins vs 2nd generation cephalosporin +Tetracycline	NA	NA	1.24 (0.58, 2.66)	1.24 (0.58, 2.66)	32 (-55, 219)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporins vs 3rd generation cephalosporin + Aminoglycoside	NA	NA	0.39 (0.11, 1.45)	0.39 (0.11, 1.45)	-81 (-117, 59)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
3rd generation cephalosporins vs Macrolides	NA	NA	1.21 (0.86, 1.72)	1.21 (0.86, 1.72)	28 (-18, 95)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
3rd generation cephalosporins vs Macrolide + Aminoglycoside	NA	NA	1.38 (0.14, 13.3)	1.38 (0.14, 13.3)	50 (-114, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
3rd generation cephalosporins vs Tetracyclines	NA	NA	1.68 (0.95, 2.99)	1.68 (0.95, 2.99)	90 (-7, 263)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
3rd generation cephalosporins vs Lefamulin	NA	NA	1.35 (0.83, 2.18)	1.35 (0.83, 2.18)	46 (-22, 156)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
3rd generation cephalosporins vs Carbapenems	1.23 (0.89, 1.72)	30 (-15, 95)	0.98 (0.57, 1.68)	1.16 (0.88, 1.52)	21 (-16, 69)	Direct	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
3rd generation cephalosporins vs Carbapenem + Macrolide	NA	NA	1.24 (0.67, 2.28)	1.24 (0.67, 2.28)	32 (-44, 169)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporins vs Respiratory fluoroquinolone + metronidazole	NA	NA	0.78 (0.3, 2.05)	0.78 (0.3, 2.05)	-29 (-92, 139)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
3rd generation cephalosporins vs Other fluoroquinolones	0.93 (0.47, 1.8)	-9 (-70, 106)	1.71 (0.86, 3.38)	1.27 (0.78, 2.08)	36 (-29, 143)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporins vs Tigecycline	NA	NA	1.41 (0.91, 2.18)	1.41 (0.91, 2.18)	54 (-12, 156)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
3rd generation cephalosporins vs Cotrimoxazole	NA	NA	1.88 (0.64, 5.49)	1.88 (0.64, 5.49)	116 (-48, 593)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporins vs Daptomycin + Aztreonam	0.78 (0.62, 0.98)	-29 (-50, -3)	NA	0.78 (0.56, 1.09)	-29 (-58, 12)	Direct	MODERATE	Not serious	Serious	LOW	DIRECT	MODERATE	RoB
3rd generation cephalosporins vs Linezolid + Aztreonam	1.38 (1.01, 1.89)	50 (1, 117)	NA	1.38 (0.93, 2.05)	50 (-9, 139)	Direct	MODERATE	Not serious	Serious	LOW	DIRECT	MODERATE	RoB
3rd generation cephalosporins vs Pristinamycin	NA	NA	0.83 (0.43, 1.59)	0.83 (0.43, 1.59)	-22 (-75, 78)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2

3rd generation cephalosporins vs Teicoplanin + Other fluoroquinolone	4.07 (1.85, 8.95)	405 (112, 1000)	NA	4.07 (1.78, 9.28)	405 (103, 1000)	Direct	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
4th generation cephalosporins vs 5th generation cephalosporins	NA	NA	1.18 (0.84, 1.67)	1.18 (0.84, 1.67)	24 (-21, 88)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
4th generation cephalosporins vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	3.36 (1.22, 9.28)	3.36 (1.22, 9.28)	312 (29, 1000)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
4th generation cephalosporins vs 2nd generation cephalosporin + Macrolide	NA	NA	1.14 (0.68, 1.93)	1.14 (0.68, 1.93)	18 (-42, 123)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
4th generation cephalosporins vs 3rd generation cephalosporin + Macrolide	NA	NA	0.91 (0.54, 1.51)	0.91 (0.54, 1.51)	-12 (-61, 67)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
4th generation cephalosporins vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	1.53 (0.87, 2.7)	1.53 (0.87, 2.7)	70 (-17, 224)	Indirect	LOW	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2, Indirectness
4th generation cephalosporins vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	1.32 (0.76, 2.29)	1.32 (0.76, 2.29)	42 (-32, 170)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
4th generation cephalosporins vs 2nd generation cephalosporin +Tetracycline	NA	NA	1.14 (0.5, 2.57)	1.14 (0.5, 2.57)	18 (-66, 207)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
4th generation cephalosporins vs 3rd generation cephalosporin + Aminoglycoside	NA	NA	0.36 (0.1, 1.37)	0.36 (0.1, 1.37)	-84 (-119, 49)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
4th generation cephalosporins vs Macrolides	NA	NA	1.12 (0.71, 1.75)	1.12 (0.71, 1.75)	16 (-38, 99)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
4th generation cephalosporins vs Macrolide + Aminoglycoside	NA	NA	1.27 (0.13, 12.46)	1.27 (0.13, 12.46)	36 (-115, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
4th generation cephalosporins vs Tetracyclines	NA	NA	1.55 (0.82, 2.94)	1.55 (0.82, 2.94)	73 (-24, 256)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecision x2
4th generation cephalosporins vs Lefamulin	NA	NA	1.24 (0.71, 2.17)	1.24 (0.71, 2.17)	32 (-38, 154)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
4th generation cephalosporins vs Carbapenems	1.59 (0.71, 3.57)	78 (-38, 339)	0.97 (0.64, 1.47)	1.07 (0.74, 1.55)	9 (-34, 73)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
4th generation cephalosporins vs Carbapenem + Macrolide	NA	NA	1.14 (0.58, 2.24)	1.14 (0.58, 2.24)	18 (-55, 164)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
4th generation cephalosporins vs Respiratory fluoroquinolone + metronidazole	NA	NA	0.72 (0.26, 1.96)	0.72 (0.26, 1.96)	-37 (-98, 127)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
4th generation cephalosporins vs Other fluoroquinolones	NA	NA	1.17 (0.67, 2.06)	1.17 (0.67, 2.06)	22 (-44, 140)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
4th generation cephalosporins vs Tigecycline	NA	NA	1.3 (0.77, 2.19)	1.3 (0.77, 2.19)	40 (-30, 157)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
4th generation cephalosporins vs Cotrimoxazole	NA	NA	1.73 (0.57, 5.25)	1.73 (0.57, 5.25)	96 (-57, 561)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2

4th generation cephalosporins vs Daptomycin + Aztreonam	NA	NA	0.72 (0.46, 1.11)	0.72 (0.46, 1.11)	-37 (-71, 15)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
4th generation cephalosporins vs Linezolid + Aztreonam	NA	NA	1.28 (0.78, 2.08)	1.28 (0.78, 2.08)	37 (-29, 143)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
4th generation cephalosporins vs Pristinamycin	NA	NA	0.76 (0.37, 1.55)	0.76 (0.37, 1.55)	-32 (-83, 73)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
4th generation cephalosporins vs Teicoplanin + Other fluoroquinolone	NA	NA	3.75 (1.56, 8.98)	3.75 (1.56, 8.98)	363 (74, 1000)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
5th generation cephalosporins vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	2.84 (1.05, 7.66)	2.84 (1.05, 7.66)	243 (7, 879)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
5th generation cephalosporins vs 2nd generation cephalosporin + Macrolide	NA	NA	0.96 (0.59, 1.56)	0.96 (0.59, 1.56)	-5 (-54, 74)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
5th generation cephalosporins vs 3rd generation cephalosporin + Macrolide	NA	NA	0.77 (0.48, 1.22)	0.77 (0.48, 1.22)	-30 (-69, 29)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
5th generation cephalosporins vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	1.3 (0.77, 2.19)	1.3 (0.77, 2.19)	40 (-30, 157)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2, Indirectness
5th generation cephalosporins vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	1.11 (0.67, 1.85)	1.11 (0.67, 1.85)	15 (-44, 112)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
5th generation cephalosporins vs 2nd generation cephalosporin +Tetracycline	NA	NA	0.96 (0.44, 2.12)	0.96 (0.44, 2.12)	-5 (-74, 148)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
5th generation cephalosporins vs 3rd generation cephalosporin + Aminoglycoside	NA	NA	0.31 (0.08, 1.15)	0.31 (0.08, 1.15)	-91 (-121, 20)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
5th generation cephalosporins vs Macrolides	NA	NA	0.94 (0.63, 1.41)	0.94 (0.63, 1.41)	-8 (-49, 54)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
5th generation cephalosporins vs Macrolide + Aminoglycoside	NA	NA	1.07 (0.11, 10.43)	1.07 (0.11, 10.43)	9 (-117, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
5th generation cephalosporins vs Tetracyclines	NA	NA	1.31 (0.72, 2.4)	1.31 (0.72, 2.4)	41 (-37, 185)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
5th generation cephalosporins vs Lefamulin	NA	NA	1.05 (0.62, 1.76)	1.05 (0.62, 1.76)	7 (-50, 100)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
5th generation cephalosporins vs Carbapenems	NA	NA	0.9 (0.65, 1.25)	0.9 (0.65, 1.25)	-13 (-46, 33)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
5th generation cephalosporins vs Carbapenem + Macrolide	NA	NA	0.96 (0.51, 1.83)	0.96 (0.51, 1.83)	-5 (-65, 110)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
5th generation cephalosporins vs Respiratory fluoroquinolone + metronidazole	NA	NA	0.61 (0.23, 1.62)	0.61 (0.23, 1.62)	-51 (-102, 82)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
5th generation cephalosporins vs Other fluoroquinolones	NA	NA	0.99 (0.58, 1.67)	0.99 (0.58, 1.67)	-1 (-55, 88)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
5th generation cephalosporins vs Tigecycline	NA	NA	1.09 (0.68, 1.77)	1.09 (0.68, 1.77)	12 (-42, 102)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision

5th generation cephalosporins vs Cotrimoxazole	NA	NA	1.46 (0.49, 4.34)	1.46 (0.49, 4.34)	61 (-67, 441)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
5th generation cephalosporins vs Daptomycin + Aztreonam	NA	NA	0.6 (0.41, 0.89)	0.6 (0.41, 0.89)	-53 (-78, -15)	Indirect	MODERATE	Not serious	Not Serious	MODERATE	NMA	NA	RoB
5th generation cephalosporins vs Linezolid + Aztreonam	NA	NA	1.08 (0.69, 1.67)	1.08 (0.69, 1.67)	11 (-41, 88)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
5th generation cephalosporins vs Pristinamycin	NA	NA	0.64 (0.33, 1.27)	0.64 (0.33, 1.27)	-48 (-88, 36)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
5th generation cephalosporins vs Teicoplanin + Other fluoroquinolone	NA	NA	3.16 (1.36, 7.37)	3.16 (1.36, 7.37)	285 (48, 841)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
3rd generation cephalosporin/β-lactamase inhibitors vs 2nd generation cephalosporin + Macrolide	NA	NA	0.34 (0.12, 0.98)	0.34 (0.12, 0.98)	-87 (-116, -3)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoBx2, Imprecisionx2
3rd generation cephalosporin/β-lactamase inhibitors vs 3rd generation cephalosporin + Macrolide	NA	NA	0.27 (0.09, 0.77)	0.27 (0.09, 0.77)	-96 (-120, -30)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoBx2, Imprecisionx2
3rd generation cephalosporin/β-lactamase inhibitors vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	0.46 (0.16, 1.35)	0.46 (0.16, 1.35)	-71 (-111, 46)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoBx2, Imprecisionx2
3rd generation cephalosporin/β-lactamase inhibitors vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	0.39 (0.13, 1.15)	0.39 (0.13, 1.15)	-81 (-115, 20)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoBx2, Imprecision x2
3rd generation cephalosporin/β-lactamase inhibitors vs 2nd generation cephalosporin +Tetracycline	NA	NA	0.34 (0.1, 1.16)	0.34 (0.1, 1.16)	-87 (-119, 21)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoBx2, Imprecision x2
3rd generation cephalosporin/β-lactamase inhibitors vs 3rd generation cephalosporin + Aminoglycoside	NA	NA	0.11 (0.02, 0.55)	0.11 (0.02, 0.55)	-117 (-129, -59)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoBx2, Imprecisionx2
3rd generation cephalosporin/β-lactamase inhibitors vs Macrolides	NA	NA	0.33 (0.12, 0.93)	0.33 (0.12, 0.93)	-88 (-116, -9)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoBx2, Imprecisionx2
3rd generation cephalosporin/β-lactamase inhibitors vs Macrolide + Aminoglycoside	NA	NA	0.38 (0.03, 4.45)	0.38 (0.03, 4.45)	-82 (-128, 455)	Indirect	LOW	Not serious	Extremely serious	VERY LOW	NMA	NA	RoBx2, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Tetracyclines	NA	NA	0.46 (0.15, 1.42)	0.46 (0.15, 1.42)	-71 (-112, 55)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoBx2, Imprecisionx2
3rd generation cephalosporin/β-lactamase inhibitors vs Lefamulin	NA	NA	0.37 (0.13, 1.09)	0.37 (0.13, 1.09)	-83 (-115, 12)	Indirect	LOW	Not serious	Very Serious	VERY LOW	NMA	NA	RoBx2, Imprecision x2
3rd generation cephalosporin/β-lactamase inhibitors vs Carbapenems	NA	NA	0.32 (0.12, 0.87)	0.32 (0.12, 0.87)	-90 (-116, -17)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoBx2, Imprecisionx2
3rd generation cephalosporin/β-lactamase inhibitors vs Carbapenem + Macrolide	NA	NA	0.34 (0.11, 1.07)	0.34 (0.11, 1.07)	-87 (-117, 9)	Indirect	LOW	Not serious	Very Serious	VERY LOW	NMA	NA	RoBx2, Imprecisionx2
3rd generation cephalosporin/β-lactamase inhibitors vs Respiratory fluoroquinolone + metronidazole	NA	NA	0.21 (0.05, 0.84)	0.21 (0.05, 0.84)	-104 (-125, -21)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoBx2, Imprecisionx2

3rd generation cephalosporin/β-lactamase inhibitors vs Other fluoroquinolones	NA	NA	0.35 (0.12, 1.04)	0.35 (0.12, 1.04)	-86 (-116, 5)	Indirect	LOW	Not serious	Very Serious	VERY LOW	NMA	NA	RoBx2, Imprecisionx2
3rd generation cephalosporin/β-lactamase inhibitors vs Tigecycline	NA	NA	0.39 (0.13, 1.11)	0.39 (0.13, 1.11)	-81 (-115, 15)	Indirect	LOW	Not serious	Very Serious	VERY LOW	NMA	NA	RoBx2, Imprecisionx2
3rd generation cephalosporin/β-lactamase inhibitors vs Cotrimoxazole	NA	NA	0.52 (0.12, 2.18)	0.52 (0.12, 2.18)	-63 (-116, 156)	Indirect	LOW	Not serious	Extremely serious	VERY LOW	NMA	NA	RoBx2, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Daptomycin + Aztreonam	NA	NA	0.21 (0.08, 0.6)	0.21 (0.08, 0.6)	-104 (-121, -53)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoBx2, Imprecisionx2
3rd generation cephalosporin/β-lactamase inhibitors vs Linezolid + Aztreonam	NA	NA	0.38 (0.13, 1.09)	0.38 (0.13, 1.09)	-82 (-115, 12)	Indirect	LOW	Not serious	Very Serious	VERY LOW	NMA	NA	RoBx2, Imprecisionx2
3rd generation cephalosporin/β-lactamase inhibitors vs Pristinamycin	NA	NA	0.23 (0.07, 0.73)	0.23 (0.07, 0.73)	-102 (-123, -36)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoBx2, Imprecisionx2
3rd generation cephalosporin/β-lactamase inhibitors vs Teicoplanin + Other fluoroquinolone	NA	NA	1.12 (0.31, 4)	1.12 (0.31, 4)	16 (-91, 396)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoBx2, Publication bias, Imprecisionx2
2nd generation cephalosporin + Macrolide vs 3rd generation cephalosporin + Macrolide	NA	NA	0.79 (0.5, 1.26)	0.79 (0.5, 1.26)	-28 (-66, 34)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	1.35 (0.8, 2.25)	1.35 (0.8, 2.25)	46 (-26, 165)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2, Indirectness
2nd generation cephalosporin + Macrolide vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	1.16 (0.7, 1.9)	1.16 (0.7, 1.9)	21 (-40, 119)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
2nd generation cephalosporin + Macrolide vs 2nd generation cephalosporin +Tetracycline	NA	NA	1 (0.48, 2.08)	1 (0.48, 2.08)	0 (-69, 143)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs 3rd generation cephalosporin + Aminoglycoside	NA	NA	0.32 (0.08, 1.25)	0.32 (0.08, 1.25)	-90 (-121, 33)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Macrolides	0.98 (0.74, 1.28)	-3 (-34, 37)	1.09 (0.36, 3.33)	0.98 (0.74, 1.3)	-3 (-34, 40)	Direct	LOW	Not serious	Serious	VERY LOW	NMA	NA	RoB x2, Imprecision
2nd generation cephalosporin + Macrolide vs Macrolide + Aminoglycoside	NA	NA	1.11 (0.11, 10.93)	1.11 (0.11, 10.93)	15 (-117, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolide vs Tetracyclines	NA	NA	1.36 (0.75, 2.48)	1.36 (0.75, 2.48)	48 (-33, 195)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Lefamulin	NA	NA	1.09 (0.66, 1.81)	1.09 (0.66, 1.81)	12 (-45, 107)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
2nd generation cephalosporin + Macrolide vs Carbapenems	NA	NA	0.94 (0.57, 1.54)	0.94 (0.57, 1.54)	-8 (-57, 71)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
2nd generation cephalosporin + Macrolide vs Carbapenem + Macrolide	NA	NA	1 (0.53, 1.89)	1 (0.53, 1.89)	0 (-62, 117)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2

2nd generation cephalosporin + Macrolide vs Respiratory fluoroquinolone + metronidazole	NA	NA	0.63 (0.24, 1.68)	0.63 (0.24, 1.68)	-49 (-100, 90)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolide vs Other fluoroquinolones	NA	NA	1.03 (0.54, 1.95)	1.03 (0.54, 1.95)	4 (-61, 125)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Tigecycline	NA	NA	1.14 (0.71, 1.82)	1.14 (0.71, 1.82)	18 (-38, 108)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
2nd generation cephalosporin + Macrolide vs Cotrimoxazole	NA	NA	1.52 (0.51, 4.51)	1.52 (0.51, 4.51)	69 (-65, 463)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Daptomycin + Aztreonam	NA	NA	0.63 (0.36, 1.09)	0.63 (0.36, 1.09)	-49 (-84, 12)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
2nd generation cephalosporin + Macrolide vs Linezolid + Aztreonam	NA	NA	1.12 (0.62, 2.02)	1.12 (0.62, 2.02)	16 (-50, 135)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Pristinamycin	NA	NA	0.67 (0.32, 1.37)	0.67 (0.32, 1.37)	-44 (-90, 49)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Teicoplanin + Other fluoroquinolone	NA	NA	3.28 (1.29, 8.37)	3.28 (1.29, 8.37)	301 (38, 973)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
3rd generation cephalosporin + Macrolide vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	1.69 (1.02, 2.8)	1.69 (1.02, 2.8)	91 (3, 238)	Indirect	LOW	Not serious	Not Serious	LOW	NMA	NA	RoB, Indirectness
3rd generation cephalosporin + Macrolide vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	1.46 (0.9, 2.36)	1.46 (0.9, 2.36)	61 (-13, 180)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
3rd generation cephalosporin + Macrolide vs 2nd generation cephalosporin +Tetracycline	NA	NA	1.26 (0.58, 2.73)	1.26 (0.58, 2.73)	34 (-55, 228)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs 3rd generation cephalosporin + Aminoglycoside	NA	NA	0.4 (0.1, 1.57)	0.4 (0.1, 1.57)	-79 (-119, 75)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
3rd generation cephalosporin + Macrolide vs Macrolides	NA	NA	1.23 (0.85, 1.79)	1.23 (0.85, 1.79)	30 (-20, 104)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
3rd generation cephalosporin + Macrolide vs Macrolide + Aminoglycoside	2.12 (0.2, 22.67)	148 (-106, 1000)	0.21 (0, 25)	1.4 (0.15, 13.31)	53 (-112, 1000)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
3rd generation cephalosporin + Macrolide vs Tetracyclines	NA	NA	1.71 (0.95, 3.08)	1.71 (0.95, 3.08)	94 (-7, 275)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
3rd generation cephalosporin + Macrolide vs Lefamulin	NA	NA	1.37 (0.84, 2.24)	1.37 (0.84, 2.24)	49 (-21, 164)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
3rd generation cephalosporin + Macrolide vs Carbapenems	4.17 (0.39, 50)	418 (-81, 1000)	1.31 (0.79, 2.18)	1.18 (0.72, 1.91)	24 (-37, 120)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
3rd generation cephalosporin + Macrolide vs Carbapenem + Macrolide	NA	NA	1.26 (0.67, 2.36)	1.26 (0.67, 2.36)	34 (-44, 180)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2

3rd generation cephalosporin + Macrolide vs Respiratory fluoroquinolone + metronidazole	NA	NA	0.79 (0.3, 2.09)	0.79 (0.3, 2.09)	-28 (-92, 144)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
3rd generation cephalosporin + Macrolide vs Other fluoroquinolones	NA	NA	1.29 (0.69, 2.43)	1.29 (0.69, 2.43)	38 (-41, 189)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Tigecycline	NA	NA	1.43 (0.91, 2.25)	1.43 (0.91, 2.25)	57 (-12, 165)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
3rd generation cephalosporin + Macrolide vs Cotrimoxazole	NA	NA	1.91 (0.65, 5.64)	1.91 (0.65, 5.64)	120 (-46, 612)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Daptomycin + Aztreonam	NA	NA	0.79 (0.46, 1.36)	0.79 (0.46, 1.36)	-28 (-71, 48)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Linezolid + Aztreonam	NA	NA	1.41 (0.79, 2.51)	1.41 (0.79, 2.51)	54 (-28, 199)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Pristinamycin	NA	NA	0.84 (0.41, 1.72)	0.84 (0.41, 1.72)	-21 (-78, 95)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Teicoplanin + Other fluoroquinolone	NA	NA	4.13 (1.63, 10.45)	4.13 (1.63, 10.45)	413 (83, 1000)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
3rd generation cephalosporin + Respiratory fluoroquinolone vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	0.86 (0.5, 1.47)	0.86 (0.5, 1.47)	-18 (-66, 62)	Indirect	LOW	Not serious	Serious	VERY LOW	NMA	NA	RoB, Imprecision, Indirectness
3rd generation cephalosporin + Respiratory fluoroquinolone vs 2nd generation cephalosporin +Tetracycline	NA	NA	0.74 (0.33, 1.67)	0.74 (0.33, 1.67)	-34 (-88, 88)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2, Indirectness
3rd generation cephalosporin + Respiratory fluoroquinolone vs 3rd generation cephalosporin + Aminoglycoside	NA	NA	0.24 (0.06, 0.95)	0.24 (0.06, 0.95)	-100 (-124, -7)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2, Indirectness
3rd generation cephalosporin + Respiratory fluoroquinolone vs Macrolides	NA	NA	0.73 (0.47, 1.13)	0.73 (0.47, 1.13)	-36 (-70, 17)	Indirect	LOW	Not serious	Serious	VERY LOW	NMA	NA	RoB, Imprecision, Indirectness
3rd generation cephalosporin + Respiratory fluoroquinolone vs Macrolide + Aminoglycoside	NA	NA	0.83 (0.08, 8.2)	0.83 (0.08, 8.2)	-22 (-121, 950)	Indirect	LOW	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3, Indirectness
3rd generation cephalosporin + Respiratory fluoroquinolone vs Tetracyclines	NA	NA	1.01 (0.54, 1.9)	1.01 (0.54, 1.9)	1 (-61, 119)	Indirect	LOW	Not serious	Extremely serious	VERY LOW	NMA	NA	Imprecisionx3, Publication bias, Indirectness
3rd generation cephalosporin + Respiratory fluoroquinolone vs Lefamulin	NA	NA	0.81 (0.47, 1.4)	0.81 (0.47, 1.4)	-25 (-70, 53)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	Imprecisionx2, Publication bias, Indirectness
3rd generation cephalosporin + Respiratory fluoroquinolone vs Carbapenems	NA	NA	0.82 (0.47, 1.43)	0.7 (0.4, 1.2)	-40 (-79, 26)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2, Indirectness

3rd generation cephalosporin + Respiratory fluoroquinolone vs Carbapenem + Macrolide	NA	NA	0.74 (0.38, 1.45)	0.74 (0.38, 1.45)	-34 (-82, 59)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2, Indirectness
3rd generation cephalosporin + Respiratory fluoroquinolone vs Respiratory fluoroquinolone + metronidazole	NA	NA	0.47 (0.17, 1.27)	0.47 (0.17, 1.27)	-70 (-110, 36)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2, Indirectness
3rd generation cephalosporin + Respiratory fluoroquinolone vs Other fluoroquinolones	NA	NA	0.76 (0.39, 1.5)	0.76 (0.39, 1.5)	-32 (-81, 66)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2, Indirectness
3rd generation cephalosporin + Respiratory fluoroquinolone vs Tigecycline	NA	NA	0.84 (0.51, 1.41)	0.84 (0.51, 1.41)	-21 (-65, 54)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	Imprecisionx2, Publication, Indirectness bias
3rd generation cephalosporin + Respiratory fluoroquinolone vs Cotrimoxazole	NA	NA	1.13 (0.37, 3.42)	1.13 (0.37, 3.42)	17 (-83, 319)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	Imprecisionx2, Publication, Indirectness bias
3rd generation cephalosporin + Respiratory fluoroquinolone vs Daptomycin + Aztreonam	NA	NA	0.47 (0.26, 0.84)	0.47 (0.26, 0.84)	-70 (-98, -21)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2, Indirectness
3rd generation cephalosporin + Respiratory fluoroquinolone vs Linezolid + Aztreonam	NA	NA	0.83 (0.44, 1.56)	0.83 (0.44, 1.56)	-22 (-74, 74)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2, Indirectness
3rd generation cephalosporin + Respiratory fluoroquinolone vs Pristinamycin	NA	NA	0.5 (0.23, 1.06)	0.5 (0.23, 1.06)	-66 (-102, 8)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	Imprecision x2, Publication bias, Indirectness
3rd generation cephalosporin + Respiratory fluoroquinolone vs Teicoplanin + Other fluoroquinolone	NA	NA	2.44 (0.94, 6.37)	2.44 (0.94, 6.37)	190 (-8, 709)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
3rd generation cephalosporin+ Other fluoroquinolone vs 2nd generation cephalosporin +Tetracycline	NA	NA	0.86 (0.39, 1.92)	0.86 (0.39, 1.92)	-18 (-81, 121)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin+ Other fluoroquinolone vs 3rd generation cephalosporin + Aminoglycoside	NA	NA	0.27 (0.07, 1.09)	0.27 (0.07, 1.09)	-96 (-123, 12)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecision x2
3rd generation cephalosporin+ Other fluoroquinolone vs Macrolides	NA	NA	0.85 (0.56, 1.29)	0.85 (0.56, 1.29)	-20 (-58, 38)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
3rd generation cephalosporin+ Other fluoroquinolone vs Macrolide + Aminoglycoside	NA	NA	0.96 (0.1, 9.49)	0.96 (0.1, 9.49)	-5 (-119, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
3rd generation cephalosporin+ Other fluoroquinolone vs Tetracyclines	NA	NA	1.18 (0.63, 2.18)	1.18 (0.63, 2.18)	24 (-49, 156)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin+ Other fluoroquinolone vs Lefamulin	NA	NA	0.94 (0.55, 1.6)	0.94 (0.55, 1.6)	-8 (-59, 79)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision

3rd generation cephalosporin+ Other fluoroquinolone vs Carbapenems	NA	NA	0.81 (0.48, 1.37)	0.81 (0.48, 1.37)	-25 (-69, 49)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecision x2
3rd generation cephalosporin+ Other fluoroquinolone vs Carbapenem + Macrolide	NA	NA	0.87 (0.45, 1.67)	0.87 (0.45, 1.67)	-17 (-73, 88)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin+ Other fluoroquinolone vs Respiratory fluoroquinolone + metronidazole	NA	NA	0.54 (0.2, 1.47)	0.54 (0.2, 1.47)	-61 (-106, 62)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin+ Other fluoroquinolone vs Other fluoroquinolones	NA	NA	0.89 (0.46, 1.72)	0.89 (0.46, 1.72)	-15 (-71, 95)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin+ Other fluoroquinolone vs Tigecycline	NA	NA	0.98 (0.6, 1.61)	0.98 (0.6, 1.61)	-3 (-53, 81)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
3rd generation cephalosporin+ Other fluoroquinolone vs Cotrimoxazole	NA	NA	1.31 (0.44, 3.94)	1.31 (0.44, 3.94)	41 (-74, 388)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin+ Other fluoroquinolone vs Daptomycin + Aztreonam	NA	NA	0.54 (0.3, 0.96)	0.54 (0.3, 0.96)	-61 (-92, -5)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin+ Other fluoroquinolone vs Linezolid + Aztreonam	NA	NA	0.97 (0.52, 1.78)	0.97 (0.52, 1.78)	-4 (-63, 103)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin+ Other fluoroquinolone vs Pristinamycin	NA	NA	0.58 (0.27, 1.21)	0.58 (0.27, 1.21)	-55 (-96, 28)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin+ Other fluoroquinolone vs Teicoplanin + Other fluoroquinolone	NA	NA	2.84 (1.1, 7.33)	2.84 (1.1, 7.33)	243 (13, 836)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
2nd generation cephalosporin +Tetracycline vs 3rd generation cephalosporin + Aminoglycoside	NA	NA	0.32 (0.07, 1.44)	0.32 (0.07, 1.44)	-90 (-123, 58)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin +Tetracycline vs Macrolides	0.98 (0.52, 1.86)	-3 (-63, 114)	NA	0.98 (0.5, 1.94)	-3 (-66, 124)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin +Tetracycline vs Macrolide + Aminoglycoside	NA	NA	1.11 (0.1, 11.91)	1.11 (0.1, 11.91)	15 (-119, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
2nd generation cephalosporin +Tetracycline vs Tetracyclines	NA	NA	1.36 (0.57, 3.24)	1.36 (0.57, 3.24)	48 (-57, 296)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin +Tetracycline vs Lefamulin	NA	NA	1.09 (0.49, 2.44)	1.09 (0.49, 2.44)	12 (-67, 190)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin +Tetracycline vs Carbapenems	NA	NA	0.94 (0.42, 2.09)	0.94 (0.42, 2.09)	-8 (-77, 144)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin +Tetracycline vs Carbapenem + Macrolide	NA	NA	1 (0.41, 2.45)	1 (0.41, 2.45)	0 (-78, 191)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin +Tetracycline vs Respiratory fluoroquinolone + metronidazole	NA	NA	0.63 (0.2, 2.02)	0.63 (0.2, 2.02)	-49 (-106, 135)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3

2nd generation cephalosporin +Tetracycline vs Other fluoroquinolones	NA	NA	1.03 (0.42, 2.52)	1.03 (0.42, 2.52)	4 (-77, 201)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin +Tetracycline vs Tigecycline	NA	NA	1.14 (0.52, 2.49)	1.14 (0.52, 2.49)	18 (-63, 197)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin +Tetracycline vs Cotrimoxazole	NA	NA	1.52 (0.43, 5.34)	1.52 (0.43, 5.34)	69 (-75, 573)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
2nd generation cephalosporin +Tetracycline vs Daptomycin + Aztreonam	NA	NA	0.63 (0.27, 1.45)	0.63 (0.27, 1.45)	-49 (-96, 59)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin +Tetracycline vs Linezolid + Aztreonam	NA	NA	1.12 (0.47, 2.65)	1.12 (0.47, 2.65)	16 (-70, 218)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin +Tetracycline vs Pristinamycin	NA	NA	0.67 (0.26, 1.74)	0.67 (0.26, 1.74)	-44 (-98, 98)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
2nd generation cephalosporin +Tetracycline vs Teicoplanin + Other fluoroquinolone	NA	NA	3.29 (1.07, 10.14)	3.29 (1.07, 10.14)	302 (9, 1000)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
3rd generation cephalosporin + Aminoglycoside vs Macrolides	NA	NA	3.08 (0.8, 11.83)	3.08 (0.8, 11.83)	275 (-26, 1000)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin + Aminoglycoside vs Macrolide + Aminoglycoside	NA	NA	3.49 (0.26, 47.3)	3.49 (0.26, 47.3)	329 (-98, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
3rd generation cephalosporin + Aminoglycoside vs Tetracyclines	NA	NA	4.27 (1.03, 17.7)	4.27 (1.03, 17.7)	432 (4, 1000)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin + Aminoglycoside vs Lefamulin	NA	NA	3.42 (0.86, 13.67)	3.42 (0.86, 13.67)	319 (-18, 1000)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin + Aminoglycoside vs Carbapenems	2.94 (0.84, 10)	256 (-21, 1000)	NA	2.94 (0.82, 10.54)	256 (-24, 1000)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin + Aminoglycoside vs Carbapenem + Macrolide	NA	NA	3.15 (0.75, 13.23)	3.15 (0.75, 13.23)	284 (-33, 1000)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin + Aminoglycoside vs Respiratory fluoroquinolone + metronidazole	NA	NA	1.98 (0.39, 9.98)	1.98 (0.39, 9.98)	129 (-81, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
3rd generation cephalosporin + Aminoglycoside vs Other fluoroquinolones	NA	NA	3.23 (0.81, 12.81)	3.23 (0.81, 12.81)	294 (-25, 1000)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin + Aminoglycoside vs Tigecycline	NA	NA	3.57 (0.91, 14.07)	3.57 (0.91, 14.07)	339 (-12, 1000)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin + Aminoglycoside vs Cotrimoxazole	NA	NA	4.77 (0.88, 25.73)	4.77 (0.88, 25.73)	498 (-16, 1000)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin + Aminoglycoside vs Daptomycin + Aztreonam	NA	NA	1.97 (0.51, 7.58)	1.97 (0.51, 7.58)	128 (-65, 869)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin + Aminoglycoside vs Linezolid + Aztreonam	NA	NA	3.51 (0.9, 13.74)	3.51 (0.9, 13.74)	331 (-13, 1000)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2

3rd generation cephalosporin + Aminoglycoside vs Pristinamycin	NA	NA	2.1 (0.49, 8.97)	2.1 (0.49, 8.97)	145 (-67, 1000)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin + Aminoglycoside vs Teicoplanin + Other fluoroquinolone	NA	NA	10.32 (2.2, 48.34)	10.32 (2.2, 48.34)	999 (158, 1000)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
Macrolides vs Macrolide + Aminoglycoside	NA	NA	1.13 (0.12, 10.96)	1.13 (0.12, 10.96)	17 (-116, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Macrolides vs Tetracyclines	NA	NA	1.39 (0.81, 2.37)	1.39 (0.81, 2.37)	51 (-25, 181)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
Macrolides vs Lefamulin	NA	NA	1.11 (0.72, 1.7)	1.11 (0.72, 1.7)	15 (-37, 92)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Macrolides vs Carbapenems	NA	NA	0.95 (0.63, 1.45)	0.95 (0.63, 1.45)	-7 (-49, 59)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Macrolides vs Carbapenem + Macrolide	NA	NA	1.02 (0.57, 1.82)	1.02 (0.57, 1.82)	3 (-57, 108)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Macrolides vs Respiratory fluoroquinolone + metronidazole	NA	NA	0.64 (0.25, 1.65)	0.64 (0.25, 1.65)	-48 (-99, 86)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Macrolides vs Other fluoroquinolones	NA	NA	1.05 (0.58, 1.87)	1.05 (0.58, 1.87)	7 (-55, 115)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Macrolides vs Tigecycline	NA	NA	1.16 (0.79, 1.7)	1.16 (0.79, 1.7)	21 (-28, 92)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
Macrolides vs Cotrimoxazole	NA	NA	1.55 (0.54, 4.45)	1.55 (0.54, 4.45)	73 (-61, 455)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Macrolides vs Daptomycin + Aztreonam	NA	NA	0.64 (0.39, 1.04)	0.64 (0.39, 1.04)	-48 (-81, 5)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Macrolides vs Linezolid + Aztreonam	NA	NA	1.14 (0.67, 1.93)	1.14 (0.67, 1.93)	18 (-44, 123)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Macrolides vs Pristinamycin	NA	NA	0.68 (0.35, 1.33)	0.68 (0.35, 1.33)	-42 (-86, 44)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Macrolides vs Teicoplanin + Other fluoroquinolone	NA	NA	3.35 (1.37, 8.2)	3.35 (1.37, 8.2)	310 (49, 950)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
Macrolide + Aminoglycoside vs Tetracyclines	NA	NA	1.22 (0.12, 12.4)	1.22 (0.12, 12.4)	29 (-116, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Lefamulin	NA	NA	0.98 (0.1, 9.71)	0.98 (0.1, 9.71)	-3 (-119, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Carbapenems	2 (0.13, 33.33)	132 (-115, 1000)	0.19 (0, 10.76)	0.84 (0.09, 8.17)	-21 (-120, 946)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Carbapenem + Macrolide	NA	NA	0.9 (0.09, 9.22)	0.9 (0.09, 9.22)	-13 (-120, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Respiratory fluoroquinolone + metronidazole	NA	NA	0.57 (0.05, 6.51)	0.57 (0.05, 6.51)	-57 (-125, 727)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Other fluoroquinolones	NA	NA	0.92 (0.09, 9.35)	0.92 (0.09, 9.35)	-11 (-120, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3

Macrolide + Aminoglycoside vs Tigecycline	NA	NA	1.02 (0.1, 10.05)	1.02 (0.1, 10.05)	3 (-119, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Cotrimoxazole	NA	NA	1.37 (0.11, 16.43)	1.37 (0.11, 16.43)	49 (-117, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Daptomycin + Aztreonam	NA	NA	0.56 (0.06, 5.59)	0.56 (0.06, 5.59)	-58 (-124, 606)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Linezolid + Aztreonam	NA	NA	1.01 (0.1, 10.06)	1.01 (0.1, 10.06)	1 (-119, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Pristinamycin	NA	NA	0.6 (0.06, 6.28)	0.6 (0.06, 6.28)	-53 (-124, 697)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Teicoplanin + Other fluoroquinolone	NA	NA	2.96 (0.26, 33.05)	2.96 (0.26, 33.05)	259 (-98, 1000)	Indirect	LOW	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx3
Tetracyclines vs Lefamulin	NA	NA	0.8 (0.43, 1.5)	0.8 (0.43, 1.5)	-26 (-75, 66)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	Imprecisionx2 Publications bias
Tetracyclines vs Carbapenems	NA	NA	0.69 (0.37, 1.28)	0.69 (0.37, 1.28)	-41 (-83, 37)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Tetracyclines vs Carbapenem + Macrolide	NA	NA	0.74 (0.35, 1.53)	0.74 (0.35, 1.53)	-34 (-86, 70)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Tetracyclines vs Respiratory fluoroquinolone + metronidazole	NA	NA	0.46 (0.16, 1.32)	0.46 (0.16, 1.32)	-71 (-111, 42)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Tetracyclines vs Other fluoroquinolones	NA	NA	0.75 (0.36, 1.58)	0.75 (0.36, 1.58)	-33 (-84, 77)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Tetracyclines vs Tigecycline	NA	NA	0.83 (0.46, 1.51)	0.83 (0.46, 1.51)	-22 (-71, 67)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	Imprecisionx2 Publications bias
Tetracyclines vs Cotrimoxazole	0.82 (0.32, 2.08)	-24 (-90, 143)	0.31 (0.01, 12.18)	1.12 (0.44, 2.82)	16 (-74, 240)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	Imprecisionx2 Publications bias
Tetracyclines vs Daptomycin + Aztreonam	NA	NA	0.46 (0.24, 0.9)	0.46 (0.24, 0.9)	-71 (-100, -13)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Tetracyclines vs Linezolid + Aztreonam	NA	NA	0.82 (0.41, 1.65)	0.82 (0.41, 1.65)	-24 (-78, 86)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Tetracyclines vs Pristinamycin	NA	NA	0.49 (0.22, 1.11)	0.49 (0.22, 1.11)	-67 (-103, 15)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	Imprecision x2 Publications bias
Tetracyclines vs Teicoplanin + Other fluoroquinolone	NA	NA	2.41 (0.88, 6.59)	2.41 (0.88, 6.59)	186 (-16, 738)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
Lefamulin vs Carbapenems	NA	NA	0.86 (0.5, 1.47)	0.86 (0.5, 1.47)	-18 (-66, 62)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Lefamulin vs Carbapenem + Macrolide	NA	NA	0.92 (0.48, 1.78)	0.92 (0.48, 1.78)	-11 (-69, 103)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Lefamulin vs Respiratory fluoroquinolone + metronidazole	NA	NA	0.58 (0.21, 1.57)	0.58 (0.21, 1.57)	-55 (-104, 75)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3

Lefamulin vs Other fluoroquinolones	NA	NA	0.94 (0.48, 1.84)	0.94 (0.48, 1.84)	-8 (-69, 111)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Lefamulin vs Tigecycline	NA	NA	1.04 (0.63, 1.73)	1.04 (0.63, 1.73)	5 (-49, 96)	Indirect	HIGH	Not serious	Serious	MODERATE	NMA	NA	Imprecision
Lefamulin vs Cotrimoxazole	NA	NA	1.39 (0.46, 4.21)	1.39 (0.46, 4.21)	51 (-71, 424)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Lefamulin vs Daptomycin + Aztreonam	NA	NA	0.58 (0.32, 1.04)	0.58 (0.32, 1.04)	-55 (-90, 5)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecision x2
Lefamulin vs Linezolid + Aztreonam	NA	NA	1.03 (0.55, 1.91)	1.03 (0.55, 1.91)	4 (-59, 120)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Lefamulin vs Pristinamycin	NA	NA	0.61 (0.29, 1.3)	0.61 (0.29, 1.3)	-51 (-94, 40)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	NA	Imprecisionx2
Lefamulin vs Teicoplanin + Other fluoroquinolone	NA	NA	3.02 (1.16, 7.84)	3.02 (1.16, 7.84)	267 (21, 903)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
Carbapenems vs Carbapenem + Macrolide	NA	NA	1.07 (0.56, 2.06)	1.07 (0.56, 2.06)	9 (-58, 140)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Carbapenems vs Respiratory fluoroquinolone + metronidazole	NA	NA	0.67 (0.25, 1.82)	0.67 (0.25, 1.82)	-44 (-99, 108)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Carbapenems vs Other fluoroquinolones	1.87 (0.77, 4.51)	115 (-30, 463)	0.85 (0.45, 1.6)	1.1 (0.65, 1.85)	13 (-46, 112)	Direct	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Carbapenems vs Tigecycline	NA	NA	1.21 (0.74, 2)	1.21 (0.74, 2)	28 (-34, 132)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
Carbapenems vs Cotrimoxazole	NA	NA	1.62 (0.54, 4.87)	1.62 (0.54, 4.87)	82 (-61, 511)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Carbapenems vs Daptomycin + Aztreonam	NA	NA	0.67 (0.44, 1.03)	0.67 (0.44, 1.03)	-44 (-74, 4)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Carbapenems vs Linezolid + Aztreonam	NA	NA	1.19 (0.74, 1.93)	1.19 (0.74, 1.93)	25 (-34, 123)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Carbapenems vs Pristinamycin	NA	NA	0.71 (0.36, 1.42)	0.71 (0.36, 1.42)	-38 (-84, 55)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Carbapenems vs Teicoplanin + Other fluoroquinolone	NA	NA	3.51 (1.47, 8.36)	3.51 (1.47, 8.36)	331 (62, 972)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
Carbapenem + Macrolide vs Respiratory fluoroquinolone + metronidazole	NA	NA	0.63 (0.22, 1.83)	0.63 (0.22, 1.83)	-49 (-103, 110)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Carbapenem + Macrolide vs Other fluoroquinolones	NA	NA	1.02 (0.47, 2.21)	1.02 (0.47, 2.21)	3 (-70, 160)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Carbapenem + Macrolide vs Tigecycline	NA	NA	1.13 (0.6, 2.14)	1.13 (0.6, 2.14)	17 (-53, 150)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Carbapenem + Macrolide vs Cotrimoxazole	NA	NA	1.51 (0.47, 4.88)	1.51 (0.47, 4.88)	67 (-70, 512)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Carbapenem + Macrolide vs Daptomycin + Aztreonam	NA	NA	0.63 (0.31, 1.26)	0.63 (0.31, 1.26)	-49 (-91, 34)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2

Carbapenem + Macrolide vs Linezolid + Aztreonam	NA	NA	1.12 (0.54, 2.31)	1.12 (0.54, 2.31)	16 (-61, 173)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Carbapenem + Macrolide vs Pristinamycin	NA	NA	0.67 (0.29, 1.54)	0.67 (0.29, 1.54)	-44 (-94, 71)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Carbapenem + Macrolide vs Teicoplanin + Other fluoroquinolone	NA	NA	3.28 (1.17, 9.15)	3.28 (1.17, 9.15)	301 (22, 1000)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
Respiratory fluoroquinolone + metronidazole vs Other fluoroquinolones	NA	NA	1.63 (0.56, 4.77)	1.63 (0.56, 4.77)	83 (-58, 498)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Respiratory fluoroquinolone + metronidazole vs Tigecycline	NA	NA	1.81 (0.68, 4.8)	1.81 (0.68, 4.8)	107 (-42, 502)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Respiratory fluoroquinolone + metronidazole vs Cotrimoxazole	NA	NA	2.41 (0.6, 9.65)	2.41 (0.6, 9.65)	186 (-53, 1000)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Respiratory fluoroquinolone + metronidazole vs Daptomycin + Aztreonam	NA	NA	1 (0.36, 2.77)	1 (0.36, 2.77)	0 (-84, 234)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Respiratory fluoroquinolone + metronidazole vs Linezolid + Aztreonam	NA	NA	1.78 (0.63, 5.04)	1.78 (0.63, 5.04)	103 (-49, 533)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Respiratory fluoroquinolone + metronidazole vs Pristinamycin	NA	NA	1.06 (0.35, 3.26)	1.06 (0.35, 3.26)	8 (-86, 298)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Respiratory fluoroquinolone + metronidazole vs Teicoplanin + Other fluoroquinolone	NA	NA	5.22 (1.47, 18.59)	5.22 (1.47, 18.59)	557 (62, 1000)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
Other fluoroquinolones vs Tigecycline	NA	NA	1.11 (0.58, 2.1)	1.11 (0.58, 2.1)	15 (-55, 145)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Other fluoroquinolones vs Cotrimoxazole	NA	NA	1.48 (0.46, 4.76)	1.48 (0.46, 4.76)	63 (-71, 496)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Other fluoroquinolones vs Daptomycin + Aztreonam	NA	NA	0.61 (0.34, 1.11)	0.61 (0.34, 1.11)	-51 (-87, 15)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecision x2
Other fluoroquinolones vs Linezolid + Aztreonam	NA	NA	1.09 (0.58, 2.05)	1.09 (0.58, 2.05)	12 (-55, 139)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Other fluoroquinolones vs Pristinamycin	NA	NA	0.65 (0.29, 1.45)	0.65 (0.29, 1.45)	-46 (-94, 59)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Other fluoroquinolones vs Teicoplanin + Other fluoroquinolone	NA	NA	3.2 (1.23, 8.36)	3.2 (1.23, 8.36)	290 (30, 972)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
Tigecycline vs Cotrimoxazole	NA	NA	1.34 (0.45, 3.97)	1.34 (0.45, 3.97)	45 (-73, 392)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Tigecycline vs Daptomycin + Aztreonam	NA	NA	0.55 (0.32, 0.96)	0.55 (0.32, 0.96)	-59 (-90, -5)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Tigecycline vs Linezolid + Aztreonam	NA	NA	0.98 (0.54, 1.78)	0.98 (0.54, 1.78)	-3 (-61, 103)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2

Tigecycline vs Pristinamycin	NA	NA	0.59 (0.29, 1.21)	0.59 (0.29, 1.21)	-54 (-94, 28)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	NA	Imprecisionx2
Tigecycline vs Teicoplanin + Other fluoroquinolone	NA	NA	2.89 (1.14, 7.36)	2.89 (1.14, 7.36)	249 (18, 840)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
Cotrimoxazole vs Daptomycin + Aztreonam	NA	NA	0.41 (0.13, 1.27)	0.41 (0.13, 1.27)	-78 (-115, 36)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Cotrimoxazole vs Linezolid + Aztreonam	NA	NA	0.74 (0.23, 2.31)	0.74 (0.23, 2.31)	-34 (-102, 173)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Cotrimoxazole vs Pristinamycin	NA	NA	0.44 (0.13, 1.49)	0.44 (0.13, 1.49)	-74 (-115, 65)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	NA	Imprecisionx2
Cotrimoxazole vs Teicoplanin + Other fluoroquinolone	NA	NA	2.16 (0.56, 8.38)	2.16 (0.56, 8.38)	153 (-58, 974)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
Daptomycin + Aztreonam vs Linezolid + Aztreonam	NA	NA	1.78 (1.06, 2.99)	1.78 (1.06, 2.99)	103 (8, 263)	Indirect	MODERATE	Not serious	Not Serious	MODERATE	NMA	NA	RoB
Daptomycin + Aztreonam vs Pristinamycin	NA	NA	1.06 (0.51, 2.21)	1.06 (0.51, 2.21)	8 (-65, 160)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Daptomycin + Aztreonam vs Teicoplanin + Other fluoroquinolone	NA	NA	5.24 (2.15, 12.76)	5.24 (2.15, 12.76)	560 (152, 1000)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
Linezolid + Aztreonam vs Pristinamycin	NA	NA	0.6 (0.28, 1.28)	0.6 (0.28, 1.28)	-53 (-95, 37)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Linezolid + Aztreonam vs Teicoplanin + Other fluoroquinolone	NA	NA	2.94 (1.18, 7.33)	2.94 (1.18, 7.33)	256 (24, 836)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2
Pristinamycin vs Teicoplanin + Other fluoroquinolone	NA	NA	4.92 (1.72, 14.07)	4.92 (1.72, 14.07)	517 (95, 1000)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Publication bias, Imprecisionx2

RR: relative risk; RD: risk difference; CI: confidence interval, NA: not applicable (no evidence), ROB: risk of bias

[1] The baseline risk was derived from the median of risk of event across the arms that randomized patients to the respiratory fluoroquinolones.

[2] Risk difference was calculated through applying the relative risk to the baseline risk. In cases that upper limit of confidence interval exceeded 1000, we truncated the value and reported 1000 as the upper limit.

[3] The effect estimate was informed by a single trial in which the majority of patients had moderate severity CAP; rated down due to indirectness because a 3rd generation cephalosporin combined with a respiratory fluoroquinolone is not clinically relevant in this setting.

Supplement 10. Direct, indirect, and network estimates and certainty of evidence for all-cause mortality

Minimal important difference	5 per 1000 patients											
Large effect threshold	15 per 1000 patients											
Baseline risk [1]	23 per 1000 patients											
	Direct evidence		**Indirect evidence**	**Network evidence**							**Best estimate**	**Reason for downgrading the certainty**
Comparison	**RR (95% CI)**	**RD** [2] **(95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RD** [2] **(95% CI)**	**Starting evidence**	**Starting certainty rating**	**Incoherence**	**Imprecision**	**Final certainty rating**		
Penicillins vs Respiratory fluoroquinolones	1.29 (0.41, 4.1)	7 (-14, 71)	1.04 (0.4, 2.7)	1.14 (0.55, 2.37)	3 (-10, 32)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillin + Other fluoroquinolone vs Respiratory fluoroquinolones	NA	NA	1.46 (0.42, 5.08)	1.46 (0.42, 5.08)	11 (-13, 94)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Respiratory fluoroquinolones	0.84 (0.21, 3.35)	-4 (-18, 54)	1.07 (0.52, 2.19)	1.01 (0.54, 1.92)	0 (-11, 21)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Respiratory fluoroquinolones	1.52 (0.8, 2.86)	12 (-5, 43)	NA	1.52 (0.8, 2.86)	12 (-5, 43)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs Respiratory fluoroquinolones	NA	NA	5.95 (0.68, 52.21)	5.95 (0.68, 52.21)	114 (-7, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs Respiratory fluoroquinolones	NA	NA	3.09 (0.22, 42.8)	3.09 (0.22, 42.8)	48 (-18, 961)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporins vs Respiratory fluoroquinolones	NA	NA	1.35 (0.55, 3.28)	1.35 (0.55, 3.28)	8 (-10, 52)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporins vs Respiratory fluoroquinolones	1.15 (0.7, 1.89)	3 (-7, 20)	0.7 (0.26, 1.89)	1.04 (0.67, 1.62)	1 (-8, 14)	Direct	MODERATE	Not serious	Serious	LOW	NMA	RoB, Imprecision
4th generation cephalosporins vs Respiratory fluoroquinolones	NA	NA	1.19 (0.59, 2.4)	1.19 (0.59, 2.4)	4 (-9, 32)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
5th generation cephalosporins vs Respiratory fluoroquinolones	NA	NA	1.01 (0.49, 2.09)	1.01 (0.49, 2.09)	0 (-12, 25)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin/β-lactamase inhibitors vs Respiratory fluoroquinolones	NA	NA	1 (0.02, 50.47)	1 (0.02, 50.47)	0 (-23, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolide vs Respiratory fluoroquinolones	NA	NA	0.6 (0.23, 1.52)	0.6 (0.23, 1.52)	-9 (-18, 12)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Respiratory fluoroquinolones	0.85 (0.51, 1.43)	-3 (-11, 10)	0.38 (0.04, 3.53)	0.82 (0.49, 1.35)	-4 (-12, 8)	Direct	MODERATE	Not serious	Serious	LOW	NMA	RoB, Imprecision
3rd generation cephalosporin + Respiratory fluoroquinolone vs Respiratory fluoroquinolones	0.67 (0.33, 1.38)	-8 (-15, 9)	NA	0.67 (0.33, 1.38)	-8 (-15, 9)	Direct	LOW	Not serious	Very serious	VERY LOW	NMA	Imprecisionx3, Publication bias, Indirectness [3]
3rd generation cephalosporin+ Other fluoroquinolone vs Respiratory fluoroquinolones	1.19 (0.77, 1.85)	4 (-5, 20)	NA	1.19 (0.77, 1.85)	4 (-5, 20)	Direct	MODERATE	Not serious	Serious	LOW	NMA	RoB, Imprecision
Macrolides vs Respiratory fluoroquinolones	0.79 (0.38, 1.66)	-5 (-14, 15)	2.13 (0.55, 8.2)	1 (0.52, 1.91)	0 (-11, 21)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Macrolide + Aminoglycoside vs Respiratory fluoroquinolones	NA	NA	0.86 (0.16, 4.59)	0.86 (0.16, 4.59)	-3 (-19, 83)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3

Tetracyclines vs Respiratory fluoroquinolones	2 (0.61, 6.67)	23 (-9, 130)	4.06 (0.05, 335.7)	2.11 (0.67, 6.66)	26 (-8, 130)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	Imprecisionx2, , Publication bias
Carbapenems vs Respiratory fluoroquinolones	0.34 (0.01, 8.13)	-15 (-23, 164)	1.02 (0.51, 2.06)	0.97 (0.49, 1.93)	-1 (-12, 21)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Carbapenem + Macrolide vs Respiratory fluoroquinolones	NA	NA	2.49 (1.01, 6.18)	2.49 (1.01, 6.18)	34 (0, 119)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Other fluoroquinolones vs Respiratory fluoroquinolones	NA	NA	1.93 (0.42, 8.88)	1.93 (0.42, 8.88)	21 (-13, 181)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Tigecycline vs Respiratory fluoroquinolones	1.09 (0.48, 2.44)	2 (-12, 33)	NA	1.08 (0.48, 2.45)	2 (-12, 33)	Direct	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
Cotrimoxazole vs Respiratory fluoroquinolones	NA	NA	3.86 (0.59, 25.3)	3.86 (0.59, 25.3)	66 (-9, 559)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Daptomycin + Aztreonam vs Respiratory fluoroquinolones	NA	NA	1.84 (0.81, 4.21)	1.84 (0.81, 4.21)	19 (-4, 74)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Linezolid + Aztreonam vs Respiratory fluoroquinolones	NA	NA	0.79 (0.36, 1.75)	0.79 (0.36, 1.75)	-5 (-15, 17)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Teicoplanin + Other fluoroquinolone vs Respiratory fluoroquinolones	NA	NA	1.43 (0.43, 4.78)	1.43 (0.43, 4.78)	10 (-13, 87)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs Penicillin + Other fluoroquinolone	NA	NA	0.78 (0.18, 3.31)	0.78 (0.18, 3.31)	-5 (-19, 53)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs β-Lactam/β-lactamase inhibitors	NA	NA	1.12 (0.45, 2.8)	1.12 (0.45, 2.8)	3 (-13, 41)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs β-Lactam/β-lactamase inhibitor + Macrolide	NA	NA	0.75 (0.28, 1.99)	0.75 (0.28, 1.99)	-6 (-17, 23)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs β-Lactam/β-lactamase inhibitor + Aminoglycoside	NA	NA	0.19 (0.02, 1.85)	0.19 (0.02, 1.85)	-19 (-23, 20)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs 1st generation cephalosporins	NA	NA	0.37 (0.03, 5.16)	0.37 (0.03, 5.16)	-14 (-22, 96)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs 2nd generation cephalosporins	1.72 (0.3, 10)	17 (-16, 207)	0.59 (0.17, 2.04)	0.85 (0.31, 2.31)	-3 (-16, 30)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs 3rd generation cephalosporins	1.69 (0.17, 16.67)	16 (-19, 360)	1.03 (0.44, 2.42)	1.09 (0.49, 2.44)	2 (-12, 33)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs 4th generation cephalosporins	NA	NA	0.96 (0.36, 2.53)	0.96 (0.36, 2.53)	-1 (-15, 35)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs 5th generation cephalosporins	NA	NA	1.13 (0.42, 3.03)	1.13 (0.42, 3.03)	3 (-13, 47)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	1.14 (0.02, 61.12)	1.14 (0.02, 61.12)	3 (-23, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs 2nd generation cephalosporin + Macrolide	NA	NA	1.91 (0.69, 5.3)	1.91 (0.69, 5.3)	21 (-7, 99)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs 3rd generation cephalosporin + Macrolide	NA	NA	1.4 (0.57, 3.39)	1.4 (0.57, 3.39)	9 (-10, 55)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	1.69 (0.61, 4.73)	1.69 (0.61, 4.73)	16 (-9, 86)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2, Indirectness
Penicillins vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	0.96 (0.41, 2.25)	0.96 (0.41, 2.25)	-1 (-14, 29)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs Macrolides	0.75 (0.28, 2.04)	-6 (-17, 24)	2.03 (0.63, 6.57)	1.14 (0.53, 2.45)	3 (-11, 33)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2

Penicillins vs Macrolide + Aminoglycoside	NA	NA	1.32 (0.22, 8.07)	1.32 (0.22, 8.07)	7 (-18, 163)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs Tetracyclines	NA	NA	0.54 (0.14, 2.06)	0.54 (0.14, 2.06)	-11 (-20, 24)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs Carbapenems	NA	NA	1.17 (0.45, 3.07)	1.17 (0.45, 3.07)	4 (-13, 48)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs Carbapenem + Macrolide	NA	NA	0.46 (0.14, 1.47)	0.46 (0.14, 1.47)	-12 (-20, 11)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs Other fluoroquinolones	NA	NA	0.59 (0.11, 3.03)	0.59 (0.11, 3.03)	-9 (-20, 47)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs Tigecycline	NA	NA	1.05 (0.35, 3.14)	1.05 (0.35, 3.14)	1 (-15, 49)	Indirect	MODERTAE	Not serious	Very serious	LOW	NMA	RoB, Imprecisionx2
Penicillins vs Cotrimoxazole	0.3 (0.03, 2.78)	-16 (-22, 41)	0.28 (0.01, 7.08)	0.3 (0.05, 1.83)	-16 (-22, 19)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs Daptomycin + Aztreonam	NA	NA	0.62 (0.21, 1.79)	0.62 (0.21, 1.79)	-9 (-18, 18)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs Linezolid + Aztreonam	NA	NA	1.44 (0.51, 4.08)	1.44 (0.51, 4.08)	10 (-11, 71)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs Teicoplanin + Other fluoroquinolone	NA	NA	0.79 (0.2, 3.15)	0.79 (0.2, 3.15)	-5 (-18, 49)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs β-Lactam/β-lactamase inhibitors	NA	NA	1.44 (0.36, 5.84)	1.44 (0.36, 5.84)	10 (-15, 111)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs β-Lactam/β-lactamase inhibitor + Macrolide	0.96 (0.33, 2.78)	-1 (-15, 41)	NA	0.97 (0.33, 2.82)	-1 (-15, 42)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillin + Other fluoroquinolone vs β-Lactam/β-lactamase inhibitor + Aminoglycoside	NA	NA	0.25 (0.02, 3)	0.25 (0.02, 3)	-17 (-23, 46)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs 1st generation cephalosporins	NA	NA	0.47 (0.03, 8.7)	0.47 (0.03, 8.7)	-12 (-22, 177)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs 2nd generation cephalosporins	NA	NA	1.09 (0.24, 5.02)	1.09 (0.24, 5.02)	2 (-17, 92)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs 3rd generation cephalosporins	NA	NA	1.4 (0.37, 5.27)	1.4 (0.37, 5.27)	9 (-14, 98)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillin + Other fluoroquinolone vs 4th generation cephalosporins	NA	NA	1.23 (0.29, 5.15)	1.23 (0.29, 5.15)	5 (-16, 95)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs 5th generation cephalosporins	NA	NA	1.45 (0.34, 6.13)	1.45 (0.34, 6.13)	10 (-15, 118)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	1.47 (0.02, 89.97)	1.47 (0.02, 89.97)	11 (-23, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs 2nd generation cephalosporin + Macrolide	NA	NA	2.46 (0.52, 11.69)	2.46 (0.52, 11.69)	34 (-11, 246)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs 3rd generation cephalosporin + Macrolide	NA	NA	1.79 (0.47, 6.87)	1.79 (0.47, 6.87)	18 (-12, 135)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillin + Other fluoroquinolone vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	2.18 (0.52, 9.16)	2.18 (0.52, 9.16)	27 (-11, 188)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2, Indirectness
Penicillin + Other fluoroquinolone vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	1.23 (0.33, 4.6)	1.23 (0.33, 4.6)	5 (-15, 83)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Macrolides	NA	NA	1.47 (0.36, 6)	1.47 (0.36, 6)	11 (-15, 115)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3

Penicillin + Other fluoroquinolone vs Macrolide + Aminoglycoside	NA	NA	1.7 (0.21, 13.7)	1.7 (0.21, 13.7)	16 (-18, 292)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Tetracyclines	NA	NA	0.69 (0.13, 3.78)	0.69 (0.13, 3.78)	-7 (-20, 64)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Carbapenems	NA	NA	1.51 (0.36, 6.25)	1.51 (0.36, 6.25)	12 (-15, 121)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Carbapenem + Macrolide	NA	NA	0.59 (0.17, 2.05)	0.59 (0.17, 2.05)	-9 (-19, 24)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Other fluoroquinolones	NA	NA	0.76 (0.11, 5.43)	0.76 (0.11, 5.43)	-6 (-20, 102)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Tigecycline	NA	NA	1.35 (0.3, 5.97)	1.35 (0.3, 5.97)	8 (-16, 114)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Cotrimoxazole	NA	NA	0.38 (0.04, 3.62)	0.38 (0.04, 3.62)	-14 (-22, 60)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Daptomycin + Aztreonam	NA	NA	0.79 (0.18, 3.54)	0.79 (0.18, 3.54)	-5 (-19, 58)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Linezolid + Aztreonam	NA	NA	1.85 (0.42, 8.12)	1.85 (0.42, 8.12)	20 (-13, 164)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Teicoplanin + Other fluoroquinolone	NA	NA	1.02 (0.18, 5.77)	1.02 (0.18, 5.77)	0 (-19, 110)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs β-Lactam/β-lactamase inhibitor + Macrolide	NA	NA	0.67 (0.27, 1.65)	0.67 (0.27, 1.65)	-8 (-17, 15)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs β-Lactam/β-lactamase inhibitor + Aminoglycoside	0.17 (0.02, 1.35)	-19 (-23, 8)	NA	0.17 (0.02, 1.36)	-19 (-23, 8)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs 1st generation cephalosporins	NA	NA	0.33 (0.02, 4.65)	0.33 (0.02, 4.65)	-15 (-23, 84)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs 2nd generation cephalosporins	0.69 (0.16, 2.89)	-7 (-19, 43)	0.8 (0.26, 2.42)	0.75 (0.31, 1.81)	-6 (-16, 19)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporins	1.12 (0.61, 2.05)	3 (-9, 24)	0.64 (0.23, 1.81)	0.97 (0.58, 1.64)	-1 (-10, 15)	Direct	MODERATE	Not serious	Serious	LOW	NMA	RoB, Imprecision
β-Lactam/β-lactamase inhibitors vs 4th generation cephalosporins	NA	NA	0.85 (0.4, 1.82)	0.85 (0.4, 1.82)	-3 (-14, 19)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs 5th generation cephalosporins	NA	NA	1.01 (0.46, 2.18)	1.01 (0.46, 2.18)	0 (-12, 27)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	1.02 (0.02, 51.95)	1.02 (0.02, 51.95)	0 (-23, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs 2nd generation cephalosporin + Macrolide	NA	NA	1.71 (0.56, 5.21)	1.71 (0.56, 5.21)	16 (-10, 97)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporin + Macrolide	NA	NA	1.24 (0.56, 2.77)	1.24 (0.56, 2.77)	6 (-10, 41)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	1.51 (0.58, 3.94)	1.51 (0.58, 3.94)	12 (-10, 68)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2, Indirectness
β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	0.85 (0.39, 1.85)	0.85 (0.39, 1.85)	-3 (-14, 20)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Macrolides	NA	NA	1.02 (0.42, 2.49)	1.02 (0.42, 2.49)	0 (-13, 34)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Macrolide + Aminoglycoside	NA	NA	1.18 (0.21, 6.53)	1.18 (0.21, 6.53)	4 (-18, 127)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3

β-Lactam/β-lactamase inhibitors vs Tetracyclines	NA	NA	0.48 (0.13, 1.79)	0.48 (0.13, 1.79)	-12 (-20, 18)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs Carbapenems	0.32 (0.04, 2.94)	-16 (-22, 45)	1.21 (0.55, 2.66)	1.05 (0.5, 2.19)	1 (-12, 27)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Carbapenem + Macrolide	NA	NA	0.41 (0.13, 1.23)	0.41 (0.13, 1.23)	-14 (-20, 5)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Other fluoroquinolones	NA	NA	0.53 (0.11, 2.45)	0.53 (0.11, 2.45)	-11 (-20, 33)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs Tigecycline	NA	NA	0.94 (0.33, 2.63)	0.94 (0.33, 2.63)	-1 (-15, 37)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Cotrimoxazole	NA	NA	0.26 (0.04, 1.86)	0.26 (0.04, 1.86)	-17 (-22, 20)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs Daptomycin + Aztreonam	NA	NA	0.55 (0.23, 1.31)	0.55 (0.23, 1.31)	-10 (-18, 7)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Linezolid + Aztreonam	NA	NA	1.28 (0.55, 2.98)	1.28 (0.55, 2.98)	6 (-10, 46)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Teicoplanin + Other fluoroquinolone	NA	NA	0.71 (0.21, 2.43)	0.71 (0.21, 2.43)	-7 (-18, 33)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs β-Lactam/β-lactamase inhibitor + Aminoglycoside	NA	NA	0.25 (0.03, 2.45)	0.25 (0.03, 2.45)	-17 (-22, 33)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs 1st generation cephalosporins	NA	NA	0.49 (0.03, 7.35)	0.49 (0.03, 7.35)	-12 (-22, 146)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs 2nd generation cephalosporins	NA	NA	1.12 (0.38, 3.36)	1.12 (0.38, 3.36)	3 (-14, 54)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs 3rd generation cephalosporins	NA	NA	1.45 (0.67, 3.16)	1.45 (0.67, 3.16)	10 (-8, 50)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs 4th generation cephalosporins	NA	NA	1.28 (0.49, 3.29)	1.28 (0.49, 3.29)	6 (-12, 53)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs 5th generation cephalosporins	NA	NA	1.5 (0.57, 3.94)	1.5 (0.57, 3.94)	12 (-10, 68)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	1.52 (0.03, 80.88)	1.52 (0.03, 80.88)	12 (-22, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs 2nd generation cephalosporin + Macrolide	NA	NA	2.55 (0.82, 7.92)	2.55 (0.82, 7.92)	36 (-4, 159)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs 3rd generation cephalosporin + Macrolide	NA	NA	1.86 (0.82, 4.18)	1.86 (0.82, 4.18)	20 (-4, 73)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	2.25 (0.86, 5.88)	2.25 (0.86, 5.88)	29 (-3, 112)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2, Indirectness
β-Lactam/β-lactamase inhibitor + Macrolide vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	1.27 (0.59, 2.76)	1.27 (0.59, 2.76)	6 (-9, 40)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Macrolides	NA	NA	1.52 (0.61, 3.79)	1.52 (0.61, 3.79)	12 (-9, 64)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Macrolide + Aminoglycoside	NA	NA	1.76 (0.29, 10.56)	1.76 (0.29, 10.56)	17 (-16, 220)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs Tetracyclines	NA	NA	0.72 (0.19, 2.68)	0.72 (0.19, 2.68)	-6 (-19, 39)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs Carbapenems	NA	NA	1.56 (0.61, 3.98)	1.56 (0.61, 3.98)	13 (-9, 69)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2

β-Lactam/β-lactamase inhibitor + Macrolide vs Carbapenem + Macrolide	0.61 (0.32, 1.16)	-9 (-16, 4)	NA	0.61 (0.32, 1.16)	-9 (-16, 4)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Other fluoroquinolones	NA	NA	0.78 (0.15, 4.1)	0.78 (0.15, 4.1)	-5 (-20, 71)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs Tigecycline	NA	NA	1.4 (0.5, 3.93)	1.4 (0.5, 3.93)	9 (-12, 67)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Cotrimoxazole	NA	NA	0.39 (0.05, 2.86)	0.39 (0.05, 2.86)	-14 (-22, 43)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs Daptomycin + Aztreonam	NA	NA	0.82 (0.29, 2.33)	0.82 (0.29, 2.33)	-4 (-16, 31)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Linezolid + Aztreonam	NA	NA	1.92 (0.69, 5.32)	1.92 (0.69, 5.32)	21 (-7, 99)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Teicoplanin + Other fluoroquinolone	NA	NA	1.06 (0.27, 4.12)	1.06 (0.27, 4.12)	1 (-17, 72)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs 1st generation cephalosporins	NA	NA	1.93 (0.07, 55.85)	1.93 (0.07, 55.85)	21 (-21, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs 2nd generation cephalosporins	NA	NA	4.42 (0.46, 42.1)	4.42 (0.46, 42.1)	79 (-12, 945)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs 3rd generation cephalosporins	NA	NA	5.71 (0.67, 48.58)	5.71 (0.67, 48.58)	108 (-8, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs 4th generation cephalosporins	NA	NA	5.01 (0.55, 45.62)	5.01 (0.55, 45.62)	92 (-10, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs 5th generation cephalosporins	NA	NA	5.9 (0.64, 54.08)	5.9 (0.64, 54.08)	113 (-8, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	5.97 (0.07, 509.69)	5.97 (0.07, 509.69)	114 (-21, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs 2nd generation cephalosporin + Macrolide	NA	NA	10 (0.95, 105.68)	10 (0.95, 105.68)	207 (-1, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs 3rd generation cephalosporin + Macrolide	NA	NA	7.3 (0.79, 67.52)	7.3 (0.79, 67.52)	145 (-5, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	8.86 (0.9, 87.15)	8.86 (0.9, 87.15)	181 (-2, 1000)	Indirect	LOW	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3, Indirectness
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	5 (0.55, 45.84)	5 (0.55, 45.84)	92 (-10, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs Macrolides	NA	NA	5.98 (0.63, 57.27)	5.98 (0.63, 57.27)	115 (-9, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs Macrolide + Aminoglycoside	NA	NA	6.92 (0.47, 101.94)	6.92 (0.47, 101.94)	136 (-12, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs Tetracyclines	NA	NA	2.82 (0.24, 32.89)	2.82 (0.24, 32.89)	42 (-17, 733)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs Carbapenems	NA	NA	6.13 (0.68, 55.56)	6.13 (0.68, 55.56)	118 (-7, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs Carbapenem + Macrolide	NA	NA	2.39 (0.23, 25.11)	2.39 (0.23, 25.11)	32 (-18, 555)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs Other fluoroquinolones	NA	NA	3.08 (0.23, 40.83)	3.08 (0.23, 40.83)	48 (-18, 916)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3

β-Lactam/β-lactamase inhibitor + Aminoglycoside vs Tigecycline	NA	NA	5.49 (0.54, 55.81)	5.49 (0.54, 55.81)	103 (-11, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs Cotrimoxazole	NA	NA	1.54 (0.09, 26.71)	1.54 (0.09, 26.71)	12 (-21, 591)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs Daptomycin + Aztreonam	NA	NA	3.23 (0.34, 30.67)	3.23 (0.34, 30.67)	51 (-15, 682)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs Linezolid + Aztreonam	NA	NA	7.53 (0.8, 70.79)	7.53 (0.8, 70.79)	150 (-5, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Aminoglycoside vs Teicoplanin + Other fluoroquinolone	NA	NA	4.15 (0.37, 46.45)	4.15 (0.37, 46.45)	72 (-14, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs 2nd generation cephalosporins	3.37 (0.14, 80.76)	55 (-20, 1000)	1.11 (0.01, 90.91)	2.29 (0.18, 29.92)	30 (-19, 665)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs 3rd generation cephalosporins	NA	NA	2.96 (0.21, 40.87)	2.96 (0.21, 40.87)	45 (-18, 917)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs 4th generation cephalosporins	NA	NA	2.6 (0.18, 37.95)	2.6 (0.18, 37.95)	37 (-19, 850)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs 5th generation cephalosporins	NA	NA	3.06 (0.21, 44.89)	3.06 (0.21, 44.89)	47 (-18, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	3.09 (0.03, 340.03)	3.09 (0.03, 340.03)	48 (-22, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs 2nd generation cephalosporin + Macrolide	NA	NA	5.19 (0.33, 81.95)	5.19 (0.33, 81.95)	96 (-15, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs 3rd generation cephalosporin + Macrolide	NA	NA	3.78 (0.26, 54.91)	3.78 (0.26, 54.91)	64 (-17, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	4.59 (0.3, 70.07)	4.59 (0.3, 70.07)	83 (-16, 1000)	Indirect	LOW	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3, Indirectness
1st generation cephalosporins vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	2.59 (0.18, 37.29)	2.59 (0.18, 37.29)	37 (-19, 835)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs Macrolides	NA	NA	3.1 (0.21, 45.07)	3.1 (0.21, 45.07)	48 (-18, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs Macrolide + Aminoglycoside	NA	NA	3.59 (0.16, 78.73)	3.59 (0.16, 78.73)	60 (-19, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs Tetracyclines	NA	NA	1.46 (0.09, 24.61)	1.46 (0.09, 24.61)	11 (-21, 543)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs Carbapenems	NA	NA	3.18 (0.22, 46.35)	3.18 (0.22, 46.35)	50 (-18, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs Carbapenem + Macrolide	NA	NA	1.24 (0.08, 19.98)	1.24 (0.08, 19.98)	6 (-21, 437)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs Other fluoroquinolones	NA	NA	1.6 (0.08, 30.27)	1.6 (0.08, 30.27)	14 (-21, 673)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs Tigecycline	NA	NA	2.85 (0.18, 44.64)	2.85 (0.18, 44.64)	43 (-19, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs Cotrimoxazole	0.46 (0.01, 20.6)	-12 (-23, 451)	1.4 (0.03, 66.67)	0.8 (0.05, 11.92)	-5 (-22, 251)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs Daptomycin + Aztreonam	NA	NA	1.67 (0.11, 25.31)	1.67 (0.11, 25.31)	15 (-20, 559)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs Linezolid + Aztreonam	NA	NA	3.91 (0.26, 58.51)	3.91 (0.26, 58.51)	67 (-17, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3

1st generation cephalosporins vs Teicoplanin + Other fluoroquinolone	NA	NA	2.15 (0.12, 37.32)	2.15 (0.12, 37.32)	26 (-20, 835)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporins vs 3rd generation cephalosporins	2.29 (0.65, 8.13)	30 (-8, 164)	0.82 (0.27, 2.46)	1.29 (0.57, 2.95)	7 (-10, 45)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporins vs 4th generation cephalosporins	NA	NA	1.13 (0.42, 3.06)	1.13 (0.42, 3.06)	3 (-13, 47)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporins vs 5th generation cephalosporins	NA	NA	1.33 (0.49, 3.65)	1.33 (0.49, 3.65)	8 (-12, 61)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporins vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	1.35 (0.03, 72.62)	1.35 (0.03, 72.62)	8 (-22, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporins vs 2nd generation cephalosporin + Macrolide	NA	NA	2.26 (0.65, 7.89)	2.26 (0.65, 7.89)	29 (-8, 158)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporins vs 3rd generation cephalosporin + Macrolide	NA	NA	1.65 (0.6, 4.55)	1.65 (0.6, 4.55)	15 (-9, 82)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporins vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	2 (0.64, 6.27)	2 (0.64, 6.27)	23 (-8, 121)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2, Indirectness
2nd generation cephalosporins vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	1.13 (0.42, 3.05)	1.13 (0.42, 3.05)	3 (-13, 47)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporins vs Macrolides	NA	NA	1.35 (0.47, 3.87)	1.35 (0.47, 3.87)	8 (-12, 66)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporins vs Macrolide + Aminoglycoside	NA	NA	1.57 (0.25, 9.76)	1.57 (0.25, 9.76)	13 (-17, 201)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporins vs Tetracyclines	NA	NA	0.64 (0.15, 2.7)	0.64 (0.15, 2.7)	-8 (-20, 39)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporins vs Carbapenems	NA	NA	1.39 (0.52, 3.73)	1.39 (0.52, 3.73)	9 (-11, 63)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporins vs Carbapenem + Macrolide	NA	NA	0.54 (0.15, 1.92)	0.54 (0.15, 1.92)	-11 (-20, 21)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporins vs Other fluoroquinolones	0.33 (0.04, 3.03)	-15 (-22, 47)	1.34 (0.17, 10.53)	0.7 (0.15, 3.15)	-7 (-20, 49)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporins vs Tigecycline	NA	NA	1.24 (0.37, 4.15)	1.24 (0.37, 4.15)	6 (-14, 72)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporins vs Cotrimoxazole	NA	NA	0.35 (0.05, 2.52)	0.35 (0.05, 2.52)	-15 (-22, 35)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporins vs Daptomycin + Aztreonam	NA	NA	0.73 (0.25, 2.15)	0.73 (0.25, 2.15)	-6 (-17, 26)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporins vs Linezolid + Aztreonam	NA	NA	1.7 (0.59, 4.91)	1.7 (0.59, 4.91)	16 (-9, 90)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporins vs Teicoplanin + Other fluoroquinolone	NA	NA	0.94 (0.23, 3.77)	0.94 (0.23, 3.77)	-1 (-18, 64)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporins vs 4th generation cephalosporins	0.96 (0.5, 1.84)	-1 (-12, 19)	0.67 (0.22, 2.01)	0.88 (0.5, 1.53)	-3 (-12, 12)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporins vs 5th generation cephalosporins	1.03 (0.58, 1.83)	1 (-10, 19)	NA	1.03 (0.58, 1.83)	1 (-10, 19)	Direct	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
3rd generation cephalosporins vs 3rd generation cephalosporin/β-lactamase inhibitors	1.04 (0.02, 50)	1 (-23, 1000)	NA	1.04 (0.02, 51.52)	1 (-23, 1000)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporins vs 2nd generation cephalosporin + Macrolide	NA	NA	1.75 (0.63, 4.87)	1.75 (0.63, 4.87)	17 (-9, 89)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2

3rd generation cephalosporins vs 3rd generation cephalosporin + Macrolide	NA	NA	1.28 (0.66, 2.46)	1.28 (0.66, 2.46)	6 (-8, 34)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporins vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	1.55 (0.67, 3.6)	1.55 (0.67, 3.6)	13 (-8, 60)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2, Indirectness
3rd generation cephalosporins vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	0.88 (0.47, 1.63)	0.88 (0.47, 1.63)	-3 (-12, 14)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporins vs Macrolides	NA	NA	1.05 (0.49, 2.26)	1.05 (0.49, 2.26)	1 (-12, 29)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporins vs Macrolide + Aminoglycoside	NA	NA	1.21 (0.23, 6.26)	1.21 (0.23, 6.26)	5 (-18, 121)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporins vs Tetracyclines	NA	NA	0.49 (0.14, 1.69)	0.49 (0.14, 1.69)	-12 (-20, 16)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporins vs Carbapenems	1.23 (0.47, 3.23)	5 (-12, 51)	1.02 (0.43, 2.44)	1.07 (0.61, 1.88)	2 (-9, 20)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporins vs Carbapenem + Macrolide	NA	NA	0.42 (0.15, 1.15)	0.42 (0.15, 1.15)	-13 (-20, 3)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporins vs Other fluoroquinolones	0.92 (0.14, 6.05)	-2 (-20, 116)	0.23 (0.02, 2.46)	0.54 (0.12, 2.35)	-11 (-20, 31)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporins vs Tigecycline	NA	NA	0.96 (0.38, 2.43)	0.96 (0.38, 2.43)	-1 (-14, 33)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporins vs Cotrimoxazole	NA	NA	0.27 (0.04, 1.82)	0.27 (0.04, 1.82)	-17 (-22, 19)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporins vs Daptomycin + Aztreonam	0.57 (0.28, 1.14)	-10 (-17, 3)	NA	0.57 (0.28, 1.14)	-10 (-17, 3)	Direct	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
3rd generation cephalosporins vs Linezolid + Aztreonam	1.32 (0.68, 2.56)	7 (-7, 36)	NA	1.32 (0.68, 2.56)	7 (-7, 36)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporins vs Teicoplanin + Other fluoroquinolone	0.73 (0.24, 2.22)	-6 (-17, 28)	NA	0.73 (0.24, 2.22)	-6 (-17, 28)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
4th generation cephalosporins vs 5th generation cephalosporins	NA	NA	1.18 (0.53, 2.62)	1.18 (0.53, 2.62)	4 (-11, 37)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
4th generation cephalosporins vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	1.19 (0.02, 61.12)	1.19 (0.02, 61.12)	4 (-23, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
4th generation cephalosporins vs 2nd generation cephalosporin + Macrolide	NA	NA	2 (0.63, 6.36)	2 (0.63, 6.36)	23 (-9, 123)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
4th generation cephalosporins vs 3rd generation cephalosporin + Macrolide	NA	NA	1.46 (0.62, 3.4)	1.46 (0.62, 3.4)	11 (-9, 55)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
4th generation cephalosporins vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	1.77 (0.65, 4.82)	1.77 (0.65, 4.82)	18 (-8, 88)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2, Indirectness
4th generation cephalosporins vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	1 (0.44, 2.29)	1 (0.44, 2.29)	0 (-13, 30)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
4th generation cephalosporins vs Macrolides	NA	NA	1.19 (0.47, 3.06)	1.19 (0.47, 3.06)	4 (-12, 47)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
4th generation cephalosporins vs Macrolide + Aminoglycoside	NA	NA	1.38 (0.26, 7.41)	1.38 (0.26, 7.41)	9 (-17, 147)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
4th generation cephalosporins vs Tetracyclines	NA	NA	0.56 (0.15, 2.16)	0.56 (0.15, 2.16)	-10 (-20, 27)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3

4th generation cephalosporins vs Carbapenems	1.45 (0.6, 3.57)	10 (-9, 59)	1.01 (0.4, 2.54)	1.22 (0.65, 2.32)	5 (-8, 30)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
4th generation cephalosporins vs Carbapenem + Macrolide	NA	NA	0.48 (0.15, 1.5)	0.48 (0.15, 1.5)	-12 (-20, 12)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
4th generation cephalosporins vs Other fluoroquinolones	NA	NA	0.62 (0.13, 2.97)	0.62 (0.13, 2.97)	-9 (-20, 45)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
4th generation cephalosporins vs Tigecycline	NA	NA	1.1 (0.37, 3.21)	1.1 (0.37, 3.21)	2 (-14, 51)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
4th generation cephalosporins vs Cotrimoxazole	NA	NA	0.31 (0.04, 2.24)	0.31 (0.04, 2.24)	-16 (-22, 29)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
4th generation cephalosporins vs Daptomycin + Aztreonam	NA	NA	0.64 (0.26, 1.57)	0.64 (0.26, 1.57)	-8 (-17, 13)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
4th generation cephalosporins vs Linezolid + Aztreonam	NA	NA	1.5 (0.63, 3.57)	1.5 (0.63, 3.57)	12 (-9, 59)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
4th generation cephalosporins vs Teicoplanin + Other fluoroquinolone	NA	NA	0.83 (0.24, 2.89)	0.83 (0.24, 2.89)	-4 (-17, 43)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
5th generation cephalosporins vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	1.01 (0.02, 52.08)	1.01 (0.02, 52.08)	0 (-23, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
5th generation cephalosporins vs 2nd generation cephalosporin + Macrolide	NA	NA	1.7 (0.52, 5.48)	1.7 (0.52, 5.48)	16 (-11, 103)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
5th generation cephalosporins vs 3rd generation cephalosporin + Macrolide	NA	NA	1.24 (0.52, 2.96)	1.24 (0.52, 2.96)	6 (-11, 45)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
5th generation cephalosporins vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	1.5 (0.54, 4.17)	1.5 (0.54, 4.17)	12 (-11, 73)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2, Indirectness
5th generation cephalosporins vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	0.85 (0.36, 1.98)	0.85 (0.36, 1.98)	-3 (-15, 23)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
5th generation cephalosporins vs Macrolides	NA	NA	1.01 (0.39, 2.65)	1.01 (0.39, 2.65)	0 (-14, 38)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
5th generation cephalosporins vs Macrolide + Aminoglycoside	NA	NA	1.17 (0.21, 6.69)	1.17 (0.21, 6.69)	4 (-18, 131)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
5th generation cephalosporins vs Tetracyclines	NA	NA	0.48 (0.12, 1.86)	0.48 (0.12, 1.86)	-12 (-20, 20)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	Imprecisionx3, Publication bias
5th generation cephalosporins vs Carbapenems	NA	NA	1.04 (0.47, 2.32)	1.04 (0.47, 2.32)	1 (-12, 30)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
5th generation cephalosporins vs Carbapenem + Macrolide	NA	NA	0.4 (0.13, 1.29)	0.4 (0.13, 1.29)	-14 (-20, 7)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
5th generation cephalosporins vs Other fluoroquinolones	NA	NA	0.52 (0.11, 2.54)	0.52 (0.11, 2.54)	-11 (-20, 35)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
5th generation cephalosporins vs Tigecycline	NA	NA	0.93 (0.31, 2.77)	0.93 (0.31, 2.77)	-2 (-16, 41)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
5th generation cephalosporins vs Cotrimoxazole	NA	NA	0.26 (0.04, 1.92)	0.26 (0.04, 1.92)	-17 (-22, 21)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
5th generation cephalosporins vs Daptomycin + Aztreonam	NA	NA	0.55 (0.22, 1.35)	0.55 (0.22, 1.35)	-10 (-18, 8)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
5th generation cephalosporins vs Linezolid + Aztreonam	NA	NA	1.28 (0.53, 3.07)	1.28 (0.53, 3.07)	6 (-11, 48)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
5th generation cephalosporins vs Teicoplanin + Other fluoroquinolone	NA	NA	0.7 (0.2, 2.48)	0.7 (0.2, 2.48)	-7 (-18, 34)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3

3rd generation cephalosporin/β-lactamase inhibitors vs 2nd generation cephalosporin + Macrolide	NA	NA	1.68 (0.03, 94.35)	1.68 (0.03, 94.35)	16 (-22, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs 3rd generation cephalosporin + Macrolide	NA	NA	1.22 (0.02, 63.73)	1.22 (0.02, 63.73)	5 (-23, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	1.48 (0.03, 80.12)	1.48 (0.03, 80.12)	11 (-22, 1000)	Indirect	LOW	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3, Indirectness
3rd generation cephalosporin/β-lactamase inhibitors vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	0.84 (0.02, 43.45)	0.84 (0.02, 43.45)	-4 (-23, 976)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Macrolides	NA	NA	1 (0.02, 53.31)	1 (0.02, 53.31)	0 (-23, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Macrolide + Aminoglycoside	NA	NA	1.16 (0.02, 79.72)	1.16 (0.02, 79.72)	4 (-23, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Tetracyclines	NA	NA	0.47 (0.01, 28.21)	0.47 (0.01, 28.21)	-12 (-23, 626)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Carbapenems	NA	NA	1.03 (0.02, 52.79)	1.03 (0.02, 52.79)	1 (-23, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Carbapenem + Macrolide	NA	NA	0.4 (0.01, 22.44)	0.4 (0.01, 22.44)	-14 (-23, 493)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Other fluoroquinolones	NA	NA	0.52 (0.01, 33.35)	0.52 (0.01, 33.35)	-11 (-23, 744)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Tigecycline	NA	NA	0.92 (0.02, 50.61)	0.92 (0.02, 50.61)	-2 (-23, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Cotrimoxazole	NA	NA	0.26 (0, 19.84)	0.26 (0, 19.84)	-17 (-23, 433)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Daptomycin + Aztreonam	NA	NA	0.54 (0.01, 28.4)	0.54 (0.01, 28.4)	-11 (-23, 630)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Linezolid + Aztreonam	NA	NA	1.26 (0.02, 65.85)	1.26 (0.02, 65.85)	6 (-23, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Teicoplanin + Other fluoroquinolone	NA	NA	0.7 (0.01, 40.16)	0.7 (0.01, 40.16)	-7 (-23, 901)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolide vs 3rd generation cephalosporin + Macrolide	NA	NA	0.73 (0.25, 2.12)	0.73 (0.25, 2.12)	-6 (-17, 26)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolide vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	0.89 (0.27, 2.88)	0.89 (0.27, 2.88)	-3 (-17, 43)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2, Indirectness
2nd generation cephalosporin + Macrolide vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	0.5 (0.18, 1.41)	0.5 (0.18, 1.41)	-12 (-19, 9)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Macrolides	0.6 (0.3, 1.17)	-9 (-16, 4)	NA	0.6 (0.3, 1.17)	-9 (-16, 4)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Macrolide + Aminoglycoside	NA	NA	0.69 (0.1, 4.68)	0.69 (0.1, 4.68)	-7 (-21, 85)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolide vs Tetracyclines	NA	NA	0.28 (0.06, 1.24)	0.28 (0.06, 1.24)	-17 (-22, 6)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolide vs Carbapenems	NA	NA	0.61 (0.19, 1.94)	0.61 (0.19, 1.94)	-9 (-19, 22)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolide vs Carbapenem + Macrolide	NA	NA	0.24 (0.06, 0.88)	0.24 (0.06, 0.88)	-17 (-22, -3)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2

2nd generation cephalosporin + Macrolide vs Other fluoroquinolones	NA	NA	0.31 (0.05, 1.82)	0.31 (0.05, 1.82)	-16 (-22, 19)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolide vs Tigecycline	NA	NA	0.55 (0.16, 1.9)	0.55 (0.16, 1.9)	-10 (-19, 21)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolide vs Cotrimoxazole	NA	NA	0.15 (0.02, 1.18)	0.15 (0.02, 1.18)	-20 (-23, 4)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Daptomycin + Aztreonam	NA	NA	0.32 (0.09, 1.11)	0.32 (0.09, 1.11)	-16 (-21, 3)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Linezolid + Aztreonam	NA	NA	0.75 (0.22, 2.55)	0.75 (0.22, 2.55)	-6 (-18, 36)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolide vs Teicoplanin + Other fluoroquinolone	NA	NA	0.41 (0.09, 1.89)	0.41 (0.09, 1.89)	-14 (-21, 20)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Macrolide vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	1.21 (0.51, 2.91)	1.21 (0.51, 2.91)	5 (-11, 44)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2, Indirectness
3rd generation cephalosporin + Macrolide vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	0.69 (0.35, 1.34)	0.69 (0.35, 1.34)	-7 (-15, 8)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Macrolides	NA	NA	0.82 (0.36, 1.87)	0.82 (0.36, 1.87)	-4 (-15, 20)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Macrolide + Aminoglycoside	0.53 (0.05, 5.67)	-11 (-22, 107)	3.23 (0.11, 100)	0.95 (0.17, 5.25)	-1 (-19, 98)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Macrolide vs Tetracyclines	NA	NA	0.39 (0.11, 1.36)	0.39 (0.11, 1.36)	-14 (-20, 8)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Carbapenems	0.35 (0.05, 3.45)	-15 (-22, 56)	1.04 (0.43, 2.53)	0.84 (0.37, 1.91)	-4 (-14, 21)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Carbapenem + Macrolide	NA	NA	0.33 (0.12, 0.92)	0.33 (0.12, 0.92)	-15 (-20, -2)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Other fluoroquinolones	NA	NA	0.42 (0.09, 2.1)	0.42 (0.09, 2.1)	-13 (-21, 25)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Macrolide vs Tigecycline	NA	NA	0.75 (0.29, 1.96)	0.75 (0.29, 1.96)	-6 (-16, 22)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Macrolide vs Cotrimoxazole	NA	NA	0.21 (0.03, 1.48)	0.21 (0.03, 1.48)	-18 (-22, 11)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Macrolide vs Daptomycin + Aztreonam	NA	NA	0.44 (0.17, 1.15)	0.44 (0.17, 1.15)	-13 (-19, 3)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Linezolid + Aztreonam	NA	NA	1.03 (0.41, 2.62)	1.03 (0.41, 2.62)	1 (-14, 37)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Teicoplanin + Other fluoroquinolone	NA	NA	0.57 (0.16, 2.08)	0.57 (0.16, 2.08)	-10 (-19, 25)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Respiratory fluoroquinolone vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	0.56 (0.24, 1.31)	0.56 (0.24, 1.31)	-10 (-17, 7)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2, Indirectness
3rd generation cephalosporin + Respiratory fluoroquinolone vs Macrolides	NA	NA	0.68 (0.26, 1.78)	0.68 (0.26, 1.78)	-7 (-17, 18)	Indirect	LOW	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3, Indirectness
3rd generation cephalosporin + Respiratory fluoroquinolone vs Macrolide + Aminoglycoside	NA	NA	0.78 (0.13, 4.82)	0.78 (0.13, 4.82)	-5 (-20, 88)	Indirect	LOW	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3, Indirectness

3rd generation cephalosporin + Respiratory fluoroquinolone vs Tetracyclines	NA	NA	0.32 (0.08, 1.24)	0.32 (0.08, 1.24)	-16 (-21, 6)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	Imprecisionx2, Publication bias, Indirectness
3rd generation cephalosporin + Respiratory fluoroquinolone vs Carbapenems	NA	NA	0.69 (0.26, 1.87)	0.69 (0.26, 1.87)	-7 (-17, 20)	Indirect	LOW	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3, Indirectness
3rd generation cephalosporin + Respiratory fluoroquinolone vs Carbapenem + Macrolide	NA	NA	0.27 (0.08, 0.86)	0.27 (0.08, 0.86)	-17 (-21, -3)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2, Indirectness
3rd generation cephalosporin + Respiratory fluoroquinolone vs Other fluoroquinolones	NA	NA	0.35 (0.06, 1.88)	0.35 (0.06, 1.88)	-15 (-22, 20)	Indirect	LOW	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3, Indirectness
3rd generation cephalosporin + Respiratory fluoroquinolone vs Tigecycline	NA	NA	0.62 (0.21, 1.83)	0.62 (0.21, 1.83)	-9 (-18, 19)	Indirect	LOW	Not serious	Extremely serious	VERY LOW	NMA	Imprecisionx3, Publication bias, Indirectness
3rd generation cephalosporin + Respiratory fluoroquinolone vs Cotrimoxazole	NA	NA	0.17 (0.02, 1.3)	0.17 (0.02, 1.3)	-19 (-23, 7)	Indirect	LOW	Not serious	Extremely serious	VERY LOW	NMA	Imprecisionx3, Publication bias, Indirectness
3rd generation cephalosporin + Respiratory fluoroquinolone vs Daptomycin + Aztreonam	NA	NA	0.36 (0.12, 1.09)	0.36 (0.12, 1.09)	-15 (-20, 2)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	Imprecisionx2, Publication bias, Indirectness
3rd generation cephalosporin + Respiratory fluoroquinolone vs Linezolid + Aztreonam	NA	NA	0.85 (0.29, 2.48)	0.85 (0.29, 2.48)	-3 (-16, 34)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2, Indirectness
3rd generation cephalosporin + Respiratory fluoroquinolone vs Teicoplanin + Other fluoroquinolone	NA	NA	0.47 (0.12, 1.9)	0.47 (0.12, 1.9)	-12 (-20, 21)	Indirect	LOW	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3, Indirectness
3rd generation cephalosporin+ Other fluoroquinolone vs Macrolides	NA	NA	1.2 (0.54, 2.63)	1.2 (0.54, 2.63)	5 (-11, 37)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin+ Other fluoroquinolone vs Macrolide + Aminoglycoside	NA	NA	1.38 (0.24, 7.81)	1.38 (0.24, 7.81)	9 (-17, 157)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin+ Other fluoroquinolone vs Tetracyclines	NA	NA	0.56 (0.16, 1.93)	0.56 (0.16, 1.93)	-10 (-19, 21)	Indirect	HIGH	Not serious	Extremely serious	VERY LOW	NMA	Imprecisionx3
3rd generation cephalosporin+ Other fluoroquinolone vs Carbapenems	NA	NA	1.23 (0.54, 2.77)	1.23 (0.54, 2.77)	5 (-11, 41)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin+ Other fluoroquinolone vs Carbapenem + Macrolide	NA	NA	0.48 (0.17, 1.31)	0.48 (0.17, 1.31)	-12 (-19, 7)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin+ Other fluoroquinolone vs Other fluoroquinolones	NA	NA	0.62 (0.13, 3.02)	0.62 (0.13, 3.02)	-9 (-20, 46)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin+ Other fluoroquinolone vs Tigecycline	NA	NA	1.1 (0.44, 2.77)	1.1 (0.44, 2.77)	2 (-13, 41)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin+ Other fluoroquinolone vs Cotrimoxazole	NA	NA	0.31 (0.04, 2.13)	0.31 (0.04, 2.13)	-16 (-22, 26)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin+ Other fluoroquinolone vs Daptomycin + Aztreonam	NA	NA	0.65 (0.25, 1.65)	0.65 (0.25, 1.65)	-8 (-17, 15)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin+ Other fluoroquinolone vs Linezolid + Aztreonam	NA	NA	1.51 (0.61, 3.74)	1.51 (0.61, 3.74)	12 (-9, 63)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2

3rd generation cephalosporin+ Other fluoroquinolone vs Teicoplanin + Other fluoroquinolone	NA	NA	0.83 (0.23, 2.99)	0.83 (0.23, 2.99)	-4 (-18, 46)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Macrolides vs Macrolide + Aminoglycoside	NA	NA	1.16 (0.19, 6.92)	1.16 (0.19, 6.92)	4 (-19, 136)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolides vs Tetracyclines	NA	NA	0.47 (0.13, 1.76)	0.47 (0.13, 1.76)	-12 (-20, 17)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolides vs Carbapenems	NA	NA	1.03 (0.4, 2.6)	1.03 (0.4, 2.6)	1 (-14, 37)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Macrolides vs Carbapenem + Macrolide	NA	NA	0.4 (0.13, 1.22)	0.4 (0.13, 1.22)	-14 (-20, 5)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Macrolides vs Other fluoroquinolones	NA	NA	0.52 (0.1, 2.66)	0.52 (0.1, 2.66)	-11 (-21, 38)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolides vs Tigecycline	NA	NA	0.92 (0.32, 2.6)	0.92 (0.32, 2.6)	-2 (-16, 37)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Macrolides vs Cotrimoxazole	NA	NA	0.26 (0.04, 1.76)	0.26 (0.04, 1.76)	-17 (-22, 17)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolides vs Daptomycin + Aztreonam	NA	NA	0.54 (0.19, 1.52)	0.54 (0.19, 1.52)	-11 (-19, 12)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Macrolides vs Linezolid + Aztreonam	NA	NA	1.26 (0.46, 3.47)	1.26 (0.46, 3.47)	6 (-12, 57)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Macrolides vs Teicoplanin + Other fluoroquinolone	NA	NA	0.69 (0.18, 2.7)	0.69 (0.18, 2.7)	-7 (-19, 39)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Tetracyclines	NA	NA	0.41 (0.05, 3.11)	0.41 (0.05, 3.11)	-14 (-22, 49)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Carbapenems	0.79 (0.16, 4)	-5 (-19, 69)	4.83 (0.05, 461.58)	0.89 (0.18, 4.28)	-3 (-19, 75)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Carbapenem + Macrolide	NA	NA	0.35 (0.05, 2.32)	0.35 (0.05, 2.32)	-15 (-22, 30)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Other fluoroquinolones	NA	NA	0.45 (0.05, 4.04)	0.45 (0.05, 4.04)	-13 (-22, 70)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Tigecycline	NA	NA	0.79 (0.12, 5.11)	0.79 (0.12, 5.11)	-5 (-20, 95)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Cotrimoxazole	NA	NA	0.22 (0.02, 2.73)	0.22 (0.02, 2.73)	-18 (-23, 40)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Daptomycin + Aztreonam	NA	NA	0.47 (0.08, 2.78)	0.47 (0.08, 2.78)	-12 (-21, 41)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Linezolid + Aztreonam	NA	NA	1.09 (0.19, 6.41)	1.09 (0.19, 6.41)	2 (-19, 124)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Teicoplanin + Other fluoroquinolone	NA	NA	0.6 (0.08, 4.38)	0.6 (0.08, 4.38)	-9 (-21, 78)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Tetracyclines vs Carbapenems	NA	NA	2.17 (0.57, 8.27)	2.17 (0.57, 8.27)	27 (-10, 167)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Tetracyclines vs Carbapenem + Macrolide	NA	NA	0.85 (0.2, 3.66)	0.85 (0.2, 3.66)	-3 (-18, 61)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Tetracyclines vs Other fluoroquinolones	NA	NA	1.09 (0.16, 7.34)	1.09 (0.16, 7.34)	2 (-19, 146)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Tetracyclines vs Tigecycline	NA	NA	1.94 (0.48, 7.96)	1.94 (0.48, 7.96)	22 (-12, 160)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	Imprecisionx2, Publication bias

Tetracyclines vs Cotrimoxazole	0.9 (0.02, 50)	-2 (-23, 1000)	0.45 (0.04, 5.12)	0.55 (0.07, 4.3)	-10 (-21, 76)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	Imprecisionx3, Publication bias
Tetracyclines vs Daptomycin + Aztreonam	NA	NA	1.14 (0.28, 4.7)	1.14 (0.28, 4.7)	3 (-17, 85)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	Imprecisionx2, Publication bias
Tetracyclines vs Linezolid + Aztreonam	NA	NA	2.67 (0.66, 10.78)	2.67 (0.66, 10.78)	38 (-8, 225)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Tetracyclines vs Teicoplanin + Other fluoroquinolone	NA	NA	1.47 (0.28, 7.75)	1.47 (0.28, 7.75)	11 (-17, 155)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Carbapenems vs Carbapenem + Macrolide	NA	NA	0.39 (0.12, 1.21)	0.39 (0.12, 1.21)	-14 (-20, 5)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Carbapenems vs Other fluoroquinolones	NA	NA	0.5 (0.1, 2.42)	0.5 (0.1, 2.42)	-12 (-21, 33)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Carbapenems vs Tigecycline	NA	NA	0.9 (0.31, 2.6)	0.9 (0.31, 2.6)	-2 (-16, 37)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Carbapenems vs Cotrimoxazole	NA	NA	0.25 (0.03, 1.82)	0.25 (0.03, 1.82)	-17 (-22, 19)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Carbapenems vs Daptomycin + Aztreonam	NA	NA	0.53 (0.22, 1.29)	0.53 (0.22, 1.29)	-11 (-18, 7)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Carbapenems vs Linezolid + Aztreonam	NA	NA	1.23 (0.52, 2.93)	1.23 (0.52, 2.93)	5 (-11, 44)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Carbapenems vs Teicoplanin + Other fluoroquinolone	NA	NA	0.68 (0.19, 2.37)	0.68 (0.19, 2.37)	-7 (-19, 32)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Carbapenem + Macrolide vs Other fluoroquinolones	NA	NA	1.29 (0.22, 7.63)	1.29 (0.22, 7.63)	7 (-18, 152)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Carbapenem + Macrolide vs Tigecycline	NA	NA	2.3 (0.68, 7.78)	2.3 (0.68, 7.78)	30 (-7, 156)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Carbapenem + Macrolide vs Cotrimoxazole	NA	NA	0.65 (0.08, 5.22)	0.65 (0.08, 5.22)	-8 (-21, 97)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Carbapenem + Macrolide vs Daptomycin + Aztreonam	NA	NA	1.35 (0.4, 4.62)	1.35 (0.4, 4.62)	8 (-14, 83)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Carbapenem + Macrolide vs Linezolid + Aztreonam	NA	NA	3.16 (0.94, 10.56)	3.16 (0.94, 10.56)	50 (-1, 220)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Carbapenem + Macrolide vs Teicoplanin + Other fluoroquinolone	NA	NA	1.74 (0.38, 7.85)	1.74 (0.38, 7.85)	17 (-14, 158)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Other fluoroquinolones vs Tigecycline	NA	NA	1.78 (0.32, 10.04)	1.78 (0.32, 10.04)	18 (-16, 208)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Other fluoroquinolones vs Cotrimoxazole	NA	NA	0.5 (0.05, 5.37)	0.5 (0.05, 5.37)	-12 (-22, 101)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Other fluoroquinolones vs Daptomycin + Aztreonam	NA	NA	1.05 (0.21, 5.34)	1.05 (0.21, 5.34)	1 (-18, 100)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Other fluoroquinolones vs Linezolid + Aztreonam	NA	NA	2.44 (0.49, 12.27)	2.44 (0.49, 12.27)	33 (-12, 259)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Other fluoroquinolones vs Teicoplanin + Other fluoroquinolone	NA	NA	1.35 (0.21, 8.55)	1.35 (0.21, 8.55)	8 (-18, 174)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Tigecycline vs Cotrimoxazole	NA	NA	0.28 (0.04, 2.18)	0.28 (0.04, 2.18)	-17 (-22, 27)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Tigecycline vs Daptomycin + Aztreonam	NA	NA	0.59 (0.18, 1.88)	0.59 (0.18, 1.88)	-9 (-19, 20)	Indirect	HIGH	Not serious	Extremely serious	VERY LOW	NMA	Imprecisionx3

Tigecycline vs Linezolid + Aztreonam	NA	NA	1.37 (0.44, 4.29)	1.37 (0.44, 4.29)	9 (-13, 76)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Tigecycline vs Teicoplanin + Other fluoroquinolone	NA	NA	0.76 (0.18, 3.23)	0.76 (0.18, 3.23)	-6 (-19, 51)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Cotrimoxazole vs Daptomycin + Aztreonam	NA	NA	2.09 (0.27, 15.92)	2.09 (0.27, 15.92)	25 (-17, 343)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Cotrimoxazole vs Linezolid + Aztreonam	NA	NA	4.88 (0.65, 36.7)	4.88 (0.65, 36.7)	89 (-8, 821)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Cotrimoxazole vs Teicoplanin + Other fluoroquinolone	NA	NA	2.69 (0.29, 24.51)	2.69 (0.29, 24.51)	39 (-16, 541)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Daptomycin + Aztreonam vs Linezolid + Aztreonam	NA	NA	2.33 (0.89, 6.1)	2.33 (0.89, 6.1)	31 (-3, 117)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Daptomycin + Aztreonam vs Teicoplanin + Other fluoroquinolone	NA	NA	1.28 (0.34, 4.8)	1.28 (0.34, 4.8)	6 (-15, 87)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Linezolid + Aztreonam vs Teicoplanin + Other fluoroquinolone	NA	NA	0.55 (0.15, 2.02)	0.55 (0.15, 2.02)	-10 (-20, 23)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3

RR: relative risk; RD: risk difference; CI: confidence interval, NA: not applicable (no evidence), ROB: risk of bias

[1] The baseline risk was derived from the median of risk of event across the arms that randomized patients to the respiratory fluoroquinolones.

[2] Risk difference was calculated through applying the relative risk to the baseline risk. In cases that upper limit of confidence interval exceeded 1000, we truncated the value and reported 1000 as the upper limit.

[3] The effect estimate was informed by a single trial in which the majority of patients had moderate severity CAP; rated down due to indirectness because a 3rd generation cephalosporin combined with a respiratory fluoroquinolone is not clinically relevant in this setting.

Supplement 11. Direct, indirect, and network estimates and certainty of evidence for duration of hospitalization

Minimal important difference	1 day										
Large effect threshold	5 days										
Baseline risk [1]	8.9 days										
	Direct evidence	**Indirect evidence**	**Network evidence**						**Best estimate**	**Final certainty rating if the best estimate is not NMA**	**Reason for downgrading the certainty**
Comparison	**MD (95% CI)**	**MD (95% CI)**	**MD (95% CI)**	**Starting evidence**	**Starting certainty rating**	**Incoherence**	**Imprecision**	**Final certainty rating**			
Penicillins vs Respiratory fluoroquinolones	NA	1.07 (-5.45, 7.6)	1.07 (-5.45, 7.6)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Respiratory fluoroquinolones	NA	-1.67 (-5.23, 1.88)	-1.67 (-5.23, 1.88)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2, Inconsistency
β-Lactam/β-lactamase inhibitor + Macrolide vs Respiratory fluoroquinolones	0.92 (-0.24, 2.08)	NA	0.92 (-2.46, 4.3)	Direct	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
2nd generation cephalosporins vs Respiratory fluoroquinolones	NA	1.37 (-3.88, 6.63)	1.37 (-3.88, 6.63)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporins vs Respiratory fluoroquinolones	0 (-0.41, 0.41)	1.93 (-3.49, 7.35)	0.53 (-2.21, 3.26)	Indirect	MODERATE	Not serious	Serious	LOW	DIRECT	MODERATE	RoB
2nd generation cephalosporin + Macrolide vs Respiratory fluoroquinolones	-0.2 (-0.94, 0.54)	NA	-0.2 (-3.46, 3.06)	Direct	MODERATE	Not serious	Serious	LOW	DIRECT	MODERATE	RoB
3rd generation cephalosporin + Macrolide vs Respiratory fluoroquinolones	0.89 (-0.18, 1.96)	3.02 (-1.91, 7.96)	1.13 (-0.46, 2.72)	Direct	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Macrolide + Aminoglycoside vs Respiratory fluoroquinolones	NA	-2.76 (-6.62, 1.09)	-2.76 (-6.62, 1.09)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
Carbapenems vs Respiratory fluoroquinolones	0.18 (-1.68, 2.04)	-3.21 (-6.38, 0.04)	-1.67 (-4.15, 0.81)	Indirect	MODERATE	Serious	Serious	VERY LOW	DIRECT	LOW	RoB, Imprecision, Incoherence
Carbapenem + Macrolide vs Respiratory fluoroquinolones	-0.8 (-2.56, 0.96)	-7.57 (-16.33, 1.18)	-1.7 (-5.07, 1.68)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	DIRECT	LOW	RoB, Imprecision
Tigecycline vs Respiratory fluoroquinolones	0.5 (-0.11, 1.11)	NA	0.5 (-2.73, 3.73)	Direct	HIGH	Not serious	Serious	MODERATE	NMA	NA	Imprecision
Other fluoroquinolones vs Respiratory fluoroquinolones	NA	1.44 (-2.86, 5.75)	1.44 (-2.86, 5.75)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Cotrimoxazole vs Respiratory fluoroquinolones	NA	3.97 (-5.03, 12.98)	3.97 (-5.03, 12.98)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Teicoplanin + Other fluoroquinolone vs Respiratory fluoroquinolones	NA	-1.07 (-5.77, 3.62)	-1.07 (-5.77, 3.62)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillins vs β-Lactam/β-lactamase inhibitors	NA	2.75 (-3.5, 8.99)	2.75 (-3.5, 8.99)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillins vs β-Lactam/β-lactamase inhibitor + Macrolide	NA	0.15 (-7.19, 7.5)	0.15 (-7.19, 7.5)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillins vs 2nd generation cephalosporins	-0.3 (-2.52, 1.92)	NA	-0.3 (-4.17, 3.57)	Direct	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Penicillins vs 3rd generation cephalosporins	NA	0.55 (-5.4, 6.5)	0.55 (-5.4, 6.5)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2, Inconsistency

Penicillins vs 2nd generation cephalosporin + Macrolide	NA	1.27 (-6.02, 8.57)	1.27 (-6.02, 8.57)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillins vs 3rd generation cephalosporin + Macrolide	NA	0.06 (-6.65, 6.77)	0.06 (-6.65, 6.77)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillins vs Macrolide + Aminoglycoside	NA	3.84 (-3.54, 11.22)	3.84 (-3.54, 11.22)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillins vs Carbapenems	NA	2.74 (-3.93, 9.41)	2.74 (-3.93, 9.41)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillins vs Carbapenem + Macrolide	NA	2.77 (-4.43, 9.97)	2.77 (-4.43, 9.97)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Penicillins vs Tigecycline	NA	0.57 (-6.71, 7.85)	0.57 (-6.71, 7.85)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillins vs Other fluoroquinolones	NA	-0.37 (-5.46, 4.72)	-0.37 (-5.46, 4.72)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillins vs Cotrimoxazole	-2.9 (-8.24, 2.44)	NA	-2.9 (-9.11, 3.31)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillins vs Teicoplanin + Other fluoroquinolone	NA	2.15 (-4.91, 9.21)	2.15 (-4.91, 9.21)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs β-Lactam/β-lactamase inhibitor + Macrolide	NA	-2.59 (-7.49, 2.31)	-2.59 (-7.49, 2.31)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2, Inconsistency
β-Lactam/β-lactamase inhibitors vs 2nd generation cephalosporins	0.8 (-9.75, 11.35)	-3.96 (-9.4, 1.48)	-3.05 (-7.95, 1.86)	Direct	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporins	-2.36 (-5.79, 1.07)	2.4 (-9.68, 14.48)	-2.2 (-4.45, 0.06)	Direct	LOW	Not serious	Serious	VERY LOW	NMA	NA	RoB, Inconsistency, Imprecision
β-Lactam/β-lactamase inhibitors vs 2nd generation cephalosporin + Macrolide	NA	-1.47 (-6.29, 3.35)	-1.47 (-6.29, 3.35)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2, Inconsistency
β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporin + Macrolide	NA	-2.69 (-6.57, 1.2)	-2.69 (-6.57, 1.2)	Indirect	LOW	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecisionx2, Inconsistency
β-Lactam/β-lactamase inhibitors vs Macrolide + Aminoglycoside	NA	1.09 (-3.88, 6.07)	1.09 (-3.88, 6.07)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2, Inconsistency
β-Lactam/β-lactamase inhibitors vs Carbapenems	NA	0 (-3.83, 3.82)	0 (-3.83, 3.82)	Indirect	LOW	Not serious	Serious	VERY LOW	NMA	NA	RoB, Imprecision, Inconsistency
β-Lactam/β-lactamase inhibitors vs Carbapenem + Macrolide	NA	0.02 (-4.67, 4.72)	0.02 (-4.67, 4.72)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2, Inconsistency
β-Lactam/β-lactamase inhibitors vs Tigecycline	NA	-2.17 (-6.97, 2.63)	-2.17 (-6.97, 2.63)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2, Inconsistency
β-Lactam/β-lactamase inhibitors vs Other fluoroquinolones	NA	-3.12 (-7.06, 0.82)	-3.12 (-7.06, 0.82)	Indirect	LOW	Not serious	Serious	VERY LOW	NMA	NA	RoB, Imprecision, Inconsistency
β-Lactam/β-lactamase inhibitors vs Cotrimoxazole	NA	-5.65 (-14.45, 3.16)	-5.65 (-14.45, 3.16)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Teicoplanin + Other fluoroquinolone	NA	-0.6 (-5.02, 3.83)	-0.6 (-5.02, 3.83)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2, Inconsistency
β-Lactam/β-lactamase inhibitor + Macrolide vs 2nd generation cephalosporins	NA	-0.45 (-6.7, 5.79)	-0.45 (-6.7, 5.79)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs 3rd generation cephalosporins	NA	0.39 (-3.95, 4.74)	0.39 (-3.95, 4.74)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs 2nd generation cephalosporin + Macrolide	NA	1.12 (-3.57, 5.81)	1.12 (-3.57, 5.81)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2

β-Lactam/β-lactamase inhibitor + Macrolide vs 3rd generation cephalosporin + Macrolide	NA	-0.1 (-3.94, 3.75)	-0.1 (-3.94, 3.75)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
β-Lactam/β-lactamase inhibitor + Macrolide vs Macrolide + Aminoglycoside	NA	3.68 (-1.44, 8.81)	3.68 (-1.44, 8.81)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
β-Lactam/β-lactamase inhibitor + Macrolide vs Carbapenems	NA	2.59 (-1.6, 6.78)	2.59 (-1.6, 6.78)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
β-Lactam/β-lactamase inhibitor + Macrolide vs Carbapenem + Macrolide	NA	2.62 (-2.16, 7.39)	2.62 (-2.16, 7.39)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Tigecycline	NA	0.42 (-4.25, 5.09)	0.42 (-4.25, 5.09)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Other fluoroquinolones	NA	-0.52 (-5.99, 4.94)	-0.52 (-5.99, 4.94)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Cotrimoxazole	NA	-3.05 (-12.67, 6.56)	-3.05 (-12.67, 6.56)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs Teicoplanin + Other fluoroquinolone	NA	1.99 (-3.79, 7.77)	1.99 (-3.79, 7.77)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporins vs 3rd generation cephalosporins	NA	0.85 (-3.67, 5.36)	0.85 (-3.67, 5.36)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2, Inconsistency
2nd generation cephalosporins vs 2nd generation cephalosporin + Macrolide	NA	1.57 (-4.61, 7.75)	1.57 (-4.61, 7.75)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporins vs 3rd generation cephalosporin + Macrolide	NA	0.36 (-5.12, 5.84)	0.36 (-5.12, 5.84)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporins vs Macrolide + Aminoglycoside	NA	4.14 (-2.15, 10.42)	4.14 (-2.15, 10.42)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporins vs Carbapenems	NA	3.04 (-2.39, 8.47)	3.04 (-2.39, 8.47)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporins vs Carbapenem + Macrolide	NA	3.07 (-3.01, 9.15)	3.07 (-3.01, 9.15)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporins vs Tigecycline	NA	0.87 (-5.29, 7.04)	0.87 (-5.29, 7.04)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporins vs Other fluoroquinolones	0.3 (-0.98, 1.58)	-4.46 (-16.26, 7.34)	-0.07 (-3.37, 3.23)	Direct	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
2nd generation cephalosporins vs Cotrimoxazole	NA	-2.6 (-9.92, 4.72)	-2.6 (-9.92, 4.72)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
2nd generation cephalosporins vs Teicoplanin + Other fluoroquinolone	NA	2.45 (-3.46, 8.36)	2.45 (-3.46, 8.36)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporins vs 2nd generation cephalosporin + Macrolide	NA	0.73 (-3.53, 4.98)	0.73 (-3.53, 4.98)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporins vs 3rd generation cephalosporin + Macrolide	NA	-0.49 (-3.64, 2.66)	-0.49 (-3.64, 2.66)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
3rd generation cephalosporins vs Macrolide + Aminoglycoside	NA	3.29 (-1.13, 7.71)	3.29 (-1.13, 7.71)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
3rd generation cephalosporins vs Carbapenems	3.2 (0.11, 6.29)	1.27 (-3.2, 5.75)	2.19 (-0.88, 5.27)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
3rd generation cephalosporins vs Carbapenem + Macrolide	NA	2.22 (-1.89, 6.33)	2.22 (-1.89, 6.33)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecision x2
3rd generation cephalosporins vs Tigecycline	NA	0.03 (-4.21, 4.26)	0.03 (-4.21, 4.26)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2

3rd generation cephalosporins vs Other fluoroquinolones	-1.3 (-2.7, 0.1)	3.46 (-8.33, 15.25)	-0.92 (-4.26, 2.42)	Direct	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
3rd generation cephalosporins vs Cotrimoxazole	NA	-3.45 (-12.05, 5.15)	-3.45 (-12.05, 5.15)	Indirect	LOW	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3, Inconsistency
3rd generation cephalosporins vs Teicoplanin + Other fluoroquinolone	1.6 (-0.51, 3.71)	NA	1.6 (-2.21, 5.41)	Direct	MODERATE	Not serious	Very serious	VERY LOW	DIRECT	LOW	RoB, Imprecision
2nd generation cephalosporin + Macrolide vs 3rd generation cephalosporin + Macrolide	NA	-1.22 (-4.95, 2.52)	-1.22 (-4.95, 2.52)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Macrolide + Aminoglycoside	NA	2.56 (-2.48, 7.61)	2.56 (-2.48, 7.61)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Carbapenems	NA	1.47 (-2.63, 5.56)	1.47 (-2.63, 5.56)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Carbapenem + Macrolide	NA	1.5 (-3.2, 6.19)	1.5 (-3.2, 6.19)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Tigecycline	NA	-0.7 (-5.29, 3.89)	-0.7 (-5.29, 3.89)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Other fluoroquinolones	NA	-1.64 (-7.04, 3.75)	-1.64 (-7.04, 3.75)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Cotrimoxazole	NA	-4.17 (-13.75, 5.4)	-4.17 (-13.75, 5.4)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolide vs Teicoplanin + Other fluoroquinolone	NA	0.87 (-4.84, 6.58)	0.87 (-4.84, 6.58)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Macrolide + Aminoglycoside	4.5 (1.96, 7.04)	-0.19 (-9.99, 9.61)	3.78 (0.05, 7.51)	Indirect	MODERATE	Not serious	Not Serious	MODERATE	NMA	NA	RoB
3rd generation cephalosporin + Macrolide vs Carbapenems	3.9 (1.85, 5.95)	1.55 (-2.15, 5.26)	2.68 (0.06, 5.3)	Direct	MODERATE	Not serious	Not Serious	MODERATE	NMA	NA	RoB
3rd generation cephalosporin + Macrolide vs Carbapenem + Macrolide	NA	2.71 (-0.96, 6.38)	2.71 (-0.96, 6.38)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
3rd generation cephalosporin + Macrolide vs Tigecycline	NA	0.52 (-3.2, 4.23)	0.52 (-3.2, 4.23)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Other fluoroquinolones	NA	-0.43 (-5.01, 4.15)	-0.43 (-5.01, 4.15)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Cotrimoxazole	NA	-2.96 (-12.1, 6.18)	-2.96 (-12.1, 6.18)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
3rd generation cephalosporin + Macrolide vs Teicoplanin + Other fluoroquinolone	NA	2.09 (-2.86, 7.04)	2.09 (-2.86, 7.04)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Macrolide + Aminoglycoside vs Carbapenems	-0.6 (-2.55, 1.35)	-5.29 (-15.49, 4.91)	-1.1 (-4.65, 2.46)	Direct	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Macrolide + Aminoglycoside vs Carbapenem + Macrolide	NA	-1.07 (-5.78, 3.65)	-1.07 (-5.78, 3.65)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Macrolide + Aminoglycoside vs Tigecycline	NA	-3.26 (-8.29, 1.77)	-3.26 (-8.29, 1.77)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Macrolide + Aminoglycoside vs Other fluoroquinolones	NA	-4.21 (-9.73, 1.31)	-4.21 (-9.73, 1.31)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Macrolide + Aminoglycoside vs Cotrimoxazole	NA	-6.74 (-16.38, 2.91)	-6.74 (-16.38, 2.91)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Macrolide + Aminoglycoside vs Teicoplanin + Other fluoroquinolone	NA	-1.69 (-7.53, 4.15)	-1.69 (-7.53, 4.15)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2

Carbapenems vs Carbapenem + Macrolide	0.98 (-0.89, 2.85)	-5.79 (-14.48, 2.89)	0.03 (-3.38, 3.43)	Direct	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Carbapenems vs Tigecycline	NA	-2.17 (-6.24, 1.9)	-2.17 (-6.24, 1.9)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Carbapenems vs Other fluoroquinolones	NA	-3.11 (-7.63, 1.41)	-3.11 (-7.63, 1.41)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Carbapenems vs Cotrimoxazole	NA	-5.64 (-14.75, 3.47)	-5.64 (-14.75, 3.47)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Carbapenems vs Teicoplanin + Other fluoroquinolone	NA	-0.59 (-5.49, 4.3)	-0.59 (-5.49, 4.3)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Carbapenem + Macrolide vs Tigecycline	NA	-2.2 (-6.87, 2.48)	-2.2 (-6.87, 2.48)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Carbapenem + Macrolide vs Other fluoroquinolones	NA	-3.14 (-8.42, 2.14)	-3.14 (-8.42, 2.14)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Carbapenem + Macrolide vs Cotrimoxazole	NA	-5.67 (-15.18, 3.84)	-5.67 (-15.18, 3.84)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Carbapenem + Macrolide vs Teicoplanin + Other fluoroquinolone	NA	-0.62 (-6.22, 4.98)	-0.62 (-6.22, 4.98)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Tigecycline vs Other fluoroquinolones	NA	-0.94 (-6.32, 4.43)	-0.94 (-6.32, 4.43)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Tigecycline vs Cotrimoxazole	NA	-3.47 (-13.04, 6.09)	-3.47 (-13.04, 6.09)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Tigecycline vs Teicoplanin + Other fluoroquinolone	NA	1.57 (-4.12, 7.27)	1.57 (-4.12, 7.27)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Other fluoroquinolones vs Cotrimoxazole	NA	-2.53 (-10.55, 5.5)	-2.53 (-10.55, 5.5)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Other fluoroquinolones vs Teicoplanin + Other fluoroquinolone	NA	2.52 (-2.55, 7.59)	2.52 (-2.55, 7.59)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Cotrimoxazole vs Teicoplanin + Other fluoroquinolone	NA	5.05 (-4.35, 14.45)	5.05 (-4.35, 14.45)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3

MD: mean difference; CI: confidence interval, NA: not applicable (no evidence), ROB: risk of bias
[1] The baseline risk was derived from the median of risk of event across the arms that randomized patients to the respiratory fluoroquinolones.

Supplement 12. Direct, indirect, and network estimates and certainty of evidence for discontinuation due to adverse events

Minimal important difference	30 per 1000 patients										
Large effect threshold	90 per 1000 patients										
Baseline risk [1]	48 per 1000 patients										
	Direct evidence		**Indirect evidence**	**Network evidence**						**Best estimate**	**Reason for downgrading the certainty**
Comparison	**RR (95% CI)**	**RD** [2] **(95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RD** [2] **(95% CI)**	**Starting evidence**	**Starting certainty rating**	**Incoherence**	**Imprecision**	**Final certainty rating**	
Penicillins vs Respiratory fluoroquinolones	0.78 (0.23, 2.67)	-11 (-37, 80)	0.94 (0.16, 5.56)	0.97 (0.45, 2.09)	-1 (-26, 52)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Respiratory fluoroquinolones	1.16 (0.59, 2.31)	8 (-20, 63)	0.88 (0.15, 5.32)	1.12 (0.59, 2.13)	6 (-20, 54)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Respiratory fluoroquinolones	0.91 (0.52, 1.6)	-4 (-23, 29)	NA	0.91 (0.52, 1.6)	-4 (-23, 29)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
1st generation cephalosporins vs Respiratory fluoroquinolones	NA	NA	0.93 (0.05, 16.78)	0.93 (0.05, 16.78)	-3 (-46, 757)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporins vs Respiratory fluoroquinolones	NA	NA	0.72 (0.22, 2.4)	0.72 (0.22, 2.4)	-13 (-37, 67)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporins vs Respiratory fluoroquinolones	1 (0.57, 1.77)	0 (-21, 37)	0.66 (0.09, 4.9)	0.99 (0.6, 1.64)	0 (-19, 31)	Direct	MODERATE	Not serious	Serious	LOW	NMA	RoB, Imprecision
4th generation cephalosporins vs Respiratory fluoroquinolones	NA	NA	0.92 (0.27, 3.14)	0.92 (0.27, 3.14)	-4 (-35, 103)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
5th generation cephalosporins vs Respiratory fluoroquinolones	NA	NA	1.22 (0.63, 2.36)	1.22 (0.63, 2.36)	11 (-18, 65)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin/β-lactamase inhibitors vs Respiratory fluoroquinolones	NA	NA	0.95 (0.02, 48.43)	0.95 (0.02, 48.43)	-2 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolides vs Respiratory fluoroquinolones	NA	NA	2.14 (1.01, 4.52)	2.14 (1.01, 4.52)	55 (0, 169)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Respiratory fluoroquinolones	1.44 (0.88, 2.35)	21 (-6, 65)	1.75 (0.03, 100)	1.42 (0.9, 2.23)	20 (-5, 59)	Direct	MODERATE	Not serious	Serious	LOW	NMA	RoB, Imprecision
3rd generation cephalosporin + Respiratory fluoroquinolone vs Respiratory fluoroquinolones	0.59 (0.33, 1.06)	-20 (-32, 3)	NA	0.59 (0.33, 1.06)	-20 (-32, 3)	Direct	HIGH	Not serious	Very serious	LOW	NMA	Imprecision x2
3rd generation cephalosporin + Other fluoroquinolone vs Respiratory fluoroquinolones	0.78 (0.21, 2.85)	-11 (-38, 89)	NA	0.78 (0.21, 2.85)	-11 (-38, 89)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Macrolides vs Respiratory fluoroquinolones	1.25 (0.88, 1.77)	12 (-6, 37)	1.46 (0.22, 9.71)	1.25 (0.89, 1.77)	12 (-5, 37)	Direct	MODERATE	Not serious	Serious	LOW	NMA	RoB, Imprecision
Macrolide + Aminoglycoside vs Respiratory fluoroquinolones	NA	NA	1.47 (0.05, 45.67)	1.47 (0.05, 45.67)	23 (-46, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Tetracyclines vs Respiratory fluoroquinolones	0.78 (0.45, 1.35)	-11 (-26, 17)	3.22 (0.13, 78.51)	0.81 (0.47, 1.4)	-9 (-25, 19)	Direct	HIGH	Not serious	serious	MODERATE	NMA	Imprecision
Lefamulin vs Respiratory fluoroquinolones	0.67 (0.28, 1.61)	-16 (-35, 29)	NA	0.67 (0.28, 1.61)	-16 (-35, 29)	Direct	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
Carbapenems vs Respiratory fluoroquinolones	NA	NA	0.83 (0.27, 2.52)	0.83 (0.27, 2.52)	-8 (-35, 73)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2

Carbapenem + Macrolide vs Respiratory fluoroquinolones	NA	NA	0.9 (0.02, 46.82)	0.9 (0.02, 46.82)	-5 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Respiratory fluoroquinolone + metronidazole vs Respiratory fluoroquinolones	0.93 (0.02, 50)	-3 (-47, 1000)	NA	0.93 (0.02, 45.56)	-3 (-47, 1000)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Other fluoroquinolones vs Respiratory fluoroquinolones	NA	NA	0.37 (0.06, 2.29)	0.37 (0.06, 2.29)	-30 (-45, 62)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Tigecycline vs Respiratory fluoroquinolones	0.81 (0.41, 1.59)	-9 (-28, 28)	NA	0.81 (0.41, 1.6)	-9 (-28, 29)	Direct	HIGH	Not serious	Serious	MODERATE	NMA	Imprecisionx1
Cotrimoxazole vs Respiratory fluoroquinolones	NA	NA	2.3 (0.56, 9.5)	2.3 (0.56, 9.5)	62 (-21, 408)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
Daptomycin + Aztreonam vs Respiratory fluoroquinolones	NA	NA	1.27 (0.55, 2.92)	1.27 (0.55, 2.92)	13 (-22, 92)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Linezolid + Aztreonam vs Respiratory fluoroquinolones	NA	NA	0.91 (0.43, 1.93)	0.91 (0.43, 1.93)	-4 (-27, 45)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Teicoplanin + Other fluoroquinolone vs Respiratory fluoroquinolones	NA	NA	0.98 (0.13, 7.27)	0.98 (0.13, 7.27)	-1 (-42, 301)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs β-Lactam/β-lactamase inhibitors	NA	NA	0.86 (0.32, 2.33)	0.86 (0.32, 2.33)	-7 (-33, 64)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs β-Lactam/β-lactamase inhibitor + Macrolide	NA	NA	1.06 (0.41, 2.74)	1.06 (0.41, 2.74)	3 (-28, 84)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs 1st generation cephalosporins	NA	NA	1.04 (0.06, 18.84)	1.04 (0.06, 18.84)	2 (-45, 856)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs 2nd generation cephalosporins	1.14 (0.07, 16.67)	7 (-45, 752)	1.42 (0.31, 6.49)	1.35 (0.36, 5.09)	17 (-31, 196)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs 3rd generation cephalosporins	NA	NA	0.98 (0.4, 2.4)	0.98 (0.4, 2.4)	-1 (-29, 67)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs 4th generation cephalosporins	NA	NA	1.06 (0.25, 4.46)	1.06 (0.25, 4.46)	3 (-36, 166)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs 5th generation cephalosporins	NA	NA	0.79 (0.29, 2.14)	0.79 (0.29, 2.14)	-10 (-34, 55)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	1.02 (0.02, 55.69)	1.02 (0.02, 55.69)	1 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs 2nd generation cephalosporin + Macrolides	NA	NA	0.45 (0.16, 1.32)	0.45 (0.16, 1.32)	-26 (-40, 15)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs 3rd generation cephalosporin + Macrolide	NA	NA	0.68 (0.28, 1.67)	0.68 (0.28, 1.67)	-15 (-35, 32)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	1.64 (0.63, 4.29)	1.64 (0.63, 4.29)	31 (-18, 158)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs 3rd generation cephalosporin + Other fluoroquinolone	NA	NA	1.25 (0.28, 5.65)	1.25 (0.28, 5.65)	12 (-35, 223)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs Macrolides	3.57 (0.16, 100)	123 (-40, 1000)	0.69 (0.29, 1.63)	0.77 (0.34, 1.78)	-11 (-32, 37)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs Macrolide + Aminoglycoside	NA	NA	0.66 (0.02, 22.15)	0.66 (0.02, 22.15)	-16 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs Tetracyclines	NA	NA	1.19 (0.47, 2.99)	1.19 (0.47, 2.99)	9 (-25, 96)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs Lefamulin	NA	NA	1.45 (0.45, 4.67)	1.45 (0.45, 4.67)	22 (-26, 176)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2

Penicillins vs Carbapenems	NA	NA	1.17 (0.31, 4.49)	1.17 (0.31, 4.49)	8 (-33, 168)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs Carbapenem + Macrolide	NA	NA	1.07 (0.02, 59.85)	1.07 (0.02, 59.85)	3 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs Respiratory fluoroquinolone + metronidazole	NA	NA	1.05 (0.02, 55.39)	1.05 (0.02, 55.39)	2 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs Other fluoroquinolones	NA	NA	2.59 (0.38, 17.84)	2.59 (0.38, 17.84)	76 (-30, 808)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs Tigecycline	NA	NA	1.2 (0.43, 3.35)	1.2 (0.43, 3.35)	10 (-27, 113)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs Cotrimoxazole	0.3 (0.07, 1.39)	-34 (-45, 19)	1.12 (0.08, 15.3)	0.42 (0.11, 1.57)	-28 (-43, 27)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs Daptomycin + Aztreonam	NA	NA	0.76 (0.25, 2.33)	0.76 (0.25, 2.33)	-12 (-36, 64)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs Linezolid + Aztreonam	NA	NA	1.06 (0.37, 3.05)	1.06 (0.37, 3.05)	3 (-30, 98)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs Teicoplanin + Other fluoroquinolone	NA	NA	0.99 (0.12, 8.44)	0.99 (0.12, 8.44)	0 (-42, 357)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs β-Lactam/β-lactamase inhibitor + Macrolide	NA	NA	1.23 (0.53, 2.87)	1.23 (0.53, 2.87)	11 (-23, 90)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs 1st generation cephalosporins	NA	NA	1.21 (0.06, 23.07)	1.21 (0.06, 23.07)	10 (-45, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs 2nd generation cephalosporins	4.8 (0.24, 94.9)	182 (-36, 1000)	1.19 (0.28, 5.13)	1.56 (0.42, 5.79)	27 (-28, 230)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporins	1 (0.02, 48.72)	0 (-47, 1000)	1.14 (0.5, 2.56)	1.13 (0.51, 2.51)	6 (-24, 72)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs 4th generation cephalosporins	NA	NA	1.22 (0.31, 4.86)	1.22 (0.31, 4.86)	11 (-33, 185)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs 5th generation cephalosporins	NA	NA	0.92 (0.37, 2.27)	0.92 (0.37, 2.27)	-4 (-30, 61)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	1.18 (0.02, 63.16)	1.18 (0.02, 63.16)	9 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs 2nd generation cephalosporin + Macrolides	NA	NA	0.53 (0.2, 1.39)	0.53 (0.2, 1.39)	-23 (-38, 19)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporin + Macrolide	NA	NA	0.79 (0.36, 1.74)	0.79 (0.36, 1.74)	-10 (-31, 36)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	1.9 (0.8, 4.51)	1.9 (0.8, 4.51)	43 (-10, 168)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporin + Other fluoroquinolone	NA	NA	1.45 (0.34, 6.16)	1.45 (0.34, 6.16)	22 (-32, 248)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Macrolides	0.33 (0.04, 3.11)	-32 (-46, 101)	1 (0.47, 2.13)	0.9 (0.44, 1.83)	-5 (-27, 40)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Macrolide + Aminoglycoside	NA	NA	0.76 (0.02, 25.04)	0.76 (0.02, 25.04)	-12 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs Tetracyclines	NA	NA	1.38 (0.6, 3.19)	1.38 (0.6, 3.19)	18 (-19, 105)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Lefamulin	NA	NA	1.69 (0.57, 4.99)	1.69 (0.57, 4.99)	33 (-21, 192)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2

β-Lactam/β-lactamase inhibitors vs Carbapenems	NA	NA	1.36 (0.38, 4.87)	1.36 (0.38, 4.87)	17 (-30, 186)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Carbapenem + Macrolide	NA	NA	1.24 (0.02, 67.84)	1.24 (0.02, 67.84)	12 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs Respiratory fluoroquinolone + metronidazole	NA	NA	1.21 (0.02, 62.77)	1.21 (0.02, 62.77)	10 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs Other fluoroquinolones	NA	NA	3 (0.45, 20.08)	3 (0.45, 20.08)	96 (-26, 916)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs Tigecycline	NA	NA	1.39 (0.55, 3.54)	1.39 (0.55, 3.54)	19 (-22, 122)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Cotrimoxazole	NA	NA	0.49 (0.1, 2.3)	0.49 (0.1, 2.3)	-24 (-43, 62)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Daptomycin + Aztreonam	NA	NA	0.88 (0.31, 2.49)	0.88 (0.31, 2.49)	-6 (-33, 72)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Linezolid + Aztreonam	NA	NA	1.23 (0.47, 3.24)	1.23 (0.47, 3.24)	11 (-25, 108)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Teicoplanin + Other fluoroquinolone	NA	NA	1.15 (0.14, 9.39)	1.15 (0.14, 9.39)	7 (-41, 403)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs 1st generation cephalosporins	NA	NA	0.98 (0.05, 18.71)	0.98 (0.05, 18.71)	-1 (-46, 850)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs 2nd generation cephalosporins	NA	NA	1.27 (0.34, 4.78)	1.27 (0.34, 4.78)	13 (-32, 181)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs 3rd generation cephalosporins	NA	NA	0.92 (0.44, 1.95)	0.92 (0.44, 1.95)	-4 (-27, 46)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs 4th generation cephalosporins	NA	NA	1 (0.26, 3.85)	1 (0.26, 3.85)	0 (-36, 137)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs 5th generation cephalosporins	NA	NA	0.75 (0.32, 1.77)	0.75 (0.32, 1.77)	-12 (-33, 37)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	0.96 (0.02, 50.94)	0.96 (0.02, 50.94)	-2 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs 2nd generation cephalosporin + Macrolides	NA	NA	0.43 (0.17, 1.09)	0.43 (0.17, 1.09)	-27 (-40, 4)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs 3rd generation cephalosporin + Macrolide	NA	NA	0.64 (0.31, 1.33)	0.64 (0.31, 1.33)	-17 (-33, 16)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	1.55 (0.69, 3.46)	1.55 (0.69, 3.46)	26 (-15, 118)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs 3rd generation cephalosporin + Other fluoroquinolone	NA	NA	1.18 (0.29, 4.85)	1.18 (0.29, 4.85)	9 (-34, 185)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Macrolides	NA	NA	0.73 (0.38, 1.41)	0.73 (0.38, 1.41)	-13 (-30, 20)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Macrolide + Aminoglycoside	NA	NA	0.62 (0.02, 20.13)	0.62 (0.02, 20.13)	-18 (-47, 918)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs Tetracyclines	NA	NA	1.12 (0.51, 2.45)	1.12 (0.51, 2.45)	6 (-24, 70)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Lefamulin	NA	NA	1.37 (0.48, 3.89)	1.37 (0.48, 3.89)	18 (-25, 139)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Carbapenems	NA	NA	1.11 (0.32, 3.85)	1.11 (0.32, 3.85)	5 (-33, 137)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2

β-Lactam/β-lactamase inhibitor + Macrolide vs Carbapenem + Macrolide	1.01 (0.02, 50.41)	0 (-47, 1000)	NA	1.01 (0.02, 50.41)	0 (-47, 1000)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs Respiratory fluoroquinolone + metronidazole	NA	NA	0.99 (0.02, 50.47)	0.99 (0.02, 50.47)	0 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs Other fluoroquinolones	NA	NA	2.44 (0.37, 16.28)	2.44 (0.37, 16.28)	69 (-30, 733)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs Tigecycline	NA	NA	1.13 (0.47, 2.73)	1.13 (0.47, 2.73)	6 (-25, 83)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Cotrimoxazole	NA	NA	0.4 (0.09, 1.82)	0.4 (0.09, 1.82)	-29 (-44, 39)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Daptomycin + Aztreonam	NA	NA	0.72 (0.26, 1.96)	0.72 (0.26, 1.96)	-13 (-36, 46)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Linezolid + Aztreonam	NA	NA	1 (0.39, 2.54)	1 (0.39, 2.54)	0 (-29, 74)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Teicoplanin + Other fluoroquinolone	NA	NA	0.94 (0.12, 7.52)	0.94 (0.12, 7.52)	-3 (-42, 313)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs 2nd generation cephalosporins	1.12 (0.02, 55.51)	6 (-47, 1000)	1.52 (0.02, 100)	1.29 (0.07, 22.73)	14 (-45, 1000)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs 3rd generation cephalosporins	NA	NA	0.94 (0.05, 17.1)	0.94 (0.05, 17.1)	-3 (-46, 773)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs 4th generation cephalosporins	NA	NA	1.01 (0.05, 22.84)	1.01 (0.05, 22.84)	0 (-46, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs 5th generation cephalosporins	NA	NA	0.76 (0.04, 14.32)	0.76 (0.04, 14.32)	-12 (-46, 639)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	0.98 (0.01, 126.41)	0.98 (0.01, 126.41)	-1 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs 2nd generation cephalosporin + Macrolides	NA	NA	0.43 (0.02, 8.62)	0.43 (0.02, 8.62)	-27 (-47, 366)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs 3rd generation cephalosporin + Macrolide	NA	NA	0.66 (0.04, 12.26)	0.66 (0.04, 12.26)	-16 (-46, 540)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	1.57 (0.08, 30.08)	1.57 (0.08, 30.08)	27 (-44, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs 3rd generation cephalosporin + Other fluoroquinolone	NA	NA	1.2 (0.05, 28.57)	1.2 (0.05, 28.57)	10 (-46, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs Macrolides	NA	NA	0.74 (0.04, 13.66)	0.74 (0.04, 13.66)	-12 (-46, 608)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs Macrolide + Aminoglycoside	NA	NA	0.63 (0.01, 55.75)	0.63 (0.01, 55.75)	-18 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs Tetracyclines	NA	NA	1.14 (0.06, 21.36)	1.14 (0.06, 21.36)	7 (-45, 977)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs Lefamulin	NA	NA	1.4 (0.07, 28.68)	1.4 (0.07, 28.68)	19 (-45, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs Carbapenems	NA	NA	1.12 (0.05, 24.29)	1.12 (0.05, 24.29)	6 (-46, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs Carbapenem + Macrolide	NA	NA	1.03 (0.01, 137.45)	1.03 (0.01, 137.45)	1 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs Respiratory fluoroquinolone + metronidazole	NA	NA	1 (0.01, 128.41)	1 (0.01, 128.41)	0 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3

1st generation cephalosporins vs Other fluoroquinolones	NA	NA	2.49 (0.09, 66.1)	2.49 (0.09, 66.1)	72 (-44, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs Tigecycline	NA	NA	1.15 (0.06, 22.47)	1.15 (0.06, 22.47)	7 (-45, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs Cotrimoxazole	0.46 (0.01, 20.6)	-26 (-48, 941)	0.34 (0, 26.64)	0.4 (0.02, 7.01)	-29 (-47, 288)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs Daptomycin + Aztreonam	NA	NA	0.73 (0.04, 14.39)	0.73 (0.04, 14.39)	-13 (-46, 643)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs Linezolid + Aztreonam	NA	NA	1.02 (0.05, 19.57)	1.02 (0.05, 19.57)	1 (-46, 891)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
1st generation cephalosporins vs Teicoplanin + Other fluoroquinolone	NA	NA	0.95 (0.03, 31.37)	0.95 (0.03, 31.37)	-2 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporins vs 3rd generation cephalosporins	0.9 (0.19, 4.41)	-5 (-39, 164)	0.56 (0.1, 3.15)	0.73 (0.23, 2.34)	-13 (-37, 64)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporins vs 4th generation cephalosporins	NA	NA	0.78 (0.15, 3.98)	0.78 (0.15, 3.98)	-11 (-41, 143)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporins vs 5th generation cephalosporins	NA	NA	0.59 (0.17, 2.04)	0.59 (0.17, 2.04)	-20 (-40, 50)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporins vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	0.76 (0.01, 44.35)	0.76 (0.01, 44.35)	-12 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporins vs 2nd generation cephalosporin + Macrolides	NA	NA	0.34 (0.08, 1.39)	0.34 (0.08, 1.39)	-32 (-44, 19)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporins vs 3rd generation cephalosporin + Macrolide	NA	NA	0.51 (0.14, 1.83)	0.51 (0.14, 1.83)	-24 (-41, 40)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporins vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	1.22 (0.32, 4.63)	1.22 (0.32, 4.63)	11 (-33, 174)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporins vs 3rd generation cephalosporin + Other fluoroquinolone	NA	NA	0.93 (0.16, 5.45)	0.93 (0.16, 5.45)	-3 (-40, 214)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporins vs Macrolides	NA	NA	0.58 (0.17, 2)	0.58 (0.17, 2)	-20 (-40, 48)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporins vs Macrolide + Aminoglycoside	NA	NA	0.49 (0.01, 18.2)	0.49 (0.01, 18.2)	-24 (-48, 826)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporins vs Tetracyclines	NA	NA	0.88 (0.24, 3.29)	0.88 (0.24, 3.29)	-6 (-36, 110)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporins vs Lefamulin	NA	NA	1.08 (0.24, 4.79)	1.08 (0.24, 4.79)	4 (-36, 182)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporins vs Carbapenems	NA	NA	0.87 (0.19, 4.08)	0.87 (0.19, 4.08)	-6 (-39, 148)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporins vs Carbapenem + Macrolide	NA	NA	0.8 (0.01, 49.41)	0.8 (0.01, 49.41)	-10 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporins vs Respiratory fluoroquinolone + metronidazole	NA	NA	0.78 (0.01, 45.79)	0.78 (0.01, 45.79)	-11 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporins vs Other fluoroquinolones	2 (0.19, 20.9)	48 (-39, 955)	1.83 (0.13, 26.32)	1.92 (0.33, 11.23)	44 (-32, 491)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporins vs Tigecycline	NA	NA	0.89 (0.22, 3.55)	0.89 (0.22, 3.55)	-5 (-37, 122)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporins vs Cotrimoxazole	NA	NA	0.31 (0.05, 1.82)	0.31 (0.05, 1.82)	-33 (-46, 39)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3

2nd generation cephalosporins vs Daptomycin + Aztreonam	NA	NA	0.57 (0.15, 2.17)	0.57 (0.15, 2.17)	-21 (-41, 56)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporins vs Linezolid + Aztreonam	NA	NA	0.79 (0.22, 2.87)	0.79 (0.22, 2.87)	-10 (-37, 90)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporins vs Teicoplanin + Other fluoroquinolone	NA	NA	0.74 (0.08, 7.12)	0.74 (0.08, 7.12)	-12 (-44, 294)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporins vs 4th generation cephalosporins	1.06 (0.33, 3.41)	3 (-32, 116)	1.43 (0.03, 83.33)	1.08 (0.35, 3.34)	4 (-31, 112)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporins vs 5th generation cephalosporins	0.81 (0.53, 1.24)	-9 (-23, 12)	NA	0.81 (0.53, 1.24)	-9 (-23, 12)	Direct	HIGH	Not serious	Not serious	HIGH	NMA	None
3rd generation cephalosporins vs 3rd generation cephalosporin/β-lactamase inhibitors	1.04 (0.02, 50)	2 (-47, 1000)	NA	1.04 (0.02, 51.52)	2 (-47, 1000)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporins vs 2nd generation cephalosporin + Macrolides	NA	NA	0.46 (0.19, 1.14)	0.46 (0.19, 1.14)	-26 (-39, 7)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporins vs 3rd generation cephalosporin + Macrolide	NA	NA	0.7 (0.36, 1.37)	0.7 (0.36, 1.37)	-14 (-31, 18)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporins vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	1.68 (0.78, 3.61)	1.68 (0.78, 3.61)	33 (-11, 125)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporins vs 3rd generation cephalosporin + Other fluoroquinolone	NA	NA	1.28 (0.32, 5.15)	1.28 (0.32, 5.15)	13 (-33, 199)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporins vs Macrolides	NA	NA	0.79 (0.43, 1.45)	0.79 (0.43, 1.45)	-10 (-27, 22)	Indirect	MODERATE	Not serious	Not serious	MODERATE	NMA	RoB
3rd generation cephalosporins vs Macrolide + Aminoglycoside	NA	NA	0.67 (0.02, 20.95)	0.67 (0.02, 20.95)	-16 (-47, 958)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporins vs Tetracyclines	NA	NA	1.22 (0.58, 2.55)	1.22 (0.58, 2.55)	11 (-20, 74)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporins vs Lefamulin	NA	NA	1.49 (0.54, 4.09)	1.49 (0.54, 4.09)	24 (-22, 148)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporins vs Carbapenems	1.2 (0.41, 3.57)	10 (-28, 123)	1.16 (0.07, 19.89)	1.2 (0.44, 3.31)	10 (-27, 111)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporins vs Carbapenem + Macrolide	NA	NA	1.1 (0.02, 58.79)	1.1 (0.02, 58.79)	5 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporins vs Respiratory fluoroquinolone + metronidazole	NA	NA	1.07 (0.02, 54.38)	1.07 (0.02, 54.38)	3 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporins vs Other fluoroquinolones	2.55 (0.24, 27.14)	74 (-36, 1000)	2.79 (0.2, 40)	2.66 (0.45, 15.53)	80 (-26, 697)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporins vs Tigecycline	NA	NA	1.23 (0.53, 2.86)	1.23 (0.53, 2.86)	11 (-23, 89)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporins vs Cotrimoxazole	NA	NA	0.43 (0.1, 1.91)	0.43 (0.1, 1.91)	-27 (-43, 44)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporins vs Daptomycin + Aztreonam	0.78 (0.4, 1.52)	-11 (-29, 25)	NA	0.78 (0.4, 1.52)	-11 (-29, 25)	Direct	HIGH	Not serious	Serious	MODERATE	NMA	Imprecisionx1
3rd generation cephalosporins vs Linezolid + Aztreonam	1.09 (0.62, 1.89)	4 (-18, 43)	NA	1.09 (0.62, 1.89)	4 (-18, 43)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporins vs Teicoplanin + Other fluoroquinolone	1.02 (0.15, 7.1)	1 (-41, 293)	NA	1.02 (0.15, 7.1)	1 (-41, 293)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
4th generation cephalosporins vs 5th generation cephalosporins	NA	NA	0.75 (0.22, 2.5)	0.75 (0.22, 2.5)	-12 (-37, 72)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2

4th generation cephalosporins vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	0.96 (0.02, 55.81)	0.96 (0.02, 55.81)	-2 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
4th generation cephalosporins vs 2nd generation cephalosporin + Macrolides	NA	NA	0.43 (0.1, 1.81)	0.43 (0.1, 1.81)	-27 (-43, 39)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
4th generation cephalosporins vs 3rd generation cephalosporin + Macrolide	NA	NA	0.65 (0.17, 2.39)	0.65 (0.17, 2.39)	-17 (-40, 67)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
4th generation cephalosporins vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	1.55 (0.4, 6.05)	1.55 (0.4, 6.05)	26 (-29, 242)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
4th generation cephalosporins vs 3rd generation cephalosporin + Other fluoroquinolone	NA	NA	1.18 (0.2, 7.08)	1.18 (0.2, 7.08)	9 (-38, 292)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
4th generation cephalosporins vs Macrolides	NA	NA	0.73 (0.2, 2.63)	0.73 (0.2, 2.63)	-13 (-38, 78)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
4th generation cephalosporins vs Macrolide + Aminoglycoside	NA	NA	0.62 (0.02, 22.88)	0.62 (0.02, 22.88)	-18 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
4th generation cephalosporins vs Tetracyclines	NA	NA	1.13 (0.29, 4.32)	1.13 (0.29, 4.32)	6 (-34, 159)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
4th generation cephalosporins vs Lefamulin	NA	NA	1.38 (0.3, 6.24)	1.38 (0.3, 6.24)	18 (-34, 252)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
4th generation cephalosporins vs Carbapenems	0.85 (0.02, 50)	-7 (-47, 1000)	1.16 (0.24, 5.57)	1.11 (0.26, 4.76)	5 (-36, 180)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
4th generation cephalosporins vs Carbapenem + Macrolide	NA	NA	1.02 (0.02, 63.46)	1.02 (0.02, 63.46)	1 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
4th generation cephalosporins vs Respiratory fluoroquinolone + metronidazole	NA	NA	0.99 (0.02, 58.82)	0.99 (0.02, 58.82)	0 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
4th generation cephalosporins vs Other fluoroquinolones	NA	NA	2.45 (0.3, 19.91)	2.45 (0.3, 19.91)	70 (-34, 908)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
4th generation cephalosporins vs Tigecycline	NA	NA	1.13 (0.28, 4.63)	1.13 (0.28, 4.63)	6 (-35, 174)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
4th generation cephalosporins vs Cotrimoxazole	NA	NA	0.4 (0.06, 2.57)	0.4 (0.06, 2.57)	-29 (-45, 75)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
4th generation cephalosporins vs Daptomycin + Aztreonam	NA	NA	0.72 (0.2, 2.67)	0.72 (0.2, 2.67)	-13 (-38, 80)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
4th generation cephalosporins vs Linezolid + Aztreonam	NA	NA	1 (0.29, 3.52)	1 (0.29, 3.52)	0 (-34, 121)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
4th generation cephalosporins vs Teicoplanin + Other fluoroquinolone	NA	NA	0.94 (0.1, 8.88)	0.94 (0.1, 8.88)	-3 (-43, 378)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
5th generation cephalosporins vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	1.29 (0.03, 64.99)	1.29 (0.03, 64.99)	14 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
5th generation cephalosporins vs 2nd generation cephalosporin + Macrolides	NA	NA	0.57 (0.21, 1.55)	0.57 (0.21, 1.55)	-21 (-38, 26)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
5th generation cephalosporins vs 3rd generation cephalosporin + Macrolide	NA	NA	0.86 (0.39, 1.91)	0.86 (0.39, 1.91)	-7 (-29, 44)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
5th generation cephalosporins vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	2.07 (0.86, 4.98)	2.07 (0.86, 4.98)	51 (-7, 191)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
5th generation cephalosporins vs 3rd generation cephalosporin + Other fluoroquinolone	NA	NA	1.58 (0.37, 6.77)	1.58 (0.37, 6.77)	28 (-30, 277)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
5th generation cephalosporins vs Macrolides	NA	NA	0.98 (0.47, 2.05)	0.98 (0.47, 2.05)	-1 (-25, 50)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2

5th generation cephalosporins vs Macrolide + Aminoglycoside	NA	NA	0.83 (0.03, 26.5)	0.83 (0.03, 26.5)	-8 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
5th generation cephalosporins vs Tetracyclines	NA	NA	1.5 (0.64, 3.52)	1.5 (0.64, 3.52)	24 (-17, 121)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
5th generation cephalosporins vs Lefamulin	NA	NA	1.84 (0.61, 5.5)	1.84 (0.61, 5.5)	40 (-19, 216)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
5th generation cephalosporins vs Carbapenems	NA	NA	1.48 (0.49, 4.44)	1.48 (0.49, 4.44)	23 (-24, 165)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
5th generation cephalosporins vs Carbapenem + Macrolide	NA	NA	1.35 (0.02, 74.12)	1.35 (0.02, 74.12)	17 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
5th generation cephalosporins vs Respiratory fluoroquinolone + metronidazole	NA	NA	1.32 (0.03, 68.58)	1.32 (0.03, 68.58)	15 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
5th generation cephalosporins vs Other fluoroquinolones	NA	NA	3.27 (0.53, 20.14)	3.27 (0.53, 20.14)	109 (-23, 919)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
5th generation cephalosporins vs Tigecycline	NA	NA	1.51 (0.59, 3.9)	1.51 (0.59, 3.9)	24 (-20, 139)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
5th generation cephalosporins vs Cotrimoxazole	NA	NA	0.53 (0.11, 2.5)	0.53 (0.11, 2.5)	-23 (-43, 72)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
5th generation cephalosporins vs Daptomycin + Aztreonam	NA	NA	0.96 (0.44, 2.12)	0.96 (0.44, 2.12)	-2 (-27, 54)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
5th generation cephalosporins vs Linezolid + Aztreonam	NA	NA	1.34 (0.67, 2.69)	1.34 (0.67, 2.69)	16 (-16, 81)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
5th generation cephalosporins vs Teicoplanin + Other fluoroquinolone	NA	NA	1.25 (0.17, 9.17)	1.25 (0.17, 9.17)	12 (-40, 392)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs 2nd generation cephalosporin + Macrolides	NA	NA	0.44 (0.01, 24.3)	0.44 (0.01, 24.3)	-27 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs 3rd generation cephalosporin + Macrolide	NA	NA	0.67 (0.01, 35.03)	0.67 (0.01, 35.03)	-16 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	1.61 (0.03, 85.51)	1.61 (0.03, 85.51)	29 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs 3rd generation cephalosporin + Other fluoroquinolone	NA	NA	1.23 (0.02, 76.93)	1.23 (0.02, 76.93)	11 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Macrolides	NA	NA	0.76 (0.01, 39.26)	0.76 (0.01, 39.26)	-12 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Macrolide + Aminoglycoside	NA	NA	0.65 (0, 116.64)	0.65 (0, 116.64)	-17 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Tetracyclines	NA	NA	1.17 (0.02, 61.71)	1.17 (0.02, 61.71)	8 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Lefamulin	NA	NA	1.43 (0.03, 80.04)	1.43 (0.03, 80.04)	21 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Carbapenems	NA	NA	1.15 (0.02, 64.56)	1.15 (0.02, 64.56)	7 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Carbapenem + Macrolide	NA	NA	1.05 (0, 276.43)	1.05 (0, 276.43)	2 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Respiratory fluoroquinolone + metronidazole	NA	NA	1.03 (0, 259.59)	1.03 (0, 259.59)	1 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3

3rd generation cephalosporin/β-lactamase inhibitors vs Other fluoroquinolones	NA	NA	2.54 (0.04, 183.64)	2.54 (0.04, 183.64)	74 (-46, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Tigecycline	NA	NA	1.18 (0.02, 63.53)	1.18 (0.02, 63.53)	9 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Cotrimoxazole	NA	NA	0.41 (0.01, 26.81)	0.41 (0.01, 26.81)	-28 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Daptomycin + Aztreonam	NA	NA	0.75 (0.01, 39.02)	0.75 (0.01, 39.02)	-12 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Linezolid + Aztreonam	NA	NA	1.04 (0.02, 53.35)	1.04 (0.02, 53.35)	2 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Teicoplanin + Other fluoroquinolone	NA	NA	0.97 (0.01, 75.89)	0.97 (0.01, 75.89)	-1 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolides vs 3rd generation cephalosporin + Macrolide	NA	NA	1.51 (0.63, 3.62)	1.51 (0.63, 3.62)	24 (-18, 126)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolides vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	3.62 (1.4, 9.34)	3.62 (1.4, 9.34)	126 (19, 400)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
2nd generation cephalosporin + Macrolides vs 3rd generation cephalosporin + Other fluoroquinolone	NA	NA	2.76 (0.61, 12.35)	2.76 (0.61, 12.35)	84 (-19, 545)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolides vs Macrolides	1.71 (0.88, 3.32)	34 (-6, 111)	NA	1.71 (0.88, 3.32)	34 (-6, 111)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolides vs Macrolide + Aminoglycoside	NA	NA	1.45 (0.04, 48.8)	1.45 (0.04, 48.8)	22 (-46, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolides vs Tetracyclines	NA	NA	2.63 (1.04, 6.63)	2.63 (1.04, 6.63)	78 (2, 270)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolides vs Lefamulin	NA	NA	3.21 (1.01, 10.18)	3.21 (1.01, 10.18)	106 (0, 441)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolides vs Carbapenems	NA	NA	2.59 (0.68, 9.9)	2.59 (0.68, 9.9)	76 (-15, 427)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolides vs Carbapenem + Macrolide	NA	NA	2.37 (0.04, 131.63)	2.37 (0.04, 131.63)	66 (-46, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolides vs Respiratory fluoroquinolone + metronidazole	NA	NA	2.31 (0.04, 121.82)	2.31 (0.04, 121.82)	63 (-46, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolides vs Other fluoroquinolones	NA	NA	5.72 (0.81, 40.57)	5.72 (0.81, 40.57)	227 (-9, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolides vs Tigecycline	NA	NA	2.65 (0.96, 7.29)	2.65 (0.96, 7.29)	79 (-2, 302)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolides vs Cotrimoxazole	NA	NA	0.93 (0.19, 4.6)	0.93 (0.19, 4.6)	-3 (-39, 173)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolides vs Daptomycin + Aztreonam	NA	NA	1.68 (0.55, 5.15)	1.68 (0.55, 5.15)	33 (-22, 199)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolides vs Linezolid + Aztreonam	NA	NA	2.34 (0.81, 6.73)	2.34 (0.81, 6.73)	64 (-9, 275)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolides vs Teicoplanin + Other fluoroquinolone	NA	NA	2.19 (0.26, 18.64)	2.19 (0.26, 18.64)	57 (-36, 847)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Macrolide vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	2.4 (1.15, 5.02)	2.4 (1.15, 5.02)	67 (7, 193)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2

3rd generation cephalosporin + Macrolide vs 3rd generation cephalosporin + Other fluoroquinolone	NA	NA	1.83 (0.46, 7.24)	1.83 (0.46, 7.24)	40 (-26, 300)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Macrolides	NA	NA	1.13 (0.64, 2)	1.13 (0.64, 2)	6 (-17, 48)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Macrolide + Aminoglycoside	1.06 (0.02, 52.41)	3 (-47, 1000)	1.47 (0, 920.47)	0.96 (0.03, 29.77)	-2 (-47, 1000)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Macrolide vs Tetracyclines	NA	NA	1.74 (0.86, 3.54)	1.74 (0.86, 3.54)	36 (-7, 122)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecision x2
3rd generation cephalosporin + Macrolide vs Lefamulin	NA	NA	2.13 (0.79, 5.72)	2.13 (0.79, 5.72)	54 (-10, 227)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Carbapenems	2.08 (0.04, 100)	52 (-46, 1000)	2.45 (0.7, 8.56)	1.71 (0.52, 5.63)	34 (-23, 222)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Carbapenem + Macrolide	NA	NA	1.57 (0.03, 83.49)	1.57 (0.03, 83.49)	27 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Macrolide vs Respiratory fluoroquinolone + metronidazole	NA	NA	1.53 (0.03, 77.22)	1.53 (0.03, 77.22)	25 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Macrolide vs Other fluoroquinolones	NA	NA	3.79 (0.59, 24.51)	3.79 (0.59, 24.51)	134 (-20, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Macrolide vs Tigecycline	NA	NA	1.75 (0.77, 3.98)	1.75 (0.77, 3.98)	36 (-11, 143)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Cotrimoxazole	NA	NA	0.62 (0.14, 2.73)	0.62 (0.14, 2.73)	-18 (-41, 83)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Daptomycin + Aztreonam	NA	NA	1.11 (0.43, 2.87)	1.11 (0.43, 2.87)	5 (-27, 90)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Linezolid + Aztreonam	NA	NA	1.55 (0.65, 3.7)	1.55 (0.65, 3.7)	26 (-17, 130)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Teicoplanin + Other fluoroquinolone	NA	NA	1.45 (0.19, 11.34)	1.45 (0.19, 11.34)	22 (-39, 496)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Respiratory fluoroquinolone vs 3rd generation cephalosporin + Other fluoroquinolone	NA	NA	0.76 (0.18, 3.16)	0.76 (0.18, 3.16)	-12 (-39, 104)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Respiratory fluoroquinolone vs Macrolides	NA	NA	0.47 (0.24, 0.93)	0.47 (0.24, 0.93)	-25 (-36, -3)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Respiratory fluoroquinolone vs Macrolide + Aminoglycoside	NA	NA	0.4 (0.01, 13.06)	0.4 (0.01, 13.06)	-29 (-48, 579)	Indirect	HIGH	Not serious	Extremely serious	VERY LOW	NMA	Imprecisionx3
3rd generation cephalosporin + Respiratory fluoroquinolone vs Tetracyclines	NA	NA	0.73 (0.33, 1.61)	0.73 (0.33, 1.61)	-13 (-32, 29)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
3rd generation cephalosporin + Respiratory fluoroquinolone vs Lefamulin	NA	NA	0.89 (0.31, 2.54)	0.89 (0.31, 2.54)	-5 (-33, 74)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
3rd generation cephalosporin + Respiratory fluoroquinolone vs Carbapenems	NA	NA	0.71 (0.2, 2.51)	0.71 (0.2, 2.51)	-14 (-38, 72)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Respiratory fluoroquinolone vs Carbapenem + Macrolide	NA	NA	0.65 (0.01, 35.37)	0.65 (0.01, 35.37)	-17 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Respiratory fluoroquinolone vs Respiratory fluoroquinolone + metronidazole	NA	NA	0.64 (0.01, 32.73)	0.64 (0.01, 32.73)	-17 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Respiratory fluoroquinolone vs Other fluoroquinolones	NA	NA	1.58 (0.24, 10.59)	1.58 (0.24, 10.59)	28 (-36, 460)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3

3rd generation cephalosporin + Respiratory fluoroquinolone vs Tigecycline	NA	NA	0.73 (0.3, 1.79)	0.73 (0.3, 1.79)	-13 (-34, 38)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
3rd generation cephalosporin + Respiratory fluoroquinolone vs Cotrimoxazole	NA	NA	0.26 (0.06, 1.19)	0.26 (0.06, 1.19)	-36 (-45, 9)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Respiratory fluoroquinolone vs Daptomycin + Aztreonam	NA	NA	0.46 (0.17, 1.28)	0.46 (0.17, 1.28)	-26 (-40, 13)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
3rd generation cephalosporin + Respiratory fluoroquinolone vs Linezolid + Aztreonam	NA	NA	0.65 (0.25, 1.66)	0.65 (0.25, 1.66)	-17 (-36, 32)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Respiratory fluoroquinolone vs Teicoplanin + Other fluoroquinolone	NA	NA	0.61 (0.07, 4.89)	0.61 (0.07, 4.89)	-19 (-45, 187)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Other fluoroquinolone vs Macrolides	NA	NA	0.62 (0.16, 2.38)	0.62 (0.16, 2.38)	-18 (-40, 66)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Other fluoroquinolone vs Macrolide + Aminoglycoside	NA	NA	0.53 (0.01, 20.72)	0.53 (0.01, 20.72)	-23 (-48, 947)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Other fluoroquinolone vs Tetracyclines	NA	NA	0.95 (0.23, 3.9)	0.95 (0.23, 3.9)	-2 (-37, 139)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Other fluoroquinolone vs Lefamulin	NA	NA	1.16 (0.24, 5.59)	1.16 (0.24, 5.59)	8 (-36, 220)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Other fluoroquinolone vs Carbapenems	NA	NA	0.94 (0.17, 5.2)	0.94 (0.17, 5.2)	-3 (-40, 202)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Other fluoroquinolone vs Carbapenem + Macrolide	NA	NA	0.86 (0.01, 54.84)	0.86 (0.01, 54.84)	-7 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Other fluoroquinolone vs Respiratory fluoroquinolone + metronidazole	NA	NA	0.84 (0.01, 50.84)	0.84 (0.01, 50.84)	-8 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Other fluoroquinolone vs Other fluoroquinolones	NA	NA	2.07 (0.22, 19.29)	2.07 (0.22, 19.29)	51 (-37, 878)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Other fluoroquinolone vs Tigecycline	NA	NA	0.96 (0.22, 4.17)	0.96 (0.22, 4.17)	-2 (-37, 152)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Other fluoroquinolone vs Cotrimoxazole	NA	NA	0.34 (0.05, 2.31)	0.34 (0.05, 2.31)	-32 (-46, 63)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Other fluoroquinolone vs Daptomycin + Aztreonam	NA	NA	0.61 (0.13, 2.85)	0.61 (0.13, 2.85)	-19 (-42, 89)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Other fluoroquinolone vs Linezolid + Aztreonam	NA	NA	0.85 (0.19, 3.8)	0.85 (0.19, 3.8)	-7 (-39, 134)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Other fluoroquinolone vs Teicoplanin + Other fluoroquinolone	NA	NA	0.79 (0.07, 8.68)	0.79 (0.07, 8.68)	-10 (-45, 369)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolides vs Macrolide + Aminoglycoside	NA	NA	0.85 (0.03, 26.81)	0.85 (0.03, 26.81)	-7 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolides vs Tetracyclines	NA	NA	1.54 (0.81, 2.93)	1.54 (0.81, 2.93)	26 (-9, 93)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Macrolides vs Lefamulin	NA	NA	1.88 (0.73, 4.83)	1.88 (0.73, 4.83)	42 (-13, 184)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Macrolides vs Carbapenems	NA	NA	1.51 (0.47, 4.86)	1.51 (0.47, 4.86)	24 (-25, 185)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Macrolides vs Carbapenem + Macrolide	NA	NA	1.39 (0.03, 72.9)	1.39 (0.03, 72.9)	19 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3

Macrolides vs Respiratory fluoroquinolone + metronidazole	NA	NA	1.35 (0.03, 67.42)	1.35 (0.03, 67.42)	17 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolides vs Other fluoroquinolones	NA	NA	3.35 (0.53, 21.14)	3.35 (0.53, 21.14)	113 (-23, 967)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolides vs Tigecycline	NA	NA	1.55 (0.72, 3.32)	1.55 (0.72, 3.32)	26 (-13, 111)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Macrolides vs Cotrimoxazole	NA	NA	0.54 (0.13, 2.33)	0.54 (0.13, 2.33)	-22 (-42, 64)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Macrolides vs Daptomycin + Aztreonam	NA	NA	0.98 (0.4, 2.42)	0.98 (0.4, 2.42)	-1 (-29, 68)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Macrolides vs Linezolid + Aztreonam	NA	NA	1.37 (0.6, 3.11)	1.37 (0.6, 3.11)	18 (-19, 101)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Macrolides vs Teicoplanin + Other fluoroquinolone	NA	NA	1.28 (0.17, 9.82)	1.28 (0.17, 9.82)	13 (-40, 423)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Tetracyclines	NA	NA	1.81 (0.06, 58.51)	1.81 (0.06, 58.51)	39 (-45, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Lefamulin	NA	NA	2.21 (0.06, 76.51)	2.21 (0.06, 76.51)	58 (-45, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Carbapenems	1.96 (0.04, 100)	46 (-46, 1000)	2.73 (0, 3678.37)	1.78 (0.06, 55.11)	37 (-45, 1000)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Carbapenem + Macrolide	NA	NA	1.63 (0.01, 305.28)	1.63 (0.01, 305.28)	30 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Respiratory fluoroquinolone + metronidazole	NA	NA	1.59 (0.01, 285.99)	1.59 (0.01, 285.99)	28 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Other fluoroquinolones	NA	NA	3.94 (0.08, 186.45)	3.94 (0.08, 186.45)	141 (-44, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Tigecycline	NA	NA	1.82 (0.05, 60.41)	1.82 (0.05, 60.41)	39 (-46, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Cotrimoxazole	NA	NA	0.64 (0.02, 26.2)	0.64 (0.02, 26.2)	-17 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Daptomycin + Aztreonam	NA	NA	1.16 (0.03, 38.34)	1.16 (0.03, 38.34)	8 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Linezolid + Aztreonam	NA	NA	1.61 (0.05, 52.31)	1.61 (0.05, 52.31)	29 (-46, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Teicoplanin + Other fluoroquinolone	NA	NA	1.51 (0.03, 78.14)	1.51 (0.03, 78.14)	24 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Tetracyclines vs Lefamulin	NA	NA	1.22 (0.43, 3.44)	1.22 (0.43, 3.44)	11 (-27, 117)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
Tetracyclines vs Carbapenems	NA	NA	0.98 (0.29, 3.4)	0.98 (0.29, 3.4)	-1 (-34, 115)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Tetracyclines vs Carbapenem + Macrolide	NA	NA	0.9 (0.02, 48.5)	0.9 (0.02, 48.5)	-5 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Tetracyclines vs Respiratory fluoroquinolone + metronidazole	NA	NA	0.88 (0.02, 44.87)	0.88 (0.02, 44.87)	-6 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Tetracyclines vs Other fluoroquinolones	NA	NA	2.18 (0.33, 14.41)	2.18 (0.33, 14.41)	57 (-32, 644)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Tetracyclines vs Tigecycline	NA	NA	1.01 (0.42, 2.41)	1.01 (0.42, 2.41)	0 (-28, 68)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2

Tetracyclines vs Cotrimoxazole	0.97 (0.06, 14.29)	-1 (-45, 638)	0.24 (0.04, 1.34)	0.35 (0.08, 1.53)	-31 (-44, 25)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Tetracyclines vs Daptomycin + Aztreonam	NA	NA	0.64 (0.24, 1.73)	0.64 (0.24, 1.73)	-17 (-36, 35)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
Tetracyclines vs Linezolid + Aztreonam	NA	NA	0.89 (0.35, 2.24)	0.89 (0.35, 2.24)	-5 (-31, 60)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Tetracyclines vs Teicoplanin + Other fluoroquinolone	NA	NA	0.83 (0.1, 6.67)	0.83 (0.1, 6.67)	-8 (-43, 272)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Lefamulin vs Carbapenems	NA	NA	0.81 (0.2, 3.33)	0.81 (0.2, 3.33)	-9 (-38, 112)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Lefamulin vs Carbapenem + Macrolide	NA	NA	0.74 (0.01, 42.12)	0.74 (0.01, 42.12)	-12 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Lefamulin vs Respiratory fluoroquinolone + metronidazole	NA	NA	0.72 (0.01, 38.99)	0.72 (0.01, 38.99)	-13 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Lefamulin vs Other fluoroquinolones	NA	NA	1.78 (0.24, 13.35)	1.78 (0.24, 13.35)	37 (-36, 593)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Lefamulin vs Tigecycline	NA	NA	0.82 (0.27, 2.51)	0.82 (0.27, 2.51)	-9 (-35, 72)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
Lefamulin vs Cotrimoxazole	NA	NA	0.29 (0.05, 1.53)	0.29 (0.05, 1.53)	-34 (-46, 25)	Indirect	HIGH	Not serious	Extremely serious	VERY LOW	NMA	Imprecisionx3
Lefamulin vs Daptomycin + Aztreonam	NA	NA	0.52 (0.16, 1.76)	0.52 (0.16, 1.76)	-23 (-40, 36)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
Lefamulin vs Linezolid + Aztreonam	NA	NA	0.73 (0.23, 2.31)	0.73 (0.23, 2.31)	-13 (-37, 63)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Lefamulin vs Teicoplanin + Other fluoroquinolone	NA	NA	0.68 (0.08, 6.1)	0.68 (0.08, 6.1)	-15 (-44, 245)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Carbapenems vs Carbapenem + Macrolide	NA	NA	0.92 (0.02, 55.35)	0.92 (0.02, 55.35)	-4 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Carbapenems vs Respiratory fluoroquinolone + metronidazole	NA	NA	0.89 (0.02, 51.28)	0.89 (0.02, 51.28)	-5 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Carbapenems vs Other fluoroquinolones	NA	NA	2.21 (0.29, 16.91)	2.21 (0.29, 16.91)	58 (-34, 764)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Carbapenems vs Tigecycline	NA	NA	1.02 (0.28, 3.78)	1.02 (0.28, 3.78)	1 (-35, 133)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Carbapenems vs Cotrimoxazole	NA	NA	0.36 (0.06, 2.16)	0.36 (0.06, 2.16)	-31 (-45, 56)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Carbapenems vs Daptomycin + Aztreonam	NA	NA	0.65 (0.19, 2.18)	0.65 (0.19, 2.18)	-17 (-39, 57)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Carbapenems vs Linezolid + Aztreonam	NA	NA	0.9 (0.29, 2.87)	0.9 (0.29, 2.87)	-5 (-34, 90)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Carbapenems vs Teicoplanin + Other fluoroquinolone	NA	NA	0.85 (0.09, 7.58)	0.85 (0.09, 7.58)	-7 (-44, 316)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Carbapenem + Macrolide vs Respiratory fluoroquinolone + metronidazole	NA	NA	0.97 (0, 249.69)	0.97 (0, 249.69)	-1 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Carbapenem + Macrolide vs Other fluoroquinolones	NA	NA	2.42 (0.03, 185.94)	2.42 (0.03, 185.94)	68 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Carbapenem + Macrolide vs Tigecycline	NA	NA	1.12 (0.02, 61.4)	1.12 (0.02, 61.4)	6 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3

Carbapenem + Macrolide vs Cotrimoxazole	NA	NA	0.39 (0.01, 26.02)	0.39 (0.01, 26.02)	-29 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Carbapenem + Macrolide vs Daptomycin + Aztreonam	NA	NA	0.71 (0.01, 40.13)	0.71 (0.01, 40.13)	-14 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Carbapenem + Macrolide vs Linezolid + Aztreonam	NA	NA	0.99 (0.02, 54.9)	0.99 (0.02, 54.9)	0 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Carbapenem + Macrolide vs Teicoplanin + Other fluoroquinolone	NA	NA	0.92 (0.01, 77.51)	0.92 (0.01, 77.51)	-4 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Respiratory fluoroquinolone + metronidazole vs Other fluoroquinolones	NA	NA	2.48 (0.03, 181.83)	2.48 (0.03, 181.83)	71 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Respiratory fluoroquinolone + metronidazole vs Tigecycline	NA	NA	1.15 (0.02, 59.8)	1.15 (0.02, 59.8)	7 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Respiratory fluoroquinolone + metronidazole vs Cotrimoxazole	NA	NA	0.4 (0.01, 25.4)	0.4 (0.01, 25.4)	-29 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Respiratory fluoroquinolone + metronidazole vs Daptomycin + Aztreonam	NA	NA	0.73 (0.01, 39.1)	0.73 (0.01, 39.1)	-13 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Respiratory fluoroquinolone + metronidazole vs Linezolid + Aztreonam	NA	NA	1.01 (0.02, 53.47)	1.01 (0.02, 53.47)	0 (-47, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Respiratory fluoroquinolone + metronidazole vs Teicoplanin + Other fluoroquinolone	NA	NA	0.95 (0.01, 75.87)	0.95 (0.01, 75.87)	-2 (-48, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Other fluoroquinolones vs Tigecycline	NA	NA	0.46 (0.07, 3.21)	0.46 (0.07, 3.21)	-26 (-45, 106)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Other fluoroquinolones vs Cotrimoxazole	NA	NA	0.16 (0.02, 1.55)	0.16 (0.02, 1.55)	-40 (-47, 26)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Other fluoroquinolones vs Daptomycin + Aztreonam	NA	NA	0.29 (0.04, 1.94)	0.29 (0.04, 1.94)	-34 (-46, 45)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Other fluoroquinolones vs Linezolid + Aztreonam	NA	NA	0.41 (0.06, 2.6)	0.41 (0.06, 2.6)	-28 (-45, 77)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Other fluoroquinolones vs Teicoplanin + Other fluoroquinolone	NA	NA	0.38 (0.03, 5.29)	0.38 (0.03, 5.29)	-30 (-47, 206)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Tigecycline vs Cotrimoxazole	NA	NA	0.35 (0.07, 1.69)	0.35 (0.07, 1.69)	-31 (-45, 33)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
Tigecycline vs Daptomycin + Aztreonam	NA	NA	0.64 (0.22, 1.86)	0.64 (0.22, 1.86)	-17 (-37, 41)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
Tigecycline vs Linezolid + Aztreonam	NA	NA	0.88 (0.32, 2.43)	0.88 (0.32, 2.43)	-6 (-33, 69)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Tigecycline vs Teicoplanin + Other fluoroquinolone	NA	NA	0.83 (0.1, 6.89)	0.83 (0.1, 6.89)	-8 (-43, 283)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Cotrimoxazole vs Daptomycin + Aztreonam	NA	NA	1.81 (0.35, 9.25)	1.81 (0.35, 9.25)	39 (-31, 396)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
Cotrimoxazole vs Linezolid + Aztreonam	NA	NA	2.52 (0.51, 12.33)	2.52 (0.51, 12.33)	73 (-24, 544)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Cotrimoxazole vs Teicoplanin + Other fluoroquinolone	NA	NA	2.36 (0.2, 27.27)	2.36 (0.2, 27.27)	65 (-38, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Daptomycin + Aztreonam vs Linezolid + Aztreonam	NA	NA	1.39 (0.59, 3.3)	1.39 (0.59, 3.3)	19 (-20, 110)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Daptomycin + Aztreonam vs Teicoplanin + Other fluoroquinolone	NA	NA	1.3 (0.17, 10.16)	1.3 (0.17, 10.16)	14 (-40, 440)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3

Linezolid + Aztreonam vs Teicoplanin + Other fluoroquinolone	NA	NA	0.94 (0.12, 7.06)	0.94 (0.12, 7.06)	-3 (-42, 291)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3

RR: relative risk; RD: risk difference; CI: confidence interval, NA: not applicable (no evidence), ROB: risk of bias
[1] The baseline risk was derived from the median of risk of event across the arms that randomized patients to the respiratory fluoroquinolones.
[2] Risk difference was calculated through applying the relative risk to the baseline risk. In cases that upper limit of confidence interval exceeded 1000, we truncated the value and reported 1000 as the upper limit.

Supplement 13. Direct, indirect, and network estimates and certainty of evidence for diarrhea

Minimal important difference	50 per 1000 patients											
Large effect threshold	150 per 1000 patients											
Baseline risk [1]	43 per 1000 patients											
	Direct evidence		**Indirect evidence**	**Network evidence**							**Best estimate**	**Reason for downgrading the certainty**
Comparison	**RR (95% CI)**	**RD** [2] **(95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RD** [2] **(95% CI)**	**Starting evidence**	**Starting certainty rating**	**Incoherence**	**Imprecision**	**Final certainty rating**		
Penicillins vs Respiratory fluoroquinolones	0.58 (0.18, 1.84)	-18 (-35, 36)	3.86 (0.59, 25)	1.01 (0.36, 2.86)	0 (-28, 80)	Direct	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
Penicillin + Other fluoroquinolone vs Respiratory fluoroquinolones	NA	NA	0.92 (0.04, 21.85)	0.92 (0.04, 21.85)	-3 (-41, 897)	Indirect	LOW	Not serious	Extremely serious	VERY LOW	NMA	RoB, Publication bias, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs Respiratory fluoroquinolones	1.86 (0.88, 3.93)	37 (-5, 126)	3.94 (1.8, 8.55)	2.8 (1.54, 5.09)	77 (23, 176)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Respiratory fluoroquinolones	10.42 (3.25, 33.4)	405 (97, 1000)	NA	10.42 (2.96, 36.73)	405 (84, 1000)	Direct	LOW	Not serious	Very serious	VERY LOW	NMA	RoB, Publication bias, Imprecisionx2
2nd generation cephalosporins vs Respiratory fluoroquinolones	NA	NA	2.07 (0.8, 5.39)	2.07 (0.8, 5.39)	46 (-9, 189)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	ROB, Imprecisionx2
3rd generation cephalosporins vs Respiratory fluoroquinolones	1.63 (0.9, 2.94)	27 (-4, 83)	0.56 (0.21, 1.49)	1.26 (0.8, 1.98)	11 (-9, 42)	Direct	MODERATE	Not serious	Serious	LOW	NMA	RoB, Imprecision
4th generation cephalosporins vs Respiratory fluoroquinolones	NA	NA	2.45 (0.83, 7.24)	2.45 (0.83, 7.24)	62 (-7, 268)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
5th generation cephalosporins vs Respiratory fluoroquinolones	NA	NA	2.17 (1.08, 4.36)	2.17 (1.08, 4.36)	50 (3, 144)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Respiratory fluoroquinolones	1.01 (0.06, 16.04)	0 (-40, 647)	1.83 (0.79, 4.24)	1.74 (0.78, 3.85)	32 (-9, 123)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Respiratory fluoroquinolones	1.47 (0.35, 6.12)	20 (-28, 220)	1.47 (0.05, 41.67)	1.46 (0.61, 3.49)	20 (-17, 107)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Respiratory fluoroquinolone vs Respiratory fluoroquinolones	0.49 (0.27, 0.89)	-22 (-31, -5)	NA	0.49 (0.23, 1.05)	-22 (-33, 2)	Direct	HIGH	Not serious	Not serious	HIGH	NMA	None
Macrolides vs Respiratory fluoroquinolones	0.84 (0.6, 1.19)	-7 (-17, 8)	0.49 (0.08, 3.01)	0.85 (0.56, 1.29)	-6 (-19, 12)	Direct	MODERATE	Not serious	Not Serious	MODERTAE	NMA	RoB
Macrolide + Aminoglycoside vs Respiratory fluoroquinolones	NA	NA	1.38 (0.06, 33.38)	1.38 (0.06, 33.38)	16 (-40, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Tetracyclines vs Respiratory fluoroquinolones	0.13 (0.05, 0.37)	-37 (-41, -27)	NA	0.13 (0.04, 0.41)	-37 (-41, -25)	Direct	HIGH	Not serious	Very Serious	LOW	NMA	Imprecisionx2
Lefamulin vs Respiratory fluoroquinolones	0.1 (0.02, 0.4)	-39 (-42, -26)	NA	0.1 (0.02, 0.43)	-39 (-42, -25)	Direct	HIGH	Not serious	Very Serious	LOW	NMA	Imprecisionx2
Carbapenems vs Respiratory fluoroquinolones	NA	NA	2.12 (0.94, 4.79)	2.12 (0.94, 4.79)	48 (-3, 163)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	ROB, Imprecisionx2

Carbapenem + Macrolide vs Respiratory fluoroquinolones	NA	NA	12.26 (2.92, 51.48)	12.26 (2.92, 51.48)	484 (83, 1000)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	RoB, Publication bias, Imprecisionx2
Other fluoroquinolones vs Respiratory fluoroquinolones	NA	NA	0.15 (0.01, 2.88)	0.15 (0.01, 2.88)	-37 (-43, 81)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Tigecycline vs Respiratory fluoroquinolones	1.28 (0.63, 2.63)	12 (-16, 70)	NA	1.27 (0.69, 2.34)	12 (-13, 58)	Direct	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
Daptomycin + Aztreonam vs Respiratory fluoroquinolones	NA	NA	0.9 (0.38, 2.15)	0.9 (0.38, 2.15)	-4 (-27, 49)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	RoB, Imprecisionx1
Linezolid + Aztreonam vs Respiratory fluoroquinolones	NA	NA	1.87 (0.69, 5.07)	1.87 (0.69, 5.07)	37 (-13, 175)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs Penicillin + Other fluoroquinolone	NA	NA	1.11 (0.04, 31.19)	1.11 (0.04, 31.19)	5 (-41, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs β-Lactam/β-lactamase inhibitors	NA	NA	0.36 (0.11, 1.15)	0.36 (0.11, 1.15)	-28 (-38, 6)	Indirect	MODERATE	Not serious	Not serious	MODERATE	NMA	ROB
Penicillins vs β-Lactam/β-lactamase inhibitor + Macrolide	NA	NA	0.1 (0.02, 0.5)	0.1 (0.02, 0.5)	-39 (-42, -22)	Indirect	LOW	Not serious	Serious	LOW	NMA	RoB ,Publication bias, Imprecisionx1
Penicillins vs 2nd generation cephalosporins	1.56 (0.2, 12.5)	24 (-34, 495)	0.26 (0.05, 1.21)	0.49 (0.14, 1.71)	-22 (-37, 31)	Indirect	MODERATE	Not serious	Not Serious	MODERTAE	NMA	RoB
Penicillins vs 3rd generation cephalosporins	NA	NA	0.8 (0.27, 2.4)	0.8 (0.27, 2.4)	-9 (-31, 60)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	ROB, Imprecisionx2
Penicillins vs 4th generation cephalosporins	NA	NA	0.41 (0.1, 1.81)	0.41 (0.1, 1.81)	-25 (-39, 35)	Indirect	MODERATE	Not serious	Not Serious	MODERTAE	NMA	RoB
Penicillins vs 5th generation cephalosporins	NA	NA	0.47 (0.14, 1.58)	0.47 (0.14, 1.58)	-23 (-37, 25)	Indirect	MODERATE	Not serious	Not Serious	MODERTAE	NMA	RoB
Penicillins vs 2nd generation cephalosporin + Macrolide	NA	NA	0.58 (0.16, 2.11)	0.58 (0.16, 2.11)	-18 (-36, 48)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	ROB, Imprecisionx1
Penicillins vs 3rd generation cephalosporin + Macrolide	NA	NA	0.69 (0.18, 2.68)	0.69 (0.18, 2.68)	-13 (-35, 72)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	ROB, Imprecisionx2
Penicillins vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	2.08 (0.57, 7.55)	2.08 (0.57, 7.55)	46 (-18, 282)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
Penicillins vs Macrolides	3.57 (0.16, 100)	111 (-36, 1000)	1.03 (0.32, 3.31)	1.19 (0.4, 3.57)	8 (-26, 111)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs Macrolide + Aminoglycoside	NA	NA	0.73 (0.03, 20.63)	0.73 (0.03, 20.63)	-12 (-42, 844)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs Tetracyclines	NA	NA	7.74 (1.66, 36.05)	7.74 (1.66, 36.05)	290 (28, 1000)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
Penicillins vs Lefamulin	NA	NA	10.65 (1.7, 66.93)	10.65 (1.7, 66.93)	415 (30, 1000)	Indirect	HIGH	Not serious	Extremely serious	VERY LOW	NMA	Imprecisionx3
Penicillins vs Carbapenems	NA	NA	0.48 (0.13, 1.73)	0.48 (0.13, 1.73)	-22 (-37, 31)	Indirect	MODERATE	Not serious	Not Serious	MODERTAE	NMA	RoB
Penicillins vs Carbapenem + Macrolide	NA	NA	0.08 (0.01, 0.49)	0.08 (0.01, 0.49)	-40 (-43, -22)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs Other fluoroquinolones	NA	NA	6.7 (0.3, 150.02)	6.7 (0.3, 150.02)	245 (-30, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs Tigecycline	NA	NA	0.8 (0.24, 2.65)	0.8 (0.24, 2.65)	-9 (-33, 71)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2

Penicillins vs Daptomycin + Aztreonam	NA	NA	1.13 (0.3, 4.25)	1.13 (0.3, 4.25)	6 (-30, 140)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
Penicillins vs Linezolid + Aztreonam	NA	NA	0.54 (0.13, 2.21)	0.54 (0.13, 2.21)	-20 (-37, 52)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillin + Other fluoroquinolone vs β-Lactam/β-lactamase inhibitors	NA	NA	0.33 (0.01, 8.24)	0.33 (0.01, 8.24)	-29 (-43, 311)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs β-Lactam/β-lactamase inhibitor + Macrolide	0.09 (0, 1.56)	-39 (-43, 24)	NA	0.09 (0, 1.62)	-39 (-43, 27)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs 2nd generation cephalosporins	NA	NA	0.44 (0.02, 12.15)	0.44 (0.02, 12.15)	-24 (-42, 479)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs 3rd generation cephalosporins	NA	NA	0.73 (0.03, 17.87)	0.73 (0.03, 17.87)	-12 (-42, 725)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs 4th generation cephalosporins	NA	NA	0.37 (0.01, 10.7)	0.37 (0.01, 10.7)	-27 (-43, 417)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs 5th generation cephalosporins	NA	NA	0.42 (0.02, 10.86)	0.42 (0.02, 10.86)	-25 (-42, 424)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	ROB, Imprecisionx3
Penicillin + Other fluoroquinolone vs 2nd generation cephalosporin + Macrolide	NA	NA	0.53 (0.02, 13.87)	0.53 (0.02, 13.87)	-20 (-42, 553)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs 3rd generation cephalosporin + Macrolide	NA	NA	0.63 (0.02, 16.79)	0.63 (0.02, 16.79)	-16 (-42, 679)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	1.88 (0.07, 49.09)	1.88 (0.07, 49.09)	38 (-40, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Macrolides	NA	NA	1.08 (0.04, 26.42)	1.08 (0.04, 26.42)	3 (-41, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Macrolide + Aminoglycoside	NA	NA	0.66 (0.01, 59.16)	0.66 (0.01, 59.16)	-15 (-43, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	ROB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Tetracyclines	NA	NA	6.98 (0.24, 203.22)	6.98 (0.24, 203.22)	257 (-33, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Lefamulin	NA	NA	9.61 (0.29, 323.88)	9.61 (0.29, 323.88)	370 (-31, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Carbapenems	NA	NA	0.43 (0.02, 11.44)	0.43 (0.02, 11.44)	-25 (-42, 449)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Carbapenem + Macrolide	NA	NA	0.07 (0, 1.49)	0.07 (0, 1.49)	-40 (-43, 21)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Other fluoroquinolones	NA	NA	6.04 (0.08, 458.51)	6.04 (0.08, 458.51)	217 (-40, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Tigecycline	NA	NA	0.72 (0.03, 18.25)	0.72 (0.03, 18.25)	-12 (-42, 742)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Daptomycin + Aztreonam	NA	NA	1.02 (0.04, 27.38)	1.02 (0.04, 27.38)	1 (-41, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Linezolid + Aztreonam	NA	NA	0.49 (0.02, 13.58)	0.49 (0.02, 13.58)	-22 (-42, 541)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs β-Lactam/β-lactamase inhibitor + Macrolide	NA	NA	0.27 (0.07, 1.08)	0.27 (0.07, 1.08)	-31 (-40, 3)	Indirect	LOW	Not serious	Serious	VERY LOW	NMA	RoB Publication bias, Imprecision x1
β-Lactam/β-lactamase inhibitors vs 2nd generation cephalosporins	0.51 (0.14, 1.9)	-21 (-37, 39)	3.03 (0.87, 10.64)	1.35 (0.53, 3.46)	15 (-20, 106)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	ROB, Imprecisionx2

β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporins	3.8 (2, 7.23)	120 (43, 268)	1.25 (0.58, 2.72)	2.22 (1.24, 3.96)	52 (10, 127)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs 4th generation cephalosporins	NA	NA	1.15 (0.37, 3.55)	1.15 (0.37, 3.55)	6 (-27, 110)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	ROB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs 5th generation cephalosporins	NA	NA	1.29 (0.59, 2.83)	1.29 (0.59, 2.83)	12 (-18, 79)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs 2nd generation cephalosporin + Macrolide	NA	NA	1.61 (0.6, 4.33)	1.61 (0.6, 4.33)	26 (-17, 143)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	ROB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporin + Macrolide	NA	NA	1.92 (0.67, 5.45)	1.92 (0.67, 5.45)	40 (-14, 191)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	ROB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	5.74 (2.17, 15.19)	5.74 (2.17, 15.19)	204 (50, 610)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Macrolides	3 (0.12, 72.1)	86 (-38, 1000)	3.31 (1.57, 6.94)	3.3 (1.6, 6.77)	99 (26, 248)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Macrolide + Aminoglycoside	NA	NA	2.02 (0.08, 50.02)	2.02 (0.08, 50.02)	44 (-40, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs Tetracyclines	NA	NA	21.38 (5.92, 77.27)	21.38 (5.92, 77.27)	876 (212, 1000)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Lefamulin	NA	NA	29.43 (5.76, 150.41)	29.43 (5.76, 150.41)	1222 (205, 1000)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Carbapenems	2.82 (0.3, 26.12)	78 (-30, 1000)	1.16 (0.44, 3.03)	1.32 (0.55, 3.16)	14 (-19, 93)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Carbapenem + Macrolide	NA	NA	0.23 (0.05, 1.08)	0.23 (0.05, 1.08)	-33 (-41, 3)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	RoB, Imprecision x1
β-Lactam/β-lactamase inhibitors vs Other fluoroquinolones	NA	NA	18.5 (0.95, 359.72)	18.5 (0.95, 359.72)	753 (-2, 15425)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs Tigecycline	NA	NA	2.21 (0.94, 5.19)	2.21 (0.94, 5.19)	52 (-3, 180)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Daptomycin + Aztreonam	NA	NA	3.12 (1.21, 8.03)	3.12 (1.21, 8.03)	91 (9, 302)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Linezolid + Aztreonam	NA	NA	1.5 (0.52, 4.31)	1.5 (0.52, 4.31)	22 (-21, 142)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs 2nd generation cephalosporins	NA	NA	5.03 (1.03, 24.49)	5.03 (1.03, 24.49)	173 (1, 1000)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	RoB ,Publication bias, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs 3rd generation cephalosporins	NA	NA	8.26 (2.17, 31.47)	8.26 (2.17, 31.47)	312 (50, 1000)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	RoB, Publication bias, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs 4th generation cephalosporins	NA	NA	4.26 (0.81, 22.48)	4.26 (0.81, 22.48)	140 (-8, 924)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	RoB ,Publication bias, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs 5th generation cephalosporins	NA	NA	4.8 (1.14, 20.26)	4.8 (1.14, 20.26)	163 (6, 828)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	RoB ,Publication bias, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs 2nd generation cephalosporin + Macrolide	NA	NA	6 (1.35, 26.6)	6 (1.35, 26.6)	215 (15, 1000)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	RoB ,Publication bias, Imprecisionx2

β-Lactam/β-lactamase inhibitor + Macrolide vs 3rd generation cephalosporin + Macrolide	NA	NA	7.12 (1.54, 32.93)	7.12 (1.54, 32.93)	263 (23, 1000)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	RoB ,Publication bias, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	21.36 (4.89, 93.4)	21.36 (4.89, 93.4)	875 (167, 1000)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	RoB ,Publication bias, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Macrolides	NA	NA	12.26 (3.25, 46.24)	12.26 (3.25, 46.24)	484 (97, 1000)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	RoB ,Publication bias, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Macrolide + Aminoglycoside	NA	NA	7.53 (0.25, 230.81)	7.53 (0.25, 230.81)	281 (-32, 1000)	Indirect	LOW	Not serious	Extremely serious	VERY LOW	NMA	RoB ,Publication bias, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs Tetracyclines	NA	NA	79.53 (14.56, 434.24)	79.53 (14.56, 434.24)	3377 (583, 1000)	Indirect	LOW	Not serious	Extremely serious	VERY LOW	NMA	RoB, Publication bias, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs Lefamulin	NA	NA	109.44 (15.22, 787.1)	109.44 (15.22, 787.1)	4663 (611, 1000)	Indirect	LOW	Not serious	Extremely serious	VERY LOW	NMA	RoB, Publication bias, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs Carbapenems	NA	NA	4.92 (1.1, 22.06)	4.92 (1.1, 22.06)	169 (4, 906)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	RoB, Publication bias, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Carbapenem + Macrolide	0.85 (0.52, 1.39)	-6 (-21, 17)	NA	0.85 (0.43, 1.69)	-6 (-25, 30)	Direct	MODERATE	Not serious	Not Serious	MODERTAE	NMA	RoB
β-Lactam/β-lactamase inhibitor + Macrolide vs Other fluoroquinolones	NA	NA	68.8 (2.79, 1693.68)	68.8 (2.79, 1693.68)	2915 (77, 1000)	Indirect	LOW	Not serious	Extremely serious	VERY LOW	NMA	RoB, Publication bias, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs Tigecycline	NA	NA	8.21 (2.03, 33.29)	8.21 (2.03, 33.29)	310 (44, 1000)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	RoB, Publication bias, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Daptomycin + Aztreonam	NA	NA	11.6 (2.51, 53.74)	11.6 (2.51, 53.74)	456 (65, 1000)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	RoB, Publication bias, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Linezolid + Aztreonam	NA	NA	5.56 (1.12, 27.68)	5.56 (1.12, 27.68)	196 (5, 1000)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	RoB, Publication bias, Imprecisionx2
2nd generation cephalosporins vs 3rd generation cephalosporins	1.11 (0.32, 3.91)	5 (-29, 125)	2.43 (0.66, 8.93)	1.64 (0.65, 4.13)	28 (-15, 135)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporins vs 4th generation cephalosporins	NA	NA	0.85 (0.22, 3.28)	0.85 (0.22, 3.28)	-6 (-34, 98)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	ROB, Imprecisionx2
2nd generation cephalosporins vs 5th generation cephalosporins	NA	NA	0.95 (0.33, 2.77)	0.95 (0.33, 2.77)	-2 (-29, 76)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	ROB, Imprecisionx2
2nd generation cephalosporins vs 2nd generation cephalosporin + Macrolide	NA	NA	1.19 (0.34, 4.12)	1.19 (0.34, 4.12)	8 (-28, 134)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporins vs 3rd generation cephalosporin + Macrolide	NA	NA	1.42 (0.39, 5.12)	1.42 (0.39, 5.12)	18 (-26, 177)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporins vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	4.24 (1.24, 14.48)	4.24 (1.24, 14.48)	139 (10, 580)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2

2nd generation cephalosporins vs Macrolides	NA	NA	2.44 (0.86, 6.89)	2.44 (0.86, 6.89)	62 (-6, 253)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	ROB, Imprecisionx2
2nd generation cephalosporins vs Macrolide + Aminoglycoside	NA	NA	1.5 (0.06, 40.26)	1.5 (0.06, 40.26)	22 (-40, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporins vs Tetracyclines	NA	NA	15.8 (3.57, 69.88)	15.8 (3.57, 69.88)	636 (111, 1000)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporins vs Lefamulin	NA	NA	21.74 (3.61, 130.87)	21.74 (3.61, 130.87)	892 (112, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporins vs Carbapenems	NA	NA	0.98 (0.31, 3.08)	0.98 (0.31, 3.08)	-1 (-30, 89)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporins vs Carbapenem + Macrolide	NA	NA	0.17 (0.03, 0.95)	0.17 (0.03, 0.95)	-36 (-42, -2)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporins vs Other fluoroquinolones	NA	NA	13.67 (0.64, 289.72)	13.67 (0.64, 289.72)	545 (-15, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporins vs Tigecycline	NA	NA	1.63 (0.52, 5.08)	1.63 (0.52, 5.08)	27 (-21, 175)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporins vs Daptomycin + Aztreonam	NA	NA	2.31 (0.7, 7.57)	2.31 (0.7, 7.57)	56 (-13, 283)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporins vs Linezolid + Aztreonam	NA	NA	1.1 (0.31, 3.98)	1.1 (0.31, 3.98)	4 (-30, 128)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporins vs 4th generation cephalosporins	0.27 (0.01, 5.07)	-31 (-43, 175)	0.56 (0.19, 1.63)	0.52 (0.19, 1.4)	-21 (-35, 17)	Indirect	MODERATE	Not serious	Not Serious	MODERTAE	NMA	RoB
3rd generation cephalosporins vs 5th generation cephalosporins	0.58 (0.37, 0.91)	-18 (-27, -4)	NA	0.58 (0.34, 0.99)	-18 (-28, 0)	Direct	MODERATE	Not serious	Not Serious	MODERATE	NMA	RoB
3rd generation cephalosporins vs 2nd generation cephalosporin + Macrolide	NA	NA	0.73 (0.3, 1.79)	0.73 (0.3, 1.79)	-12 (-30, 34)	Indirect	MODERATE	Not serious	Not Serious	MODERTAE	NMA	RoB
3rd generation cephalosporins vs 3rd generation cephalosporin + Macrolide	NA	NA	0.86 (0.33, 2.27)	0.86 (0.33, 2.27)	-6 (-29, 55)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	ROB, Imprecisionx2
3rd generation cephalosporins vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	2.59 (1.06, 6.31)	2.59 (1.06, 6.31)	68 (3, 228)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporins vs Macrolides	NA	NA	1.48 (0.81, 2.72)	1.48 (0.81, 2.72)	21 (-8, 74)	Indirect	MODERATE	Not serious	Very Serious	VERY LOW	NMA	ROB, Imprecision x2
3rd generation cephalosporins vs Macrolide + Aminoglycoside	NA	NA	0.91 (0.04, 21.7)	0.91 (0.04, 21.7)	-4 (-41, 890)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	ROB, Imprecisionx3
3rd generation cephalosporins vs Tetracyclines	NA	NA	9.63 (2.83, 32.77)	9.63 (2.83, 32.77)	371 (79, 1000)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporins vs Lefamulin	NA	NA	13.26 (2.72, 64.64)	13.26 (2.72, 64.64)	527 (74, 1000)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporins vs Carbapenems	0.58 (0.28, 1.18)	-18 (-31, 8)	0.73 (0.14, 3.77)	0.6 (0.3, 1.2)	-17 (-30, 9)	Direct	MODERATE	Not serious	Not Serious	MODERTAE	NMA	RoB
3rd generation cephalosporins vs Carbapenem + Macrolide	NA	NA	0.1 (0.02, 0.46)	0.1 (0.02, 0.46)	-39 (-42, -23)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	RoB, Imprecisionx1
3rd generation cephalosporins vs Other fluoroquinolones	8.33 (0.47, 147.07)	315 (-23, 1000)	NA	8.33 (0.45, 153.05)	315 (-24, 1000)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporins vs Tigecycline	NA	NA	0.99 (0.47, 2.11)	0.99 (0.47, 2.11)	0 (-23, 48)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	RoB, Imprecisionx1
3rd generation cephalosporins vs Daptomycin + Aztreonam	1.41 (0.79, 2.49)	18 (-9, 64)	NA	1.41 (0.67, 2.97)	18 (-14, 85)	Direct	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2

3rd generation cephalosporins vs Linezolid + Aztreonam	0.67 (0.32, 1.42)	-14 (-29, 18)	NA	0.67 (0.28, 1.63)	-14 (-31, 27)	Direct	MODERATE	Not serious	Not Serious	MODERTAE	NMA	RoB
4th generation cephalosporins vs 5th generation cephalosporins	NA	NA	1.13 (0.36, 3.49)	1.13 (0.36, 3.49)	6 (-28, 107)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	ROB, Imprecisionx2
4th generation cephalosporins vs 2nd generation cephalosporin + Macrolide	NA	NA	1.41 (0.37, 5.34)	1.41 (0.37, 5.34)	18 (-27, 187)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
4th generation cephalosporins vs 3rd generation cephalosporin + Macrolide	NA	NA	1.67 (0.43, 6.5)	1.67 (0.43, 6.5)	29 (-25, 237)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
4th generation cephalosporins vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	5.01 (1.33, 18.95)	5.01 (1.33, 18.95)	172 (14, 772)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
4th generation cephalosporins vs Macrolides	NA	NA	2.88 (0.91, 9.14)	2.88 (0.91, 9.14)	81 (-4, 350)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
4th generation cephalosporins vs Macrolide + Aminoglycoside	NA	NA	1.77 (0.07, 43.97)	1.77 (0.07, 43.97)	33 (-40, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
4th generation cephalosporins vs Tetracyclines	NA	NA	18.66 (3.87, 89.94)	18.66 (3.87, 89.94)	759 (123, 1000)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
4th generation cephalosporins vs Lefamulin	NA	NA	25.68 (3.97, 166.07)	25.68 (3.97, 166.07)	1061 (128, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
4th generation cephalosporins vs Carbapenems	1.1 (0.6, 2.04)	4 (-17, 45)	2.27 (0.11, 47.75)	1.15 (0.54, 2.45)	6 (-20, 62)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
4th generation cephalosporins vs Carbapenem + Macrolide	NA	NA	0.2 (0.03, 1.21)	0.2 (0.03, 1.21)	-34 (-42, 9)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
4th generation cephalosporins vs Other fluoroquinolones	NA	NA	16.14 (0.74, 350.18)	16.14 (0.74, 350.18)	651 (-11, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
4th generation cephalosporins vs Tigecycline	NA	NA	1.93 (0.56, 6.67)	1.93 (0.56, 6.67)	40 (-19, 244)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
4th generation cephalosporins vs Daptomycin + Aztreonam	NA	NA	2.72 (0.78, 9.47)	2.72 (0.78, 9.47)	74 (-9, 364)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
4th generation cephalosporins vs Linezolid + Aztreonam	NA	NA	1.3 (0.34, 4.96)	1.3 (0.34, 4.96)	13 (-28, 170)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
5th generation cephalosporins vs 2nd generation cephalosporin + Macrolide	NA	NA	1.25 (0.44, 3.55)	1.25 (0.44, 3.55)	11 (-24, 110)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
5th generation cephalosporins vs 3rd generation cephalosporin + Macrolide	NA	NA	1.48 (0.49, 4.47)	1.48 (0.49, 4.47)	21 (-22, 149)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
5th generation cephalosporins vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	4.45 (1.58, 12.55)	4.45 (1.58, 12.55)	148 (25, 497)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
5th generation cephalosporins vs Macrolides	NA	NA	2.55 (1.14, 5.71)	2.55 (1.14, 5.71)	67 (6, 203)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
5th generation cephalosporins vs Macrolide + Aminoglycoside	NA	NA	1.57 (0.06, 39.01)	1.57 (0.06, 39.01)	25 (-40, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
5th generation cephalosporins vs Tetracyclines	NA	NA	16.56 (4.36, 62.91)	16.56 (4.36, 62.91)	669 (144, 1000)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
5th generation cephalosporins vs Lefamulin	NA	NA	22.79 (4.29, 121.2)	22.79 (4.29, 121.2)	937 (141, 1000)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
5th generation cephalosporins vs Carbapenems	NA	NA	1.02 (0.42, 2.47)	1.02 (0.42, 2.47)	1 (-25, 63)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2

5th generation cephalosporins vs Carbapenem + Macrolide	NA	NA	0.18 (0.04, 0.87)	0.18 (0.04, 0.87)	-35 (-41, -6)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	RoB, Imprecisionx1
5th generation cephalosporins vs Other fluoroquinolones	NA	NA	14.33 (0.74, 276.19)	14.33 (0.74, 276.19)	573 (-11, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
5th generation cephalosporins vs Tigecycline	NA	NA	1.71 (0.68, 4.3)	1.71 (0.68, 4.3)	31 (-14, 142)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
5th generation cephalosporins vs Daptomycin + Aztreonam	NA	NA	2.42 (0.97, 6.05)	2.42 (0.97, 6.05)	61 (-1, 217)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
5th generation cephalosporins vs Linezolid + Aztreonam	NA	NA	1.16 (0.41, 3.26)	1.16 (0.41, 3.26)	7 (-25, 97)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs 3rd generation cephalosporin + Macrolide	NA	NA	1.19 (0.37, 3.86)	1.19 (0.37, 3.86)	8 (-27, 123)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	ROB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	3.56 (1.18, 10.76)	3.56 (1.18, 10.76)	110 (8, 420)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Macrolides	2.25 (0.84, 6.03)	54 (-7, 216)	1.17 (0.07, 20)	2.04 (1.03, 4.06)	45 (1, 132)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Macrolide + Aminoglycoside	NA	NA	1.26 (0.05, 33.28)	1.26 (0.05, 33.28)	11 (-41, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolide vs Tetracyclines	NA	NA	13.26 (3.31, 53.13)	13.26 (3.31, 53.13)	527 (99, 1000)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Lefamulin	NA	NA	18.25 (3.29, 101.29)	18.25 (3.29, 101.29)	742 (98, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolide vs Carbapenems	NA	NA	0.82 (0.27, 2.53)	0.82 (0.27, 2.53)	-8 (-31, 66)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Carbapenem + Macrolide	NA	NA	0.14 (0.03, 0.73)	0.14 (0.03, 0.73)	-37 (-42, -12)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	RoB, Imprecisionx1
2nd generation cephalosporin + Macrolide vs Other fluoroquinolones	NA	NA	11.47 (0.55, 241.38)	11.47 (0.55, 241.38)	450 (-19, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolide vs Tigecycline	NA	NA	1.37 (0.5, 3.72)	1.37 (0.5, 3.72)	16 (-22, 117)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Daptomycin + Aztreonam	NA	NA	1.93 (0.6, 6.23)	1.93 (0.6, 6.23)	40 (-17, 225)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Linezolid + Aztreonam	NA	NA	0.93 (0.26, 3.28)	0.93 (0.26, 3.28)	-3 (-32, 98)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	3 (0.94, 9.57)	3 (0.94, 9.57)	86 (-3, 369)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Macrolides	NA	NA	1.72 (0.66, 4.52)	1.72 (0.66, 4.52)	31 (-15, 151)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Macrolide + Aminoglycoside	1.06 (0.02, 52.41)	3 (-42, 1000)	1.05 (0, 333.33)	1.06 (0.04, 26.71)	3 (-41, 1106)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Macrolide vs Tetracyclines	NA	NA	11.16 (2.66, 46.77)	11.16 (2.66, 46.77)	437 (71, 1000)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Lefamulin	NA	NA	15.36 (2.67, 88.43)	15.36 (2.67, 88.43)	617 (72, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Macrolide vs Carbapenems	0.69 (0.03, 16.67)	-14 (-44, 705)	0.69 (0.2, 2.38)	0.69 (0.22, 2.19)	-13 (-34, 51)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	ROB, Imprecisionx2

3rd generation cephalosporin + Macrolide vs Carbapenem + Macrolide	NA	NA	0.12 (0.02, 0.64)	0.12 (0.02, 0.64)	-38 (-42, -15)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Macrolide vs Other fluoroquinolones	NA	NA	9.66 (0.45, 207.46)	9.66 (0.45, 207.46)	372 (-24, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Macrolide vs Tigecycline	NA	NA	1.15 (0.4, 3.34)	1.15 (0.4, 3.34)	6 (-26, 101)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Daptomycin + Aztreonam	NA	NA	1.63 (0.48, 5.53)	1.63 (0.48, 5.53)	27 (-22, 195)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Linezolid + Aztreonam	NA	NA	0.78 (0.21, 2.9)	0.78 (0.21, 2.9)	-9 (-34, 82)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Respiratory fluoroquinolone vs Macrolides	NA	NA	0.57 (0.24, 1.38)	0.57 (0.24, 1.38)	-18 (-33, 16)	Indirect	MODERATE	Not serious	Not Serious	MODERTAE	NMA	RoB
3rd generation cephalosporin + Respiratory fluoroquinolone vs Macrolide + Aminoglycoside	NA	NA	0.35 (0.01, 9.31)	0.35 (0.01, 9.31)	-28 (-43, 357)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Respiratory fluoroquinolone vs Tetracyclines	NA	NA	3.72 (0.94, 14.69)	3.72 (0.94, 14.69)	117 (-3, 589)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
3rd generation cephalosporin + Respiratory fluoroquinolone vs Lefamulin	NA	NA	5.12 (0.93, 28.09)	5.12 (0.93, 28.09)	177 (-3, 1000)	Indirect	HIGH	Not serious	Extremely serious	VERY LOW	NMA	Imprecisionx3
3rd generation cephalosporin + Respiratory fluoroquinolone vs Carbapenems	NA	NA	0.23 (0.08, 0.71)	0.23 (0.08, 0.71)	-33 (-40, -12)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	RoB, Imprecisionx1
3rd generation cephalosporin + Respiratory fluoroquinolone vs Carbapenem + Macrolide	NA	NA	0.04 (0.01, 0.2)	0.04 (0.01, 0.2)	-41 (-43, -34)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	RoB ,Imprecisionx1
3rd generation cephalosporin + Respiratory fluoroquinolone vs Other fluoroquinolones	NA	NA	3.22 (0.15, 67.58)	3.22 (0.15, 67.58)	95 (-37, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Respiratory fluoroquinolone vs Tigecycline	NA	NA	0.38 (0.14, 1.03)	0.38 (0.14, 1.03)	-27 (-37, 1)	Indirect	HIGH	Not serious	Not Serious	HIGH	NMA	None
3rd generation cephalosporin + Respiratory fluoroquinolone vs Daptomycin + Aztreonam	NA	NA	0.54 (0.17, 1.74)	0.54 (0.17, 1.74)	-20 (-36, 32)	Indirect	HIGH	Not serious	Not Serious	HIGH	NMA	None
3rd generation cephalosporin + Respiratory fluoroquinolone vs Linezolid + Aztreonam	NA	NA	0.26 (0.07, 0.91)	0.26 (0.07, 0.91)	-32 (-40, -4)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	RoB, Imprecisionx1
Macrolides vs Macrolide + Aminoglycoside	NA	NA	0.61 (0.02, 15.19)	0.61 (0.02, 15.19)	-17 (-42, 610)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolides vs Tetracyclines	NA	NA	6.49 (1.93, 21.81)	6.49 (1.93, 21.81)	236 (40, 895)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Macrolides vs Lefamulin	NA	NA	8.93 (1.85, 43.14)	8.93 (1.85, 43.14)	341 (37, 1000)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Macrolides vs Carbapenems	NA	NA	0.4 (0.16, 1)	0.4 (0.16, 1)	-26 (-36, 0)	Indirect	MODERATE	Not serious	Not Serious	MODERTAE	NMA	RoB
Macrolides vs Carbapenem + Macrolide	NA	NA	0.07 (0.02, 0.31)	0.07 (0.02, 0.31)	-40 (-42, -30)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	RoB, Imprecisionx1
Macrolides vs Other fluoroquinolones	NA	NA	5.61 (0.29, 109.67)	5.61 (0.29, 109.67)	198 (-31, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolides vs Tigecycline	NA	NA	0.67 (0.32, 1.4)	0.67 (0.32, 1.4)	-14 (-29, 17)	Indirect	MODERATE	Not serious	Not serious	MODERATE	NMA	RoB
Macrolides vs Daptomycin + Aztreonam	NA	NA	0.95 (0.36, 2.47)	0.95 (0.36, 2.47)	-2 (-28, 63)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Macrolides vs Linezolid + Aztreonam	NA	NA	0.45 (0.16, 1.33)	0.45 (0.16, 1.33)	-24 (-36, 14)	Indirect	MODERATE	Not serious	Not Serious	MODERTAE	NMA	RoB

Macrolide + Aminoglycoside vs Tetracyclines	NA	NA	10.56 (0.36, 310.24)	10.56 (0.36, 310.24)	411 (-28, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Lefamulin	NA	NA	14.54 (0.43, 494.24)	14.54 (0.43, 494.24)	582 (-25, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Carbapenems	0.65 (0.03, 16.67)	-15 (-42, 674)	0.65 (0, 623.1)	0.65 (0.03, 14.9)	-15 (-42, 598)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Carbapenem + Macrolide	NA	NA	0.11 (0, 3.71)	0.11 (0, 3.71)	-38 (-43, 117)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	ROB, Imprecisionx3
Macrolide + Aminoglycoside vs Other fluoroquinolones	NA	NA	9.14 (0.12, 675.72)	9.14 (0.12, 675.72)	350 (-38, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Tigecycline	NA	NA	1.09 (0.04, 27.84)	1.09 (0.04, 27.84)	4 (-41, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Daptomycin + Aztreonam	NA	NA	1.54 (0.06, 40.02)	1.54 (0.06, 40.02)	23 (-40, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Linezolid + Aztreonam	NA	NA	0.74 (0.03, 19.85)	0.74 (0.03, 19.85)	-11 (-42, 811)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Tetracyclines vs Lefamulin	NA	NA	1.38 (0.21, 9.18)	1.38 (0.21, 9.18)	16 (-34, 352)	Indirect	HIGH	Not serious	Extremely serious	VERY LOW	NMA	Imprecisionx3
Tetracyclines vs Carbapenems	NA	NA	0.06 (0.02, 0.25)	0.06 (0.02, 0.25)	-40 (-42, -32)	Indirect	MODERATE	Not serious	Not Serious	MODERTAE	NMA	RoB
Tetracyclines vs Carbapenem + Macrolide	NA	NA	0.01 (0, 0.07)	0.01 (0, 0.07)	-43 (-43, -40)	Indirect	MODERATE	Not serious	Not Serious	MODERATE	NMA	RoB
Tetracyclines vs Other fluoroquinolones	NA	NA	0.87 (0.04, 20.34)	0.87 (0.04, 20.34)	-6 (-41, 832)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Tetracyclines vs Tigecycline	NA	NA	0.1 (0.03, 0.38)	0.1 (0.03, 0.38)	-39 (-42, -27)	Indirect	HIGH	Not serious	Serious	MODERATE	NMA	Imprecisionx1
Tetracyclines vs Daptomycin + Aztreonam	NA	NA	0.15 (0.03, 0.61)	0.15 (0.03, 0.61)	-37 (-42, -17)	Indirect	HIGH	Not serious	Serious	MODERATE	NMA	Imprecisionx1
Tetracyclines vs Linezolid + Aztreonam	NA	NA	0.07 (0.02, 0.32)	0.07 (0.02, 0.32)	-40 (-42, -29)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	RoB, Imprecisionx1
Lefamulin vs Carbapenems	NA	NA	0.04 (0.01, 0.25)	0.04 (0.01, 0.25)	-41 (-43, -32)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	RoB, Imprecisionx1
Lefamulin vs Carbapenem + Macrolide	NA	NA	0.01 (0, 0.06)	0.01 (0, 0.06)	-43 (-43, -40)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Lefamulin vs Other fluoroquinolones	NA	NA	0.63 (0.02, 17.28)	0.63 (0.02, 17.28)	-16 (-42, 700)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Lefamulin vs Tigecycline	NA	NA	0.08 (0.01, 0.39)	0.08 (0.01, 0.39)	-40 (-43, -26)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Lefamulin vs Daptomycin + Aztreonam	NA	NA	0.11 (0.02, 0.61)	0.11 (0.02, 0.61)	-38 (-42, -17)	Indirect	HIGH	Not serious	Extremely serious	VERY LOW	NMA	Imprecisionx3
Lefamulin vs Linezolid + Aztreonam	NA	NA	0.05 (0.01, 0.31)	0.05 (0.01, 0.31)	-41 (-43, -30)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Carbapenems vs Carbapenem + Macrolide	NA	NA	0.17 (0.03, 0.9)	0.17 (0.03, 0.9)	-36 (-42, -4)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	RoB, Imprecision
Carbapenems vs Other fluoroquinolones	NA	NA	13.99 (0.7, 279.27)	13.99 (0.7, 279.27)	559 (-13, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	ROB, Imprecisionx3
Carbapenems vs Tigecycline	NA	NA	1.67 (0.6, 4.61)	1.67 (0.6, 4.61)	29 (-17, 155)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2

Carbapenems vs Daptomycin + Aztreonam	NA	NA	2.36 (0.85, 6.58)	2.36 (0.85, 6.58)	58 (-6, 240)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Carbapenems vs Linezolid + Aztreonam	NA	NA	1.13 (0.36, 3.5)	1.13 (0.36, 3.5)	6 (-28, 108)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Carbapenem + Macrolide vs Other fluoroquinolones	NA	NA	80.91 (3.06, 2142.46)	80.91 (3.06, 2142.46)	3436 (89, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Carbapenem + Macrolide vs Tigecycline	NA	NA	9.66 (2.03, 45.93)	9.66 (2.03, 45.93)	372 (44, 1000)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Carbapenem + Macrolide vs Daptomycin + Aztreonam	NA	NA	13.65 (2.54, 73.21)	13.65 (2.54, 73.21)	544 (66, 1000)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	ROB, Imprecisionx2
Carbapenem + Macrolide vs Linezolid + Aztreonam	NA	NA	6.54 (1.14, 37.49)	6.54 (1.14, 37.49)	238 (6, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Other fluoroquinolones vs Tigecycline	NA	NA	0.12 (0.01, 2.41)	0.12 (0.01, 2.41)	-38 (-43, 61)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Other fluoroquinolones vs Daptomycin + Aztreonam	NA	NA	0.17 (0.01, 3.4)	0.17 (0.01, 3.4)	-36 (-43, 103)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Other fluoroquinolones vs Linezolid + Aztreonam	NA	NA	0.08 (0, 1.69)	0.08 (0, 1.69)	-40 (-43, 30)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Tigecycline vs Daptomycin + Aztreonam	NA	NA	1.41 (0.49, 4.09)	1.41 (0.49, 4.09)	18 (-22, 133)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
Tigecycline vs Linezolid + Aztreonam	NA	NA	0.68 (0.21, 2.17)	0.68 (0.21, 2.17)	-14 (-34, 50)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Daptomycin + Aztreonam vs Linezolid + Aztreonam	NA	NA	0.48 (0.15, 1.53)	0.48 (0.15, 1.53)	-22 (-37, 23)	Indirect	MODERATE	Not serious	Not serious	MODERATE	NMA	RoB

RR: relative risk; RD: risk difference; CI: confidence interval, NA: not applicable (no evidence), ROB: risk of bias

[1] The baseline risk was derived from the median of risk of event across the arms that randomized patients to the respiratory fluoroquinolones.

[2] Risk difference was calculated through applying the relative risk to the baseline risk. In cases that upper limit of confidence interval exceeded 1000, we truncated the value and reported 1000 as the upper limit.

Supplement 14. Direct, indirect, and network estimates and certainty of evidence for nausea and/or vomiting

Minimal important difference	50 per 1000 patients												
Large effect threshold	150 per 1000 patients												
Baseline risk [1]	45 per 1000 patients												
	Direct evidence		**Indirect evidence**	**Network evidence**							**Best estimate**	**Final certainty rating if the best estimate is not NMA**	**Reason for downgrading the certainty**
Comparison	**RR (95% CI)**	**RD** [2] **(95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RD** [2] **(95% CI)**	**Starting evidence**	**Starting certainty rating**	**Incoherence**	**Imprecision**	**Final certainty rating**			
Penicillins vs Respiratory fluoroquinolones	0.55 (0.04, 7.53)	-20 (-43, 294)	NA	0.79 (0.24, 2.66)	-9 (-34, 75)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	Inconsistency, Imprecisionx2
Penicillin + Other fluoroquinolone vs Respiratory fluoroquinolones	NA	NA	0.31 (0.01, 9.58)	0.31 (0.01, 9.58)	-31 (-45, 386)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs Respiratory fluoroquinolones	1.09 (0.32, 3.7)	4 (-31, 122)	2.5 (0.68, 9.09)	1.66 (0.66, 4.2)	30 (-15, 144)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Respiratory fluoroquinolones	0.98 (0.35, 2.73)	-1 (-29, 78)	NA	0.98 (0.31, 3.06)	-1 (-31, 93)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
1st generation cephalosporins vs Respiratory fluoroquinolones	NA	NA	5.1 (0.16, 166.44)	5.1 (0.16, 166.44)	185 (-38, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
2nd generation cephalosporins vs Respiratory fluoroquinolones	NA	NA	1.52 (0.4, 5.78)	1.52 (0.4, 5.78)	23 (-27, 215)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporins vs Respiratory fluoroquinolones	0.83 (0.35, 1.94)	-8 (-29, 42)	0.35 (0.07, 1.79)	0.78 (0.39, 1.56)	-10 (-27, 25)	Direct	MODERATE	Not serious	Not serious	MODERATE	NMA	NA	RoB
5th generation cephalosporins vs Respiratory fluoroquinolones	NA	NA	1.52 (0.6, 3.84)	1.52 (0.6, 3.84)	23 (-18, 128)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin/β-lactamase inhibitors vs Respiratory fluoroquinolones	NA	NA	0.79 (0.13, 4.66)	0.79 (0.13, 4.66)	-9 (-39, 165)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolide vs Respiratory fluoroquinolones	0.67 (0.11, 3.99)	-15 (-40, 135)	4.98 (2.27, 10.99)	3.52 (1.57, 7.88)	113 (26, 310)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Respiratory fluoroquinolones	0.67 (0.31, 1.42)	-15 (-31, 19)	1.69 (0.03, 100)	0.69 (0.31, 1.56)	-14 (-31, 25)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2

3rd generation cephalosporin + Respiratory fluoroquinolone vs Respiratory fluoroquinolones	1.01 (0.4, 2.51)	0 (-27, 68)	NA	1.01 (0.36, 2.86)	0 (-29, 84)	Direct	HIGH	Not serious	Not serious	MODERATE	NMA	NA	RoB
Macrolides vs Respiratory fluoroquinolones	0.93 (0.58, 1.48)	-3 (-19, 22)	0.25 (0.05, 1.19)	0.84 (0.54, 1.31)	-7 (-21, 14)	Direct	MODERATE	Not serious	Not serious	MODERATE	NMA	NA	RoB
Macrolide + Aminoglycoside vs Respiratory fluoroquinolones	NA	NA	0.98 (0.03, 32.31)	0.98 (0.03, 32.31)	-1 (-44, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Tetracyclines vs Respiratory fluoroquinolones	0.71 (0.4, 1.27)	-13 (-27, 12)	NA	0.71 (0.33, 1.53)	-13 (-30, 24)	Direct	HIGH	Not serious	Not serious	HIGH	NMA	NA	None
Lefamulin vs Respiratory fluoroquinolones	1.33 (0.47, 3.79)	15 (-24, 126)	NA	1.33 (0.42, 4.25)	15 (-26, 146)	Direct	HIGH	Not serious	Very serious	LOW	NMA	NA	Imprecisionx2
Carbapenems vs Respiratory fluoroquinolones	NA	NA	0.74 (0.2, 2.81)	0.74 (0.2, 2.81)	-12 (-36, 81)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Tigecycline vs Respiratory fluoroquinolones	3.13 (2.32, 4.17)	96 (59, 143)	NA	3.21 (2.01, 5.14)	99 (45, 186)	Direct	HIGH	Not serious	Serious	MODERATE	DIRECT	HIGH	Imprecision
Cotrimoxazole vs Respiratory fluoroquinolones	NA	NA	0.47 (0.05, 4.29)	0.47 (0.05, 4.29)	-24 (-43, 148)	Indirect	HIGH	Not serious	Extremely serious	VERY LOW	NMA	NA	Imprecisionx3
Daptomycin + Aztreonam vs Respiratory fluoroquinolones	NA	NA	0.52 (0.2, 1.39)	0.52 (0.2, 1.39)	-22 (-36, 18)	Indirect	MODERATE	Not serious	Not serious	MODERATE	NMA	NA	RoB
Linezolid + Aztreonam vs Respiratory fluoroquinolones	NA	NA	1.94 (0.51, 7.36)	1.94 (0.51, 7.36)	42 (-22, 286)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillins vs Penicillin + Other fluoroquinolone	NA	NA	2.52 (0.07, 94.44)	2.52 (0.07, 94.44)	68 (-42, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Inconsistency, Imprecisionx3
Penicillins vs β-Lactam/β-lactamase inhibitors	NA	NA	0.48 (0.1, 2.17)	0.48 (0.1, 2.17)	-23 (-41, 53)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Inconsistency, Imprecisionx2
Penicillins vs β-Lactam/β-lactamase inhibitor + Macrolide	NA	NA	0.81 (0.15, 4.29)	0.81 (0.15, 4.29)	-9 (-38, 148)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Inconsistency, Imprecisionx2
Penicillins vs 1st generation cephalosporins	NA	NA	0.16 (0, 6.14)	0.16 (0, 6.14)	-38 (-45, 231)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Inconsistency, Imprecisionx2
Penicillins vs 2nd generation cephalosporins	NA	NA	0.52 (0.09, 3.11)	0.52 (0.09, 3.11)	-22 (-41, 95)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Inconsistency, Imprecisionx3
Penicillins vs 3rd generation cephalosporins	NA	NA	1.02 (0.26, 3.99)	1.02 (0.26, 3.99)	1 (-33, 135)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Inconsistency, Imprecisionx2
Penicillins vs 5th generation cephalosporins	NA	NA	0.52 (0.12, 2.28)	0.52 (0.12, 2.28)	-22 (-40, 58)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Inconsistency, Imprecisionx2
Penicillins vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	1 (0.12, 8.36)	1 (0.12, 8.36)	0 (-40, 331)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Inconsistency, Imprecisionx3
Penicillins vs 2nd generation cephalosporin + Macrolide	NA	NA	0.23 (0.05, 0.94)	0.23 (0.05, 0.94)	-35 (-43, -3)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Inconsistency, Imprecision
Penicillins vs 3rd generation cephalosporin + Macrolide	NA	NA	1.14 (0.27, 4.92)	1.14 (0.27, 4.92)	6 (-33, 176)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Inconsistency, Imprecisionx2
Penicillins vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	0.79 (0.16, 3.88)	0.79 (0.16, 3.88)	-9 (-38, 130)	Indirect	MODERATE	Not serious	Very serious	LOW	NMA	NA	Inconsistency, Imprecisionx2

Penicillins vs Macrolides	NA	NA	0.94 (0.26, 3.4)	0.94 (0.26, 3.4)	-3 (-33, 108)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Inconsistency, Imprecisionx2
Penicillins vs Macrolide + Aminoglycoside	NA	NA	0.81 (0.02, 32.87)	0.81 (0.02, 32.87)	-9 (-44, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Inconsistency, Imprecisionx3
Penicillins vs Tetracyclines	NA	NA	1.11 (0.27, 4.63)	1.11 (0.27, 4.63)	5 (-33, 163)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	Inconsistency, Imprecisionx2
Penicillins vs Lefamulin	NA	NA	0.59 (0.11, 3.18)	0.59 (0.11, 3.18)	-18 (-40, 98)	Indirect	MODERATE	Not serious	very serious	VERY LOW	NMA	NA	Inconsistency, Imprecisionx2
Penicillins vs Carbapenems	NA	NA	1.07 (0.18, 6.34)	1.07 (0.18, 6.34)	3 (-37, 240)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Inconsistency, Imprecisionx3
Penicillins vs Tigecycline	NA	NA	0.25 (0.07, 0.91)	0.25 (0.07, 0.91)	-34 (-42, -4)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	Inconsistency, Imprecision
Penicillins vs Cotrimoxazole	NA	NA	1.69 (0.14, 21.13)	1.69 (0.14, 21.13)	31 (-39, 906)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Inconsistency, Imprecisionx3
Penicillins vs Daptomycin + Aztreonam	NA	NA	1.52 (0.33, 6.96)	1.52 (0.33, 6.96)	23 (-30, 268)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Inconsistency, Imprecisionx2
Penicillins vs Linezolid + Aztreonam	NA	NA	0.41 (0.07, 2.42)	0.41 (0.07, 2.42)	-27 (-42, 64)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Inconsistency, Imprecisionx3
Penicillin + Other fluoroquinolone vs β-Lactam/β-lactamase inhibitors	NA	NA	0.19 (0.01, 6.52)	0.19 (0.01, 6.52)	-36 (-45, 248)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs β-Lactam/β-lactamase inhibitor + Macrolide	0.32 (0.01, 7.69)	-31 (-45, 301)	NA	0.32 (0.01, 8.06)	-31 (-45, 318)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs 1st generation cephalosporins	NA	NA	0.06 (0, 8.11)	0.06 (0, 8.11)	-42 (-45, 320)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Penicillin + Other fluoroquinolone vs 2nd generation cephalosporins	NA	NA	0.21 (0.01, 8.14)	0.21 (0.01, 8.14)	-36 (-45, 321)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs 3rd generation cephalosporins	NA	NA	0.41 (0.01, 13.26)	0.41 (0.01, 13.26)	-27 (-45, 552)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs 5th generation cephalosporins	NA	NA	0.21 (0.01, 7.12)	0.21 (0.01, 7.12)	-36 (-45, 275)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	0.4 (0.01, 18.63)	0.4 (0.01, 18.63)	-27 (-45, 793)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs 2nd generation cephalosporin + Macrolide	NA	NA	0.09 (0, 2.99)	0.09 (0, 2.99)	-41 (-45, 90)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs 3rd generation cephalosporin + Macrolide	NA	NA	0.45 (0.01, 15.2)	0.45 (0.01, 15.2)	-25 (-45, 639)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3

Penicillin + Other fluoroquinolone vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	0.31 (0.01, 11.1)	0.31 (0.01, 11.1)	-31 (-45, 455)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Macrolides	NA	NA	0.37 (0.01, 11.74)	0.37 (0.01, 11.74)	-28 (-45, 483)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Macrolide + Aminoglycoside	NA	NA	0.32 (0, 42.96)	0.32 (0, 42.96)	-31 (-45, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Tetracyclines	NA	NA	0.44 (0.01, 14.58)	0.44 (0.01, 14.58)	-25 (-45, 611)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Lefamulin	NA	NA	0.24 (0.01, 8.71)	0.24 (0.01, 8.71)	-34 (-45, 347)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Carbapenems	NA	NA	0.42 (0.01, 16.59)	0.42 (0.01, 16.59)	-26 (-45, 702)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Tigecycline	NA	NA	0.1 (0, 3.08)	0.1 (0, 3.08)	-41 (-45, 94)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Cotrimoxazole	NA	NA	0.67 (0.01, 39.45)	0.67 (0.01, 39.45)	-15 (-45, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Daptomycin + Aztreonam	NA	NA	0.6 (0.02, 21.02)	0.6 (0.02, 21.02)	-18 (-44, 901)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Linezolid + Aztreonam	NA	NA	0.16 (0, 6.37)	0.16 (0, 6.37)	-38 (-45, 242)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs β-Lactam/β-lactamase inhibitor + Macrolide	NA	NA	1.7 (0.39, 7.41)	1.7 (0.39, 7.41)	32 (-27, 288)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs 1st generation cephalosporins	NA	NA	0.33 (0.01, 10.44)	0.33 (0.01, 10.44)	-30 (-45, 425)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs 2nd generation cephalosporins	1.55 (0.2, 12.03)	25 (-36, 496)	0.74 (0.11, 4.76)	1.1 (0.3, 4)	5 (-32, 135)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporins	3.04 (0.63, 14.82)	92 (-17, 622)	1.82 (0.54, 5.88)	2.14 (0.81, 5.7)	51 (-9, 212)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs 5th generation cephalosporins	NA	NA	1.09 (0.35, 3.4)	1.09 (0.35, 3.4)	4 (-29, 108)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	2.1 (0.31, 14.02)	2.1 (0.31, 14.02)	50 (-31, 586)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3

β-Lactam/β-lactamase inhibitors vs 2nd generation cephalosporin + Macrolide	NA	NA	0.47 (0.14, 1.55)	0.47 (0.14, 1.55)	-24 (-39, 25)	Indirect	MODERATE	Not serious	Not serious	MODERATE	NMA	NA	RoB
β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporin + Macrolide	NA	NA	2.4 (0.7, 8.19)	2.4 (0.7, 8.19)	63 (-14, 324)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	1.65 (0.41, 6.65)	1.65 (0.41, 6.65)	29 (-27, 254)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Macrolides	2 (0.19, 21.43)	45 (-36, 919)	1.96 (0.65, 5.88)	1.98 (0.73, 5.34)	44 (-12, 195)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Macrolide + Aminoglycoside	NA	NA	1.7 (0.05, 62.22)	1.7 (0.05, 62.22)	32 (-43, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs Tetracyclines	NA	NA	2.33 (0.7, 7.71)	2.33 (0.7, 7.71)	60 (-14, 302)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Lefamulin	NA	NA	1.25 (0.28, 5.5)	1.25 (0.28, 5.5)	11 (-32, 203)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Carbapenems	NA	NA	2.24 (0.49, 10.18)	2.24 (0.49, 10.18)	56 (-23, 413)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Tigecycline	NA	NA	0.52 (0.18, 1.47)	0.52 (0.18, 1.47)	-22 (-37, 21)	Indirect	MODERATE	Not serious	Not serious	MODERATE	NMA	NA	RoB
β-Lactam/β-lactamase inhibitors vs Cotrimoxazole	NA	NA	3.55 (0.32, 39.2)	3.55 (0.32, 39.2)	115 (-31, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs Daptomycin + Aztreonam	NA	NA	3.18 (0.96, 10.49)	3.18 (0.96, 10.49)	98 (-2, 427)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Linezolid + Aztreonam	NA	NA	0.86 (0.19, 3.85)	0.86 (0.19, 3.85)	-6 (-36, 128)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs 1st generation cephalosporins	NA	NA	0.19 (0, 7.49)	0.19 (0, 7.49)	-36 (-45, 292)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs 2nd generation cephalosporins	NA	NA	0.64 (0.11, 3.75)	0.64 (0.11, 3.75)	-16 (-40, 124)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs 3rd generation cephalosporins	NA	NA	1.26 (0.33, 4.81)	1.26 (0.33, 4.81)	12 (-30, 171)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs 5th generation cephalosporins	NA	NA	0.64 (0.15, 2.79)	0.64 (0.15, 2.79)	-16 (-38, 81)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	1.23 (0.15, 10.15)	1.23 (0.15, 10.15)	10 (-38, 412)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs 2nd	NA	NA	0.28 (0.07, 1.12)	0.28 (0.07, 1.12)	-32 (-42, 5)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision

generation cephalosporin + Macrolide													
β-Lactam/β-lactamase inhibitor + Macrolide vs 3rd generation cephalosporin + Macrolide	NA	NA	1.41 (0.35, 5.73)	1.41 (0.35, 5.73)	18 (-29, 213)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	0.97 (0.21, 4.55)	0.97 (0.21, 4.55)	-1 (-36, 160)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Macrolides	NA	NA	1.16 (0.34, 3.97)	1.16 (0.34, 3.97)	7 (-30, 134)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Macrolide + Aminoglycoside	NA	NA	1 (0.03, 39.83)	1 (0.03, 39.83)	0 (-44, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs Tetracyclines	NA	NA	1.37 (0.35, 5.39)	1.37 (0.35, 5.39)	17 (-29, 198)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Lefamulin	NA	NA	0.73 (0.14, 3.74)	0.73 (0.14, 3.74)	-12 (-39, 123)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Carbapenems	NA	NA	1.32 (0.23, 7.61)	1.32 (0.23, 7.61)	14 (-35, 297)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs Tigecycline	NA	NA	0.3 (0.09, 1.05)	0.3 (0.09, 1.05)	-32 (-41, 2)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
β-Lactam/β-lactamase inhibitor + Macrolide vs Cotrimoxazole	NA	NA	2.09 (0.17, 25.26)	2.09 (0.17, 25.26)	49 (-37, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs Daptomycin + Aztreonam	NA	NA	1.87 (0.42, 8.4)	1.87 (0.42, 8.4)	39 (-26, 333)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitor + Macrolide vs Linezolid + Aztreonam	NA	NA	0.5 (0.09, 2.93)	0.5 (0.09, 2.93)	-23 (-41, 87)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs 2nd generation cephalosporins	3.37 (0.14, 80.76)	107 (-39, 1000)	NA	3.37 (0.13, 84.03)	107 (-39, 1000)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs 3rd generation cephalosporins	NA	NA	6.58 (0.21, 206.7)	6.58 (0.21, 206.7)	251 (-36, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs 5th generation cephalosporins	NA	NA	3.35 (0.1, 109.62)	3.35 (0.1, 109.62)	106 (-41, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs 3rd generation	NA	NA	6.44 (0.14, 291.41)	6.44 (0.14, 291.41)	245 (-39, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3

cephalosporin/β-lactamase inhibitors													
1st generation cephalosporins vs 2nd generation cephalosporin + Macrolide	NA	NA	1.45 (0.04, 50.73)	1.45 (0.04, 50.73)	20 (-43, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs 3rd generation cephalosporin + Macrolide	NA	NA	7.36 (0.21, 263.25)	7.36 (0.21, 263.25)	286 (-36, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	5.06 (0.13, 192.29)	5.06 (0.13, 192.29)	183 (-39, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs Macrolides	NA	NA	6.08 (0.18, 201.67)	6.08 (0.18, 201.67)	229 (-37, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs Macrolide + Aminoglycoside	NA	NA	5.23 (0.04, 707.38)	5.23 (0.04, 707.38)	190 (-43, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs Tetracyclines	NA	NA	7.14 (0.2, 252.76)	7.14 (0.2, 252.76)	276 (-36, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs Lefamulin	NA	NA	3.83 (0.1, 150.66)	3.83 (0.1, 150.66)	127 (-41, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs Carbapenems	NA	NA	6.88 (0.18, 262.77)	6.88 (0.18, 262.77)	265 (-37, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs Tigecycline	NA	NA	1.59 (0.05, 53.7)	1.59 (0.05, 53.7)	27 (-43, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs Cotrimoxazole	NA	NA	10.91 (0.18, 677.33)	10.91 (0.18, 677.33)	446 (-37, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs Daptomycin + Aztreonam	NA	NA	9.77 (0.29, 327.88)	9.77 (0.29, 327.88)	395 (-32, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
1st generation cephalosporins vs Linezolid + Aztreonam	NA	NA	2.64 (0.07, 99.4)	2.64 (0.07, 99.4)	74 (-42, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
2nd generation cephalosporins vs 3rd generation cephalosporins	2.56 (0.59, 11.1)	70 (-18, 455)	1.22 (0.15, 10)	1.95 (0.57, 6.74)	43 (-19, 258)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporins vs 5th generation cephalosporins	NA	NA	1 (0.26, 3.82)	1 (0.26, 3.82)	0 (-33, 127)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporins vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	1.91 (0.25, 14.78)	1.91 (0.25, 14.78)	41 (-34, 620)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
2nd generation cephalosporins vs 2nd generation cephalosporin + Macrolide	NA	NA	0.43 (0.09, 1.95)	0.43 (0.09, 1.95)	-26 (-41, 43)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
2nd generation cephalosporins vs 3rd generation cephalosporin + Macrolide	NA	NA	2.19 (0.46, 10.44)	2.19 (0.46, 10.44)	54 (-24, 425)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2

2nd generation cephalosporins vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	1.5 (0.28, 8.2)	1.5 (0.28, 8.2)	23 (-32, 324)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporins vs Macrolides	NA	NA	1.8 (0.45, 7.2)	1.8 (0.45, 7.2)	36 (-25, 279)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporins vs Macrolide + Aminoglycoside	NA	NA	1.55 (0.04, 63.15)	1.55 (0.04, 63.15)	25 (-43, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
2nd generation cephalosporins vs Tetracyclines	NA	NA	2.12 (0.45, 9.89)	2.12 (0.45, 9.89)	50 (-25, 400)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporins vs Lefamulin	NA	NA	1.14 (0.19, 6.69)	1.14 (0.19, 6.69)	6 (-36, 256)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
2nd generation cephalosporins vs Carbapenems	NA	NA	2.04 (0.37, 11.29)	2.04 (0.37, 11.29)	47 (-28, 463)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
2nd generation cephalosporins vs Tigecycline	NA	NA	0.47 (0.11, 1.97)	0.47 (0.11, 1.97)	-24 (-40, 44)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
2nd generation cephalosporins vs Cotrimoxazole	NA	NA	3.24 (0.24, 43.08)	3.24 (0.24, 43.08)	101 (-34, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
2nd generation cephalosporins vs Daptomycin + Aztreonam	NA	NA	2.9 (0.71, 11.92)	2.9 (0.71, 11.92)	86 (-13, 491)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporins vs Linezolid + Aztreonam	NA	NA	0.78 (0.15, 4.21)	0.78 (0.15, 4.21)	-10 (-38, 144)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporins vs 5th generation cephalosporins	0.53 (0.3, 0.96)	-21 (-32, -2)	NA	0.51 (0.31, 0.85)	-22 (-31, -7)	Direct	MODERATE	Not serious	Not serious	MODERATE	NMA	NA	RoB
3rd generation cephalosporins vs 3rd generation cephalosporin/β-lactamase inhibitors	0.98 (0.21, 4.55)	-1 (-36, 160)	NA	0.98 (0.19, 4.98)	-1 (-36, 179)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporins vs 2nd generation cephalosporin + Macrolide	NA	NA	0.22 (0.08, 0.59)	0.22 (0.08, 0.59)	-35 (-41, -18)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
3rd generation cephalosporins vs 3rd generation cephalosporin + Macrolide	NA	NA	1.12 (0.39, 3.24)	1.12 (0.39, 3.24)	5 (-27, 101)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporins vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	0.77 (0.22, 2.7)	0.77 (0.22, 2.7)	-10 (-35, 77)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporins vs Macrolides	NA	NA	0.92 (0.42, 2.03)	0.92 (0.42, 2.03)	-4 (-26, 46)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
3rd generation cephalosporins vs Macrolide + Aminoglycoside	NA	NA	0.8 (0.02, 26.58)	0.8 (0.02, 26.58)	-9 (-44, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
3rd generation cephalosporins vs Tetracyclines	NA	NA	1.08 (0.39, 3.04)	1.08 (0.39, 3.04)	4 (-27, 92)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporins vs Lefamulin	NA	NA	0.58 (0.15, 2.25)	0.58 (0.15, 2.25)	-19 (-38, 56)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2

3rd generation cephalosporins vs Carbapenems	0.88 (0.21, 3.7)	-5 (-36, 122)	2.46 (0.04, 146)	1.04 (0.32, 3.44)	2 (-31, 110)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporins vs Tigecycline	NA	NA	0.24 (0.1, 0.57)	0.24 (0.1, 0.57)	-34 (-41, -19)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
3rd generation cephalosporins vs Cotrimoxazole	NA	NA	1.66 (0.16, 16.88)	1.66 (0.16, 16.88)	30 (-38, 715)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
3rd generation cephalosporins vs Daptomycin + Aztreonam	1.48 (0.94, 2.35)	22 (-3, 61)	NA	1.48 (0.75, 2.93)	22 (-11, 87)	Direct	HIGH	Not serious	Very serious	LOW	NMA	NA	Imprecisionx2
3rd generation cephalosporins vs Linezolid + Aztreonam	0.4 (0.14, 1.11)	-27 (-39, 5)	NA	0.4 (0.13, 1.25)	-27 (-39, 11)	Direct	MODERATE	Not serious	Not serious	MODERATE	NMA	NA	RoB
5th generation cephalosporins vs 3rd generation cephalosporin/β-lactamase inhibitors	NA	NA	1.92 (0.35, 10.57)	1.92 (0.35, 10.57)	41 (-29, 431)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
5th generation cephalosporins vs 2nd generation cephalosporin + Macrolide	NA	NA	0.43 (0.14, 1.33)	0.43 (0.14, 1.33)	-26 (-39, 15)	Indirect	MODERATE	Not serious	Not serious	MODERATE	NMA	NA	RoB
5th generation cephalosporins vs 3rd generation cephalosporin + Macrolide	NA	NA	2.19 (0.64, 7.5)	2.19 (0.64, 7.5)	54 (-16, 293)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
5th generation cephalosporins vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	1.51 (0.37, 6.08)	1.51 (0.37, 6.08)	23 (-28, 229)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
5th generation cephalosporins vs Macrolides	NA	NA	1.81 (0.68, 4.83)	1.81 (0.68, 4.83)	36 (-14, 172)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
5th generation cephalosporins vs Macrolide + Aminoglycoside	NA	NA	1.56 (0.04, 54.68)	1.56 (0.04, 54.68)	25 (-43, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
5th generation cephalosporins vs Tetracyclines	NA	NA	2.13 (0.64, 7.05)	2.13 (0.64, 7.05)	51 (-16, 272)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
5th generation cephalosporins vs Lefamulin	NA	NA	1.14 (0.26, 5.03)	1.14 (0.26, 5.03)	6 (-33, 181)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
5th generation cephalosporins vs Carbapenems	NA	NA	2.05 (0.55, 7.58)	2.05 (0.55, 7.58)	47 (-20, 296)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
5th generation cephalosporins vs Tigecycline	NA	NA	0.47 (0.16, 1.37)	0.47 (0.16, 1.37)	-24 (-38, 17)	Indirect	MODERATE	Not serious	Not serious	MODERATE	NMA	NA	RoB
5th generation cephalosporins vs Cotrimoxazole	NA	NA	3.25 (0.3, 35.79)	3.25 (0.3, 35.79)	101 (-32, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
5th generation cephalosporins vs Daptomycin + Aztreonam	NA	NA	2.91 (1.24, 6.82)	2.91 (1.24, 6.82)	86 (11, 262)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
5th generation cephalosporins vs Linezolid + Aztreonam	NA	NA	0.79 (0.23, 2.73)	0.79 (0.23, 2.73)	-9 (-35, 78)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin/β-lactamase inhibitors vs 2nd generation cephalosporin + Macrolide	NA	NA	0.23 (0.03, 1.51)	0.23 (0.03, 1.51)	-35 (-44, 23)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
3rd generation cephalosporin/β-lactamase	NA	NA	1.14 (0.16, 7.99)	1.14 (0.16, 7.99)	6 (-38, 315)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3

inhibitors vs 3rd generation cephalosporin + Macrolide													
3rd generation cephalosporin/β-lactamase inhibitors vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	0.79 (0.1, 6.13)	0.79 (0.1, 6.13)	-9 (-41, 231)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Macrolides	NA	NA	0.94 (0.15, 5.75)	0.94 (0.15, 5.75)	-3 (-38, 214)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Macrolide + Aminoglycoside	NA	NA	0.81 (0.02, 38.89)	0.81 (0.02, 38.89)	-9 (-44, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Tetracyclines	NA	NA	1.11 (0.16, 7.61)	1.11 (0.16, 7.61)	5 (-38, 297)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Lefamulin	NA	NA	0.59 (0.07, 4.94)	0.59 (0.07, 4.94)	-18 (-42, 177)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Carbapenems	NA	NA	1.07 (0.14, 8.02)	1.07 (0.14, 8.02)	3 (-39, 316)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Tigecycline	NA	NA	0.25 (0.04, 1.55)	0.25 (0.04, 1.55)	-34 (-43, 25)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
3rd generation cephalosporin/β-lactamase inhibitors vs Cotrimoxazole	NA	NA	1.69 (0.1, 28.84)	1.69 (0.1, 28.84)	31 (-41, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Daptomycin + Aztreonam	NA	NA	1.52 (0.26, 8.85)	1.52 (0.26, 8.85)	23 (-33, 353)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
3rd generation cephalosporin/β-lactamase inhibitors vs Linezolid + Aztreonam	NA	NA	0.41 (0.06, 2.98)	0.41 (0.06, 2.98)	-27 (-42, 89)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolide vs 3rd generation cephalosporin + Macrolide	NA	NA	5.08 (1.61, 16.02)	5.08 (1.61, 16.02)	184 (27, 676)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	3.49 (0.93, 13.04)	3.49 (0.93, 13.04)	112 (-3, 542)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Macrolides	5.41 (2.91, 10.04)	198 (86, 407)	0.73 (0.11, 4.76)	4.19 (2.1, 8.36)	144 (50, 331)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Macrolide + Aminoglycoside	NA	NA	3.61 (0.1, 130.13)	3.61 (0.1, 130.13)	117 (-41, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3

2nd generation cephalosporin + Macrolide vs Tetracyclines	NA	NA	4.92 (1.63, 14.92)	4.92 (1.63, 14.92)	176 (28, 626)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Lefamulin	NA	NA	2.64 (0.64, 10.84)	2.64 (0.64, 10.84)	74 (-16, 443)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Carbapenems	NA	NA	4.74 (1.04, 21.66)	4.74 (1.04, 21.66)	168 (2, 930)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Tigecycline	NA	NA	1.1 (0.43, 2.82)	1.1 (0.43, 2.82)	5 (-26, 82)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Cotrimoxazole	NA	NA	7.52 (0.71, 79.4)	7.52 (0.71, 79.4)	293 (-13, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolide vs Daptomycin + Aztreonam	NA	NA	6.73 (2.03, 22.33)	6.73 (2.03, 22.33)	258 (46, 960)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
2nd generation cephalosporin + Macrolide vs Linezolid + Aztreonam	NA	NA	1.82 (0.4, 8.2)	1.82 (0.4, 8.2)	37 (-27, 324)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs 3rd generation cephalosporin + Respiratory fluoroquinolone	NA	NA	0.69 (0.18, 2.58)	0.69 (0.18, 2.58)	-14 (-37, 71)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Macrolides	NA	NA	0.83 (0.33, 2.09)	0.83 (0.33, 2.09)	-8 (-30, 49)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
3rd generation cephalosporin + Macrolide vs Macrolide + Aminoglycoside	1.06 (0.02, 52.41)	3 (-44, 1000)	0.16 (0, 333.33)	0.71 (0.02, 23.33)	-13 (-44, 1000)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
3rd generation cephalosporin + Macrolide vs Tetracyclines	NA	NA	0.97 (0.32, 2.95)	0.97 (0.32, 2.95)	-1 (-31, 88)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Lefamulin	NA	NA	0.52 (0.13, 2.14)	0.52 (0.13, 2.14)	-22 (-39, 51)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Carbapenems	2.08 (0.04, 100)	49 (-43, 1000)	0.82 (0.16, 4.18)	0.93 (0.21, 4.25)	-3 (-36, 146)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Tigecycline	NA	NA	0.22 (0.08, 0.55)	0.22 (0.08, 0.55)	-35 (-41, -20)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
3rd generation cephalosporin + Macrolide vs Cotrimoxazole	NA	NA	1.48 (0.14, 15.69)	1.48 (0.14, 15.69)	22 (-39, 661)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
3rd generation cephalosporin + Macrolide vs Daptomycin + Aztreonam	NA	NA	1.33 (0.37, 4.7)	1.33 (0.37, 4.7)	15 (-28, 167)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Linezolid + Aztreonam	NA	NA	0.36 (0.08, 1.7)	0.36 (0.08, 1.7)	-29 (-41, 32)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
3rd generation cephalosporin + Respiratory fluoroquinolone vs Macrolides	NA	NA	1.2 (0.39, 3.73)	1.2 (0.39, 3.73)	9 (-27, 123)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin + Respiratory fluoroquinolone vs Macrolide + Aminoglycoside	NA	NA	1.03 (0.03, 39.88)	1.03 (0.03, 39.88)	1 (-44, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3

3rd generation cephalosporin + Respiratory fluoroquinolone vs Tetracyclines	NA	NA	1.41 (0.39, 5.12)	1.41 (0.39, 5.12)	18 (-27, 185)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	NA	Imprecisionx2
3rd generation cephalosporin + Respiratory fluoroquinolone vs Lefamulin	NA	NA	0.76 (0.16, 3.6)	0.76 (0.16, 3.6)	-11 (-38, 117)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	NA	Imprecisionx2
3rd generation cephalosporin + Respiratory fluoroquinolone vs Carbapenems	NA	NA	1.36 (0.25, 7.37)	1.36 (0.25, 7.37)	16 (-34, 287)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
3rd generation cephalosporin + Respiratory fluoroquinolone vs Tigecycline	NA	NA	0.31 (0.1, 0.99)	0.31 (0.1, 0.99)	-31 (-41, 0)	Indirect	HIGH	Not serious	Serious	MODERATE	NMA	NA	Imprecision
3rd generation cephalosporin + Respiratory fluoroquinolone vs Cotrimoxazole	NA	NA	2.16 (0.19, 24.93)	2.16 (0.19, 24.93)	52 (-36, 1000)	Indirect	HIGH	Not serious	Extremely serious	VERY LOW	NMA	NA	Imprecisionx3
3rd generation cephalosporin + Respiratory fluoroquinolone vs Daptomycin + Aztreonam	NA	NA	1.93 (0.46, 8.04)	1.93 (0.46, 8.04)	42 (-24, 317)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	NA	Imprecisionx2
3rd generation cephalosporin + Respiratory fluoroquinolone vs Linezolid + Aztreonam	NA	NA	0.52 (0.1, 2.83)	0.52 (0.1, 2.83)	-22 (-41, 82)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Macrolides vs Macrolide + Aminoglycoside	NA	NA	0.86 (0.03, 29.27)	0.86 (0.03, 29.27)	-6 (-44, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Macrolides vs Tetracyclines	NA	NA	1.18 (0.49, 2.84)	1.18 (0.49, 2.84)	8 (-23, 83)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Macrolides vs Lefamulin	NA	NA	0.63 (0.18, 2.18)	0.63 (0.18, 2.18)	-17 (-37, 53)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Macrolides vs Carbapenems	NA	NA	1.13 (0.28, 4.53)	1.13 (0.28, 4.53)	6 (-32, 159)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Macrolides vs Tigecycline	NA	NA	0.26 (0.14, 0.5)	0.26 (0.14, 0.5)	-33 (-39, -23)	Indirect	MODERATE	Not serious	Not serious	MODERATE	NMA	NA	RoB
Macrolides vs Cotrimoxazole	NA	NA	1.8 (0.19, 17.19)	1.8 (0.19, 17.19)	36 (-36, 729)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Macrolides vs Daptomycin + Aztreonam	NA	NA	1.61 (0.57, 4.56)	1.61 (0.57, 4.56)	27 (-19, 160)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Macrolides vs Linezolid + Aztreonam	NA	NA	0.43 (0.11, 1.73)	0.43 (0.11, 1.73)	-26 (-40, 33)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Macrolide + Aminoglycoside vs Tetracyclines	NA	NA	1.36 (0.04, 49.04)	1.36 (0.04, 49.04)	16 (-43, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Lefamulin	NA	NA	0.73 (0.02, 29.22)	0.73 (0.02, 29.22)	-12 (-44, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Carbapenems	1.96 (0.04, 100)	43 (-43, 1000)	0.3 (0, 579.52)	1.31 (0.04, 43.14)	14 (-43, 1000)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Tigecycline	NA	NA	0.3 (0.01, 10.4)	0.3 (0.01, 10.4)	-32 (-45, 423)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Cotrimoxazole	NA	NA	2.08 (0.03, 131.2)	2.08 (0.03, 131.2)	49 (-44, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Daptomycin + Aztreonam	NA	NA	1.87 (0.05, 66.59)	1.87 (0.05, 66.59)	39 (-43, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3

Macrolide + Aminoglycoside vs Linezolid + Aztreonam	NA	NA	0.5 (0.01, 20.15)	0.5 (0.01, 20.15)	-23 (-45, 862)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Tetracyclines vs Lefamulin	NA	NA	0.54 (0.13, 2.15)	0.54 (0.13, 2.15)	-21 (-39, 52)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	NA	Imprecisionx2
Tetracyclines vs Carbapenems	NA	NA	0.96 (0.21, 4.46)	0.96 (0.21, 4.46)	-2 (-36, 156)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Tetracyclines vs Tigecycline	NA	NA	0.22 (0.09, 0.54)	0.22 (0.09, 0.54)	-35 (-41, -21)	Indirect	HIGH	Not serious	Serious	MODERATE	NMA	NA	Imprecision
Tetracyclines vs Cotrimoxazole	1.52 (0.2, 12.5)	23 (-36, 518)	NA	1.53 (0.19, 12.24)	24 (-36, 506)	Direct	HIGH	Not serious	Extremely serious	VERY LOW	NMA	NA	Imprecisionx3
Tetracyclines vs Daptomycin + Aztreonam	NA	NA	1.37 (0.4, 4.71)	1.37 (0.4, 4.71)	17 (-27, 167)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	NA	Imprecisionx2
Tetracyclines vs Linezolid + Aztreonam	NA	NA	0.37 (0.08, 1.72)	0.37 (0.08, 1.72)	-28 (-41, 32)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Lefamulin vs Carbapenems	NA	NA	1.8 (0.31, 10.51)	1.8 (0.31, 10.51)	36 (-31, 428)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Lefamulin vs Tigecycline	NA	NA	0.42 (0.12, 1.45)	0.42 (0.12, 1.45)	-26 (-40, 20)	Indirect	HIGH	Not serious	Serious	MODERATE	NMA	NA	Imprecision
Lefamulin vs Cotrimoxazole	NA	NA	2.85 (0.23, 34.74)	2.85 (0.23, 34.74)	83 (-35, 1000)	Indirect	HIGH	Not serious	Extremely serious	VERY LOW	NMA	NA	Imprecisionx3
Lefamulin vs Daptomycin + Aztreonam	NA	NA	2.55 (0.56, 11.62)	2.55 (0.56, 11.62)	70 (-20, 478)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	NA	Imprecisionx2
Lefamulin vs Linezolid + Aztreonam	NA	NA	0.69 (0.12, 4.04)	0.69 (0.12, 4.04)	-14 (-40, 137)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Carbapenems vs Tigecycline	NA	NA	0.23 (0.06, 0.96)	0.23 (0.06, 0.96)	-35 (-42, -2)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Carbapenems vs Cotrimoxazole	NA	NA	1.59 (0.12, 21.02)	1.59 (0.12, 21.02)	27 (-40, 901)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Carbapenems vs Daptomycin + Aztreonam	NA	NA	1.42 (0.36, 5.6)	1.42 (0.36, 5.6)	19 (-29, 207)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Carbapenems vs Linezolid + Aztreonam	NA	NA	0.38 (0.07, 1.99)	0.38 (0.07, 1.99)	-28 (-42, 45)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision
Tigecycline vs Cotrimoxazole	NA	NA	6.86 (0.71, 66.08)	6.86 (0.71, 66.08)	264 (-13, 1000)	Indirect	HIGH	Not serious	Extremely serious	VERY LOW	NMA	NA	Imprecisionx3
Tigecycline vs Daptomycin + Aztreonam	NA	NA	6.14 (2.05, 18.39)	6.14 (2.05, 18.39)	231 (47, 783)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	NA	Imprecisionx2
Tigecycline vs Linezolid + Aztreonam	NA	NA	1.66 (0.4, 6.9)	1.66 (0.4, 6.9)	30 (-27, 266)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	NA	RoB, Imprecisionx2
Cotrimoxazole vs Daptomycin + Aztreonam	NA	NA	0.9 (0.08, 10.06)	0.9 (0.08, 10.06)	-5 (-41, 408)	Indirect	HIGH	Not serious	Extremely serious	VERY LOW	NMA	NA	Imprecisionx3
Cotrimoxazole vs Linezolid + Aztreonam	NA	NA	0.24 (0.02, 3.2)	0.24 (0.02, 3.2)	-34 (-44, 99)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	NA	RoB, Imprecisionx3
Daptomycin + Aztreonam vs Linezolid + Aztreonam	NA	NA	0.27 (0.07, 1.02)	0.27 (0.07, 1.02)	-33 (-42, 1)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	NA	RoB, Imprecision

RR: relative risk; RD: risk difference; CI: confidence interval, NA: not applicable (no evidence), ROB: risk of bias

[1] The baseline risk was derived from the median of risk of event across the arms that randomized patients to the respiratory fluoroquinolones.

[2] Risk difference was calculated through applying the relative risk to the baseline risk. In cases that upper limit of confidence interval exceeded 1000, we truncated the value and reported 1000 as the upper limit.

Supplement 15. Direct, indirect, and network estimates and certainty of evidence for any allergic reactions

Minimal important difference	40 per 1000 patients											
Large effect threshold	120 per 1000 patients											
Baseline risk [1]	24 per 1000 patients											
	Direct evidence		**Indirect evidence**	**Network evidence**							**Best estimate**	**Reason for downgrading the certainty**
Comparison	**RR (95% CI)**	**RD** [2] **(95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RD** [2] **(95% CI)**	**Starting evidence**	**Starting certainty rating**	**Incoherence**	**Imprecision**	**Final certainty rating**		
Penicillins vs Respiratory fluoroquinolones	1.15 (0.15, 8.82)	4 (-20, 188)	0.88 (0.19, 4.17)	1.16 (0.43, 3.12)	4 (-14, 51)	Direct	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
Penicillin + Other fluoroquinolone vs Respiratory fluoroquinolones	NA	NA	1.89 (0.06, 58.01)	1.89 (0.06, 58.01)	21 (-23, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs Respiratory fluoroquinolones	0.65 (0.16, 2.69)	-8 (-20, 41)	1.41 (0.29, 6.67)	0.92 (0.32, 2.63)	-2 (-16, 39)	Direct	MODERATE	Not serious	Very Serious	VERY LOW	NMA	RoB, Imprecision x2
β-Lactam/β-lactamase inhibitor + Macrolide vs Respiratory fluoroquinolones	0.39 (0.08, 1.99)	-15 (-22, 24)	NA	0.39 (0.08, 1.99)	-15 (-22, 24)	Direct	MODERATE	Not serious	Not serious	MODERATE	NMA	RoB
2nd generation cephalosporins vs Respiratory fluoroquinolones	NA	NA	0.39 (0.12, 1.27)	0.39 (0.12, 1.27)	-15 (-21, 6)	Indirect	MODERATE	Not serious	Not serious	MODERATE	NMA	RoB
3rd generation cephalosporins vs Respiratory fluoroquinolones	0.56 (0.08, 4)	-11 (-22, 72)	0.87 (0.17, 4.55)	0.49 (0.2, 1.18)	-12 (-19, 4)	Direct	MODERATE	Not serious	Not serious	MODERATE	NMA	RoB
4th generation cephalosporins vs Respiratory fluoroquinolones	NA	NA	0.22 (0.02, 2.17)	0.22 (0.02, 2.17)	-19 (-24, 28)	Indirect	MODERATE	Not serious	Not serious	MODERATE	NMA	RoB
5th generation cephalosporins vs Respiratory fluoroquinolones	NA	NA	0.67 (0.21, 2.15)	0.67 (0.21, 2.15)	-8 (-19, 28)	Indirect	MODERATE	Not serious	Not serious	MODERATE	NMA	RoB
2nd generation cephalosporin + Macrolide vs Respiratory fluoroquinolones	0.34 (0.01, 8.22)	-16 (-24, 173)	NA	0.34 (0.01, 8.22)	-16 (-24, 173)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Macrolide vs Respiratory fluoroquinolones	0.88 (0.44, 1.77)	-3 (-13, 18)	0.37 (0.01, 12.5)	0.85 (0.43, 1.69)	-4 (-14, 17)	Direct	MODERATE	Not serious	Not serious	MODERATE	NMA	RoB
3rd generation cephalosporin+ Other fluoroquinolone vs Respiratory fluoroquinolones	2.9 (0.3, 27.6)	46 (-17, 638)	NA	2.9 (0.3, 27.6)	46 (-17, 638)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolides vs Respiratory fluoroquinolones	0.86 (0.27, 2.76)	-3 (-18, 42)	0.36 (0.07, 1.95)	0.65 (0.25, 1.7)	-8 (-18, 17)	Direct	MODERATE	Not serious	Not serious	MODERATE	NMA	RoB
Macrolide + Aminoglycoside vs Respiratory fluoroquinolones	NA	NA	0.49 (0.02, 12.79)	0.49 (0.02, 12.79)	-12 (-24, 283)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Tetracyclines vs Respiratory fluoroquinolones	0.68 (0.19, 2.38)	-8 (-19, 33)	NA	0.68 (0.19, 2.38)	-8 (-19, 33)	Direct	HIGH	Not serious	serious	MODERATE	NMA	Imprecision
Carbapenems vs Respiratory fluoroquinolones	NA	NA	1.12 (0.23, 5.55)	1.12 (0.23, 5.55)	3 (-18, 109)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Carbapenem + Macrolide vs Respiratory fluoroquinolones	NA	NA	0.13 (0, 4.6)	0.13 (0, 4.6)	-21 (-24, 86)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Other fluoroquinolones vs Respiratory fluoroquinolones	NA	NA	1.18 (0.04, 34.4)	1.18 (0.04, 34.4)	4 (-23, 802)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3

Cotrimoxazole vs Respiratory fluoroquinolones	NA	NA	3.25 (0.13, 82.85)	3.25 (0.13, 82.85)	54 (-21, 1000)	Indirect	HIGH	Not serious	Extremely serious	VERY LOW	NMA	Imprecisionx3
Teicoplanin + Other fluoroquinolone vs Respiratory fluoroquinolones	NA	NA	0.72 (0.1, 5.22)	0.72 (0.1, 5.22)	-7 (-22, 101)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs Penicillin + Other fluoroquinolone	NA	NA	0.61 (0.02, 21.65)	0.61 (0.02, 21.65)	-9 (-24, 496)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs β-Lactam/β-lactamase inhibitors	NA	NA	1.25 (0.33, 4.75)	1.25 (0.33, 4.75)	6 (-16, 90)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs β-Lactam/β-lactamase inhibitor + Macrolide	NA	NA	2.96 (0.44, 19.86)	2.96 (0.44, 19.86)	47 (-13, 453)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs 2nd generation cephalosporins	1.67 (0.21, 12.5)	16 (-19, 276)	4.36 (0.79, 24.11)	2.94 (0.79, 10.96)	47 (-5, 239)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs 3rd generation cephalosporins	NA	NA	2.36 (0.68, 8.25)	2.36 (0.68, 8.25)	33 (-8, 174)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs 4th generation cephalosporins	NA	NA	5.15 (0.45, 59.05)	5.15 (0.45, 59.05)	100 (-13, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs 5th generation cephalosporins	NA	NA	1.72 (0.4, 7.47)	1.72 (0.4, 7.47)	17 (-14, 155)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs 2nd generation cephalosporin + Macrolide	NA	NA	3.43 (0.12, 97.26)	3.43 (0.12, 97.26)	58 (-21, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs 3rd generation cephalosporin + Macrolide	NA	NA	1.36 (0.41, 4.52)	1.36 (0.41, 4.52)	9 (-14, 84)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	0.4 (0.03, 4.69)	0.4 (0.03, 4.69)	-14 (-23, 89)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs Macrolides	1.89 (0.38, 9.09)	21 (-15, 194)	1.68 (0.35, 8.09)	1.78 (0.58, 5.47)	19 (-10, 107)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Penicillins vs Macrolide + Aminoglycoside	NA	NA	2.38 (0.08, 71.05)	2.38 (0.08, 71.05)	33 (-22, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs Tetracyclines	NA	NA	1.71 (0.34, 8.46)	1.71 (0.34, 8.46)	17 (-16, 179)	Indirect	HIGH	Not serious	Very serious	LOW	NMA	Imprecisionx2
Penicillins vs Carbapenems	NA	NA	1.03 (0.16, 6.47)	1.03 (0.16, 6.47)	1 (-20, 131)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs Carbapenem + Macrolide	NA	NA	8.98 (0.22, 367.49)	8.98 (0.22, 367.49)	192 (-19, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs Other fluoroquinolones	NA	NA	0.98 (0.03, 30.07)	0.98 (0.03, 30.07)	0 (-23, 698)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillins vs Cotrimoxazole	NA	NA	0.36 (0.01, 10.51)	0.36 (0.01, 10.51)	-15 (-24, 228)	Indirect	HIGH	Not serious	Extremely serious	VERY LOW	NMA	Imprecisionx3
Penicillins vs Teicoplanin + Other fluoroquinolone	NA	NA	1.6 (0.18, 14)	1.6 (0.18, 14)	14 (-20, 312)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs β-Lactam/β-lactamase inhibitors	NA	NA	2.05 (0.06, 73.59)	2.05 (0.06, 73.59)	25 (-23, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs β-Lactam/β-lactamase inhibitor + Macrolide	4.76 (0.24, 100)	90 (-18, 1000)	NA	4.83 (0.24, 98.44)	92 (-18, 1000)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs 2nd generation cephalosporins	NA	NA	4.8 (0.13, 179.25)	4.8 (0.13, 179.25)	91 (-21, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs 3rd generation cephalosporins	NA	NA	3.86 (0.11, 132.74)	3.86 (0.11, 132.74)	69 (-21, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3

Penicillin + Other fluoroquinolone vs 4th generation cephalosporins	NA	NA	8.42 (0.14, 512.2)	8.42 (0.14, 512.2)	178 (-21, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs 5th generation cephalosporins	NA	NA	2.82 (0.08, 105.09)	2.82 (0.08, 105.09)	44 (-22, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs 2nd generation cephalosporin + Macrolide	NA	NA	5.6 (0.05, 606.14)	5.6 (0.05, 606.14)	110 (-23, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs 3rd generation cephalosporin + Macrolide	NA	NA	2.22 (0.07, 73.03)	2.22 (0.07, 73.03)	29 (-22, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	0.65 (0.01, 39.37)	0.65 (0.01, 39.37)	-8 (-24, 921)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Macrolides	NA	NA	2.9 (0.08, 101.85)	2.9 (0.08, 101.85)	46 (-22, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Macrolide + Aminoglycoside	NA	NA	3.88 (0.03, 442.42)	3.88 (0.03, 442.42)	69 (-23, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Tetracyclines	NA	NA	2.79 (0.07, 107.13)	2.79 (0.07, 107.13)	43 (-22, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Carbapenems	NA	NA	1.68 (0.04, 73.68)	1.68 (0.04, 73.68)	16 (-23, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Carbapenem + Macrolide	NA	NA	14.67 (0.18, 1178.23)	14.67 (0.18, 1178.23)	328 (-20, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Other fluoroquinolones	NA	NA	1.6 (0.01, 195.66)	1.6 (0.01, 195.66)	14 (-24, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Cotrimoxazole	NA	NA	0.58 (0.01, 64.74)	0.58 (0.01, 64.74)	-10 (-24, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Penicillin + Other fluoroquinolone vs Teicoplanin + Other fluoroquinolone	NA	NA	2.62 (0.05, 136.77)	2.62 (0.05, 136.77)	39 (-23, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs β-Lactam/β-lactamase inhibitor + Macrolide	NA	NA	2.36 (0.34, 16.34)	2.36 (0.34, 16.34)	33 (-16, 368)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs 2nd generation cephalosporins	2.8 (0.59, 13.38)	43 (-10, 297)	1.85 (0.32, 11.11)	2.34 (0.73, 7.57)	32 (-6, 158)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporins	1 (0.07, 15.12)	0 (-22, 339)	2.17 (0.59, 8.33)	1.89 (0.58, 6.12)	21 (-10, 123)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs 4th generation cephalosporins	NA	NA	4.11 (0.37, 45.69)	4.11 (0.37, 45.69)	75 (-15, 1000)	Indirect	LOW	Not serious	Extremely serious	VERY LOW	NMA	RoBx2, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs 5th generation cephalosporins	NA	NA	1.38 (0.34, 5.6)	1.38 (0.34, 5.6)	9 (-16, 110)	Indirect	LOW	Not serious	Very serious	VERY LOW	NMA	RoBx2, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs 2nd generation cephalosporin + Macrolide	NA	NA	2.74 (0.09, 78.99)	2.74 (0.09, 78.99)	42 (-22, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporin + Macrolide	NA	NA	1.08 (0.31, 3.77)	1.08 (0.31, 3.77)	2 (-17, 66)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	0.32 (0.03, 3.83)	0.32 (0.03, 3.83)	-16 (-23, 68)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs Macrolides	7 (0.37, 132.46)	144 (-15, 1000)	0.95 (0.22, 4.17)	1.42 (0.38, 5.27)	10 (-15, 102)	Direct	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Macrolide + Aminoglycoside	NA	NA	1.9 (0.06, 56.06)	1.9 (0.06, 56.06)	22 (-23, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3

β-Lactam/β-lactamase inhibitors vs Tetracyclines	NA	NA	1.36 (0.26, 7)	1.36 (0.26, 7)	9 (-18, 144)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
β-Lactam/β-lactamase inhibitors vs Carbapenems	NA	NA	0.82 (0.13, 5)	0.82 (0.13, 5)	-4 (-21, 96)	Indirect	LOW	Not serious	Extremely serious	VERY LOW	NMA	RoBx2, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs Carbapenem + Macrolide	NA	NA	7.17 (0.17, 297.96)	7.17 (0.17, 297.96)	148 (-20, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs Other fluoroquinolones	NA	NA	0.78 (0.03, 22.77)	0.78 (0.03, 22.77)	-5 (-23, 522)	Indirect	LOW	Not serious	Extremely serious	VERY LOW	NMA	RoBx2, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs Cotrimoxazole	NA	NA	0.28 (0.01, 8.54)	0.28 (0.01, 8.54)	-17 (-24, 181)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitors vs Teicoplanin + Other fluoroquinolone	NA	NA	1.28 (0.15, 10.72)	1.28 (0.15, 10.72)	7 (-20, 233)	Indirect	LOW	Not serious	Extremely serious	VERY LOW	NMA	RoBx2, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs 2nd generation cephalosporins	NA	NA	0.99 (0.13, 7.38)	0.99 (0.13, 7.38)	0 (-21, 153)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs 3rd generation cephalosporins	NA	NA	0.8 (0.13, 5.09)	0.8 (0.13, 5.09)	-5 (-21, 98)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs 4th generation cephalosporins	NA	NA	1.74 (0.11, 28.41)	1.74 (0.11, 28.41)	18 (-21, 658)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs 5th generation cephalosporins	NA	NA	0.58 (0.08, 4.32)	0.58 (0.08, 4.32)	-10 (-22, 80)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs 2nd generation cephalosporin + Macrolide	NA	NA	1.16 (0.03, 41.81)	1.16 (0.03, 41.81)	4 (-23, 979)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs 3rd generation cephalosporin + Macrolide	NA	NA	0.46 (0.08, 2.68)	0.46 (0.08, 2.68)	-13 (-22, 40)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	0.13 (0.01, 2.18)	0.13 (0.01, 2.18)	-21 (-24, 28)	Indirect	MODERATE	Not serious	Not serious	MODERATE	NMA	RoB
β-Lactam/β-lactamase inhibitor + Macrolide vs Macrolides	NA	NA	0.6 (0.09, 3.97)	0.6 (0.09, 3.97)	-10 (-22, 71)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs Macrolide + Aminoglycoside	NA	NA	0.8 (0.02, 31)	0.8 (0.02, 31)	-5 (-24, 720)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs Tetracyclines	NA	NA	0.58 (0.07, 4.51)	0.58 (0.07, 4.51)	-10 (-22, 84)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs Carbapenems	NA	NA	0.35 (0.04, 3.4)	0.35 (0.04, 3.4)	-16 (-23, 58)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs Carbapenem + Macrolide	3.04 (0.13, 73.46)	49 (-21, 1000)	NA	3.04 (0.13, 73.46)	49 (-21, 1000)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs Other fluoroquinolones	NA	NA	0.33 (0.01, 13.99)	0.33 (0.01, 13.99)	-16 (-24, 312)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs Cotrimoxazole	NA	NA	0.12 (0, 4.51)	0.12 (0, 4.51)	-21 (-24, 84)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
β-Lactam/β-lactamase inhibitor + Macrolide vs Teicoplanin + Other fluoroquinolone	NA	NA	0.54 (0.04, 7.02)	0.54 (0.04, 7.02)	-11 (-23, 144)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporins vs 3rd generation cephalosporins	0.7 (0.15, 3.17)	-7 (-20, 52)	0.97 (0.17, 5.56)	0.8 (0.26, 2.51)	-5 (-18, 36)	Direct	MODERATE	Not serious	Serious	LOW	NMA	RoB, Imprecision
2nd generation cephalosporins vs 4th generation cephalosporins	NA	NA	1.75 (0.16, 19.28)	1.75 (0.16, 19.28)	18 (-20, 439)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporins vs 5th generation cephalosporins	NA	NA	0.59 (0.15, 2.31)	0.59 (0.15, 2.31)	-10 (-20, 31)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	RoB, Imprecision

2nd generation cephalosporins vs 2nd generation cephalosporin + Macrolide	NA	NA	1.17 (0.04, 35.1)	1.17 (0.04, 35.1)	4 (-23, 818)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporins vs 3rd generation cephalosporin + Macrolide	NA	NA	0.46 (0.12, 1.78)	0.46 (0.12, 1.78)	-13 (-21, 19)	Indirect	MODERATE	Not serious	Not serious	MODERATE	NMA	RoB
2nd generation cephalosporins vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	0.14 (0.01, 1.73)	0.14 (0.01, 1.73)	-21 (-24, 18)	Indirect	MODERATE	Not serious	Not serious	MODERATE	NMA	RoB
2nd generation cephalosporins vs Macrolides	NA	NA	0.61 (0.15, 2.49)	0.61 (0.15, 2.49)	-9 (-20, 36)	Indirect	MODERATE	Not serious	Serious	LOW	NMA	RoB, Imprecision
2nd generation cephalosporins vs Macrolide + Aminoglycoside	NA	NA	0.81 (0.03, 24.04)	0.81 (0.03, 24.04)	-5 (-23, 553)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporins vs Tetracyclines	NA	NA	0.58 (0.1, 3.24)	0.58 (0.1, 3.24)	-10 (-22, 54)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporins vs Carbapenems	NA	NA	0.35 (0.06, 2.13)	0.35 (0.06, 2.13)	-16 (-23, 27)	Indirect	MODERATE	Not serious	Not serious	MODERATE	NMA	RoB
2nd generation cephalosporins vs Carbapenem + Macrolide	NA	NA	3.06 (0.07, 131.87)	3.06 (0.07, 131.87)	49 (-22, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporins vs Other fluoroquinolones	0.33 (0.01, 7.87)	-16 (-24, 165)	NA	0.33 (0.01, 7.87)	-16 (-24, 165)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporins vs Cotrimoxazole	NA	NA	0.12 (0, 3.79)	0.12 (0, 3.79)	-21 (-24, 67)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporins vs Teicoplanin + Other fluoroquinolone	NA	NA	0.55 (0.07, 4.48)	0.55 (0.07, 4.48)	-11 (-22, 84)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporins vs 4th generation cephalosporins	1.95 (0.13, 29.78)	23 (-21, 691)	2.56 (0.09, 100)	2.18 (0.26, 18.26)	28 (-18, 414)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporins vs 5th generation cephalosporins	0.73 (0.34, 1.57)	-6 (-16, 14)	NA	0.73 (0.34, 1.57)	-6 (-16, 14)	Direct	MODERATE	Not serious	Not serious	MODERATE	NMA	RoB
3rd generation cephalosporins vs 2nd generation cephalosporin + Macrolide	NA	NA	1.45 (0.05, 39.89)	1.45 (0.05, 39.89)	11 (-23, 933)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporins vs 3rd generation cephalosporin + Macrolide	NA	NA	0.57 (0.19, 1.71)	0.57 (0.19, 1.71)	-10 (-19, 17)	Indirect	MODERATE	Not serious	Not serious	MODERATE	NMA	RoB
3rd generation cephalosporins vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	0.17 (0.01, 1.9)	0.17 (0.01, 1.9)	-20 (-24, 22)	Indirect	MODERATE	Not serious	Not serious	MODERATE	NMA	RoB
3rd generation cephalosporins vs Macrolides	NA	NA	0.75 (0.21, 2.66)	0.75 (0.21, 2.66)	-6 (-19, 40)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporins vs Macrolide + Aminoglycoside	NA	NA	1.01 (0.04, 25.45)	1.01 (0.04, 25.45)	0 (-23, 587)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporins vs Tetracyclines	NA	NA	0.72 (0.16, 3.35)	0.72 (0.16, 3.35)	-7 (-20, 56)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporins vs Carbapenems	0.85 (0.03, 25)	-4 (-23, 576)	0.26 (0.02, 3.26)	0.44 (0.1, 1.86)	-13 (-22, 21)	Direct	MODERATE	Not serious	Not serious	MODERATE	NMA	RoB
3rd generation cephalosporins vs Carbapenem + Macrolide	NA	NA	3.8 (0.1, 151.2)	3.8 (0.1, 151.2)	67 (-22, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporins vs Other fluoroquinolones	NA	NA	0.41 (0.01, 11.92)	0.41 (0.01, 11.92)	-14 (-24, 262)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporins vs Cotrimoxazole	NA	NA	0.15 (0.01, 4.31)	0.15 (0.01, 4.31)	-20 (-24, 79)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3

3rd generation cephalosporins vs Teicoplanin + Other fluoroquinolone	0.68 (0.12, 3.98)	-8 (-21, 72)	NA	0.68 (0.12, 3.98)	-8 (-21, 72)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
4th generation cephalosporins vs 5th generation cephalosporins	NA	NA	0.33 (0.03, 3.2)	0.33 (0.03, 3.2)	-16 (-23, 53)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
4th generation cephalosporins vs 2nd generation cephalosporin + Macrolide	NA	NA	0.67 (0.01, 33.48)	0.67 (0.01, 33.48)	-8 (-24, 780)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
4th generation cephalosporins vs 3rd generation cephalosporin + Macrolide	NA	NA	0.26 (0.03, 2.73)	0.26 (0.03, 2.73)	-18 (-23, 42)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
4th generation cephalosporins vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	0.08 (0, 1.9)	0.08 (0, 1.9)	-22 (-24, 22)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
4th generation cephalosporins vs Macrolides	NA	NA	0.35 (0.03, 3.97)	0.35 (0.03, 3.97)	-16 (-23, 71)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
4th generation cephalosporins vs Macrolide + Aminoglycoside	NA	NA	0.46 (0.01, 17.79)	0.46 (0.01, 17.79)	-13 (-24, 403)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
4th generation cephalosporins vs Tetracyclines	NA	NA	0.33 (0.02, 4.43)	0.33 (0.02, 4.43)	-16 (-24, 82)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
4th generation cephalosporins vs Carbapenems	0.17 (0.01, 3.57)	-20 (-24, 62)	0.23 (0.01, 5.32)	0.2 (0.02, 1.76)	-19 (-24, 18)	Direct	MODERATE	Not serious	Not serious	MODERATE	NMA	RoB
4th generation cephalosporins vs Carbapenem + Macrolide	NA	NA	1.74 (0.03, 120.4)	1.74 (0.03, 120.4)	18 (-23, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
4th generation cephalosporins vs Other fluoroquinolones	NA	NA	0.19 (0, 10.04)	0.19 (0, 10.04)	-19 (-24, 217)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
4th generation cephalosporins vs Cotrimoxazole	NA	NA	0.07 (0, 3.6)	0.07 (0, 3.6)	-22 (-24, 62)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
4th generation cephalosporins vs Teicoplanin + Other fluoroquinolone	NA	NA	0.31 (0.02, 4.95)	0.31 (0.02, 4.95)	-17 (-24, 95)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
5th generation cephalosporins vs 2nd generation cephalosporin + Macrolide	NA	NA	1.99 (0.07, 59.67)	1.99 (0.07, 59.67)	24 (-22, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
5th generation cephalosporins vs 3rd generation cephalosporin + Macrolide	NA	NA	0.79 (0.21, 2.98)	0.79 (0.21, 2.98)	-5 (-19, 48)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
5th generation cephalosporins vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	0.23 (0.02, 2.93)	0.23 (0.02, 2.93)	-18 (-24, 46)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
5th generation cephalosporins vs Macrolides	NA	NA	1.03 (0.24, 4.51)	1.03 (0.24, 4.51)	1 (-18, 84)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
5th generation cephalosporins vs Macrolide + Aminoglycoside	NA	NA	1.38 (0.05, 38.15)	1.38 (0.05, 38.15)	9 (-23, 892)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
5th generation cephalosporins vs Tetracyclines	NA	NA	0.99 (0.18, 5.5)	0.99 (0.18, 5.5)	0 (-20, 108)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
5th generation cephalosporins vs Carbapenems	NA	NA	0.6 (0.12, 3.08)	0.6 (0.12, 3.08)	-10 (-21, 50)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
5th generation cephalosporins vs Carbapenem + Macrolide	NA	NA	5.21 (0.12, 224.22)	5.21 (0.12, 224.22)	101 (-21, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
5th generation cephalosporins vs Other fluoroquinolones	NA	NA	0.57 (0.02, 17.81)	0.57 (0.02, 17.81)	-10 (-24, 403)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
5th generation cephalosporins vs Cotrimoxazole	NA	NA	0.21 (0.01, 6.44)	0.21 (0.01, 6.44)	-19 (-24, 131)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3

5th generation cephalosporins vs Teicoplanin + Other fluoroquinolone	NA	NA	0.93 (0.13, 6.4)	0.93 (0.13, 6.4)	-2 (-21, 130)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolide vs 3rd generation cephalosporin + Macrolide	NA	NA	0.4 (0.02, 10.39)	0.4 (0.02, 10.39)	-14 (-24, 225)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolide vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	0.12 (0, 5.8)	0.12 (0, 5.8)	-21 (-24, 115)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolide vs Macrolides	NA	NA	0.52 (0.02, 14.56)	0.52 (0.02, 14.56)	-12 (-24, 325)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolide vs Macrolide + Aminoglycoside	NA	NA	0.69 (0.01, 66.98)	0.69 (0.01, 66.98)	-7 (-24, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolide vs Tetracyclines	NA	NA	0.5 (0.02, 15.4)	0.5 (0.02, 15.4)	-12 (-24, 346)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolide vs Carbapenems	NA	NA	0.3 (0.01, 10.68)	0.3 (0.01, 10.68)	-17 (-24, 232)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolide vs Carbapenem + Macrolide	NA	NA	2.62 (0.02, 316.64)	2.62 (0.02, 316.64)	39 (-24, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolide vs Other fluoroquinolones	NA	NA	0.29 (0, 29.7)	0.29 (0, 29.7)	-17 (-24, 689)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolide vs Cotrimoxazole	NA	NA	0.1 (0, 9.79)	0.1 (0, 9.79)	-22 (-24, 211)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
2nd generation cephalosporin + Macrolide vs Teicoplanin + Other fluoroquinolone	NA	NA	0.47 (0.01, 20.02)	0.47 (0.01, 20.02)	-13 (-24, 456)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Macrolide vs 3rd generation cephalosporin+ Other fluoroquinolone	NA	NA	0.29 (0.03, 3.1)	0.29 (0.03, 3.1)	-17 (-23, 50)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Macrolide vs Macrolides	NA	NA	1.31 (0.4, 4.25)	1.31 (0.4, 4.25)	7 (-14, 78)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Macrolide + Aminoglycoside	1.06 (0.02, 52.41)	1 (-24, 1000)	5.88 (0.01, 4096.68)	1.75 (0.07, 46.71)	18 (-22, 1000)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Macrolide vs Tetracyclines	NA	NA	1.26 (0.3, 5.26)	1.26 (0.3, 5.26)	6 (-17, 102)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Carbapenems	0.42 (0.02, 8.33)	-14 (-24, 176)	0.98 (0.13, 7.21)	0.76 (0.14, 3.99)	-6 (-21, 72)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
3rd generation cephalosporin + Macrolide vs Carbapenem + Macrolide	NA	NA	6.61 (0.17, 252.13)	6.61 (0.17, 252.13)	135 (-20, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Macrolide vs Other fluoroquinolones	NA	NA	0.72 (0.02, 22.38)	0.72 (0.02, 22.38)	-7 (-24, 513)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Macrolide vs Cotrimoxazole	NA	NA	0.26 (0.01, 7.16)	0.26 (0.01, 7.16)	-18 (-24, 148)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin + Macrolide vs Teicoplanin + Other fluoroquinolone	NA	NA	1.18 (0.15, 9.43)	1.18 (0.15, 9.43)	4 (-20, 202)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin+ Other fluoroquinolone vs Macrolides	NA	NA	4.45 (0.38, 51.65)	4.45 (0.38, 51.65)	83 (-15, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin+ Other fluoroquinolone vs Macrolide + Aminoglycoside	NA	NA	5.96 (0.11, 316.19)	5.96 (0.11, 316.19)	119 (-21, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin+ Other fluoroquinolone vs Tetracyclines	NA	NA	4.28 (0.32, 56.51)	4.28 (0.32, 56.51)	79 (-16, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3

3rd generation cephalosporin+ Other fluoroquinolone vs Carbapenems	NA	NA	2.58 (0.16, 40.9)	2.58 (0.16, 40.9)	38 (-20, 958)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin+ Other fluoroquinolone vs Carbapenem + Macrolide	NA	NA	22.5 (0.33, 1543.18)	22.5 (0.33, 1543.18)	516 (-16, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin+ Other fluoroquinolone vs Other fluoroquinolones	NA	NA	2.45 (0.04, 141.72)	2.45 (0.04, 141.72)	35 (-23, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin+ Other fluoroquinolone vs Cotrimoxazole	NA	NA	0.89 (0.02, 46.07)	0.89 (0.02, 46.07)	-3 (-24, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
3rd generation cephalosporin+ Other fluoroquinolone vs Teicoplanin + Other fluoroquinolone	NA	NA	4.02 (0.2, 80.65)	4.02 (0.2, 80.65)	72 (-19, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolides vs Macrolide + Aminoglycoside	NA	NA	1.34 (0.04, 39.96)	1.34 (0.04, 39.96)	8 (-23, 935)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolides vs Tetracyclines	NA	NA	0.96 (0.2, 4.67)	0.96 (0.2, 4.67)	-1 (-19, 88)	Indirect	MODERATE	Not serious	Very serious	VERY LOW	NMA	RoB, Imprecisionx2
Macrolides vs Carbapenems	NA	NA	0.58 (0.09, 3.65)	0.58 (0.09, 3.65)	-10 (-22, 64)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolides vs Carbapenem + Macrolide	NA	NA	5.05 (0.12, 205)	5.05 (0.12, 205)	97 (-21, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolides vs Other fluoroquinolones	NA	NA	0.55 (0.02, 17.58)	0.55 (0.02, 17.58)	-11 (-24, 398)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolides vs Cotrimoxazole	NA	NA	0.2 (0.01, 5.86)	0.2 (0.01, 5.86)	-19 (-24, 117)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolides vs Teicoplanin + Other fluoroquinolone	NA	NA	0.9 (0.1, 7.93)	0.9 (0.1, 7.93)	-2 (-22, 166)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Tetracyclines	NA	NA	0.72 (0.02, 23.85)	0.72 (0.02, 23.85)	-7 (-24, 548)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Carbapenems	0.39 (0.02, 8.33)	-15 (-24, 176)	2.19 (0, 3746.67)	0.43 (0.02, 8.61)	-14 (-24, 183)	Direct	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Carbapenem + Macrolide	NA	NA	3.78 (0.03, 480.72)	3.78 (0.03, 480.72)	67 (-23, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Other fluoroquinolones	NA	NA	0.41 (0, 42.49)	0.41 (0, 42.49)	-14 (-24, 996)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Cotrimoxazole	NA	NA	0.15 (0, 14.91)	0.15 (0, 14.91)	-20 (-24, 334)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Macrolide + Aminoglycoside vs Teicoplanin + Other fluoroquinolone	NA	NA	0.67 (0.02, 26.86)	0.67 (0.02, 26.86)	-8 (-24, 621)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Tetracyclines vs Carbapenems	NA	NA	0.6 (0.08, 4.61)	0.6 (0.08, 4.61)	-10 (-22, 87)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Tetracyclines vs Carbapenem + Macrolide	NA	NA	5.26 (0.12, 233.19)	5.26 (0.12, 233.19)	102 (-21, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Tetracyclines vs Other fluoroquinolones	NA	NA	0.57 (0.02, 20.97)	0.57 (0.02, 20.97)	-10 (-24, 479)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Tetracyclines vs Cotrimoxazole	0.21 (0.01, 4.17)	-19 (-24, 76)	NA	0.21 (0.01, 4.12)	-19 (-24, 75)	Direct	HIGH	Not serious	Extremely serious	VERY LOW	NMA	Imprecisionx3
Tetracyclines vs Teicoplanin + Other fluoroquinolone	NA	NA	0.94 (0.09, 9.79)	0.94 (0.09, 9.79)	-1 (-22, 211)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Carbapenems vs Carbapenem + Macrolide	NA	NA	8.72 (0.17, 438.39)	8.72 (0.17, 438.39)	185 (-20, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3

Carbapenems vs Other fluoroquinolones	NA	NA	0.95 (0.02, 36.22)	0.95 (0.02, 36.22)	-1 (-24, 845)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Carbapenems vs Cotrimoxazole	NA	NA	0.35 (0.01, 12.78)	0.35 (0.01, 12.78)	-16 (-24, 283)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Carbapenems vs Teicoplanin + Other fluoroquinolone	NA	NA	1.56 (0.16, 15.38)	1.56 (0.16, 15.38)	13 (-20, 345)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Carbapenem + Macrolide vs Other fluoroquinolones	NA	NA	0.11 (0, 14.88)	0.11 (0, 14.88)	-21 (-24, 333)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Carbapenem + Macrolide vs Cotrimoxazole	NA	NA	0.04 (0, 4.93)	0.04 (0, 4.93)	-23 (-24, 94)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Carbapenem + Macrolide vs Teicoplanin + Other fluoroquinolone	NA	NA	0.18 (0, 10.64)	0.18 (0, 10.64)	-20 (-24, 231)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Other fluoroquinolones vs Cotrimoxazole	NA	NA	0.36 (0, 38.95)	0.36 (0, 38.95)	-15 (-24, 911)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Other fluoroquinolones vs Teicoplanin + Other fluoroquinolone	NA	NA	1.64 (0.04, 73.05)	1.64 (0.04, 73.05)	15 (-23, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3
Cotrimoxazole vs Teicoplanin + Other fluoroquinolone	NA	NA	4.51 (0.1, 200.51)	4.51 (0.1, 200.51)	84 (-22, 1000)	Indirect	MODERATE	Not serious	Extremely serious	VERY LOW	NMA	RoB, Imprecisionx3

RR: relative risk; RD: risk difference; CI: confidence interval, NA: not applicable (no evidence), ROB: risk of bias

[1] The baseline risk was derived from the median of risk of event across the arms that randomized patients to the respiratory fluoroquinolones.

[2] Risk difference was calculated through applying the relative risk to the baseline risk. In cases that upper limit of confidence interval exceeded 1000, we truncated the value and reported 1000 as the upper limit.

Supplement 16. Definition of treatment failure across included trials in the review

First author, year	Treatment failure definition
Anzueto, 2006	Failure to respond or insufficient improvement of the signs and symptoms of infection such that additional antimicrobial therapy was required.
Aquino, 1994	Not reported.
Aubier, 1998	Persistence of fever, chills, chest pains, cough, or dyspnea, and sputum production.
Aufiero, 1997	Persistence or worsening of signs and symptoms for 72 hours or more after the start of therapy with the study drug and clinical decision to change the antimicrobial agent.
Barrera, 2016	Lack of resolution; worsening of baseline symptoms or development of new symptoms; or need for new antibacterial treatment.
Bartoloni, 1999	No improvement or deterioration of signs and symptoms; or initial improvement at the end of therapy, followed by a general decline and worsening of clinical condition at follow-up.
Bergallo, 2009	Persistence, lack of improvement, or worsening of signs and symptoms of pneumonia and chest radiographs; need for further antibiotic therapy; or development of new signs and symptoms of pneumonia.
Berman, 1997	No change in or worsening of clinical signs and symptoms of infection requiring change in antibiotics or infection-related death after 48 hours of treatment.
Bertrand, 1988	Failure to achieve apyrexia with disappearance of general, functional and clinical signs, and normalization or decrease of radiologic findings.
Bittner, 1986	No apparent improvement in clinical findings.
Bonfitto, 1999	Persistence or lack of improvement in baseline signs, symptoms and radiologic features.
Brambilla, 1992	Persistence of signs and symptoms of infection at the end of treatment.
Carbon, 1992	All signs and symptoms persisted posttreatment or when clinical improvement appeared inordinately slow (i.e., a temperature of >37.80C and/or continued respiratory symptoms), justifying treatment modification.
Castro, 1986	Persistence of clinical signs and symptoms.
Chaudhary, 2018	Persistence or progression of most or all pre-therapy signs and symptoms; use of additional antibiotics for the current infection; development of new symptoms, radiologic findings and complications of pneumonia such as empyema or lung abscess; or death related to pneumonia.
Chen, 2014	Continued or incomplete disappearance or deterioration of all signs and symptoms at the time of inclusion at follow-up after treatment; new signs or symptoms of the disease appear; or other antibacterial treatments for the disease are used.
Colardyn, 1996	Patient's condition was unchanged or worse or when infection relapsed after treatment during the 2-4 weeks follow-up.
Correa, 2003	Progression of primary signs and symptoms; development of new findings consistent with pneumonia; or death due to pneumonia.
Covington, 2013	Not reported.
Dal Negro, 2001	No change/worsened, symptom score was >80% of the baseline score and there was evidence of bacterial resistance in culture.
Dall, 1986	No objective improvement, or deterioration of symptoms and signs of infection during therapy.
de Celis, 2002	Not reported.
Ebright, 1983	Persistence of fever and purulent sputum production during antibiotic administration.
Edelstein, 1991	Persistent, increased, or new clinical signs or symptoms of respiratory infection at follow-up or a new infiltrate on post-therapy chest X-ray.
Fang, 2019	After the treatment, clinical symptoms and signs, laboratory test indices and pathogen examination indices were not improved.
Feldman, 2001	Not reported.
File, 2019	Persistent of signs and symptoms such that additional antibacterial therapy was administered.
File, 1983	No appreciable change or worsening of symptoms by the completion of

	therapy
File, 2011	Persistence in signs and symptoms of pneumonia including fever or lack of improvement of signs and symptoms that required further antimicrobial therapy.
File, 2016	Lack of improvement at 72 hours after the first dose in at least 2 of the 4 cardinal symptoms; or need for another antibiotic.
Finch, 2002	Failure to respond or and an insufficient response to the study drug that required a modification in antibacterial therapy or that resulted in death from the primary diagnosis.
Fink, 1994	Insufficient lessening of the signs and symptoms of infection such that additional therapy was necessary.
Fogarty, 2004	No apparent response to therapy or as an incomplete response requiring additional antimicrobial therapy.
Frank, 2002	Persistence of pretreatment clinical signs and symptoms and need for additional antimicrobial therapy or incomplete resolution in clinical findings during therapy or at follow-up evaluation in a patient not requiring additional antimicrobial therapy.
Gaillat, 1994	Fever or chest X-ray abnormalities remained unchanged, worsened or relapsed; death of infectious origin occurred; or antibiotic regimen was modified, for whatever reason.
Garcìa-Contreras, 2000	Persistence or worsening in signs and symptoms.
Geckler, 1984	No objective improvement or deterioration in symptoms and signs of infection during therapy; or progression of the original infection or development of a superinfection.
Geerts, 1971	Persistence of fever, cough, dyspnea, auscultation findings, elevated sedimentation rate, or radiologic findings.
Genne, 1997	Persistence or progression of all signs and symptoms after 3 to 5 days of therapy; development of new pulmonary or extrapulmonary clinical findings consistent with active infection; persistence or progression of radiographic abnormalities; death due to pneumonia; or inability to complete the study because of adverse effects.
Gotfried, 1997	No improvement in signs and symptoms.
Grieco, 1982	Lack of reduction in clinical signs and symptoms of pneumonia.
Grossman, 1999	Lack of resolution of signs and symptoms or progression in chest X-ray findings.
Hirata-Dulas, 1991	Death during the study regardless of whether or not it was related to study drug administration; early termination of the study drug due to lack of improvement, adverse event, or superinfection,
Ho, 1997	Lack clinical improvement and/or radiological deterioration after initial therapy.
Horcajada, 2019	Lack of improvement or worsening in chest pain, frequency or severity of cough, amount and quality of productive sputum, dyspnea, or other symptoms.
Huang, 2023	Not reported.
Issei Oi, 2020	Not reported.
Ito, 2010	Deterioration of signs and symptoms, lack of resolution, or need for alternative antibiotic(s) for pneumonia.
Izadi, 2018	Clinical deterioration; or antibiotic escalation.
Jardim, 2003	Insufficient reduction in infection-related signs and symptoms such that the patient required additional or alternative antibiotic treatment; or death due to pneumonia.
Kalbermatter, 2000	Lack of resolution of fever and radiological findings.
Keeton, 1983	Not reported.
Kouno, 2003	No alleviation of subjective and objective symptoms; disappearance or alleviation of subjective and objective symptoms was noted, but the study drug was administered systemically for the primary disease during the period until the final assessment day.
Kouno, 2011	No improvement in fever, X-ray findings, leucocytosis, or CRP level.
Kuzman, 2005	Lack of improvement or progression or recurrence of signs and symptoms of pneumonia after at least 72 hours of study treatment necessitating the institution of rescue therapy; death from pneumonia; or institution of alternative antimicrobial therapy due to adverse event related study drug discontinuation
LeFrock, 1982	Persistent infection or adverse reactions necessitating a change of antibiotic therapy.

Leophonte, 1993	Persistence, worsening or recurrence of one or more symptoms of infection.
Leophonte, 2004	insufficient improvement or deterioration of signs and symptoms such that additional antibacterial therapy was required.
Leroy, 2005	Any modification of antimicrobial treatment that was motivated by the isolation of a causative organism resistant to the study medication; lack of clinical improvement 3 days after treatment initiation (i.e., worsening or persistent fever or hypothermia, or worsening of pulmonary infiltrates or respiratory function as assessed by Pao2/Fio2 ratio); insufficient clinical response; secondary clinical deterioration due to sepsis-related complications (i.e., septic shock or ARDS); lower respiratory tract superinfection; or the occurrence of an adverse event.
Leuenberger, 1983	Persistence or worsening of signs and symptoms.
Li, 2007	No significant improvement or aggravation of signs and symptoms after 72 hours of treatment.
Li, 2024	Persistence or worsening of main baseline symptoms, signs, laboratory abnormalities related to pneumonia; emergence of new symptoms or signs related to pneumonia made the patient's condition worse, chest X-ray film or CT scans showed deterioration of the disease; occurrence of complex complications, such as empyema or lung abscess; requiring other antibacterial drugs to target pneumonia due to treatment failure; or death due to pneumonia.
Lin, 2007	No improvement or worsening of condition after 72 hours of medication.
Lin, 2007	No apparent response to therapy or an incomplete response requiring additional antimicrobial therapy.
Lin, 2007	No significant improvement or aggravation of signs and symptoms after 72 hours of treatment.
Lode, 2002	Insufficient improvement or deterioration in the signs and symptoms recorded at screening, such that additional antimicrobial therapy was indicated.
López-Véjar, 2013	Lack of improvement in leukocytosis, fever, sputum, dyspnea and need for ventilatory support.
Low, 2011	Persistence, incomplete clinical resolution, or worsening in signs and symptoms that required alternative antimicrobial therapy.
McCabe, 1993	Persistence or worsening of signs and symptoms of infection.
Miyazaki, 2019	No improvement in fever, X-ray findings, leucocytosis, or CRP level.
Moola, 1999	No improvement during or after treatment; discontinuation of therapy because of drug related adverse event; Resolution or improvement after treatment with recurrence of clinical symptoms, including radiographic evidence, at follow-up; or significant deviations from protocol.
Mouton, 1995	No improvement or deterioration in signs and symptoms.
Ni, 2012	No significant improvement in symptoms, pulmonary signs and chest X-ray; or need to administration of other antibiotics.
Nicholson, 2012	Persistence in signs and symptoms of infection (return to pre-infection status) or lack of sufficient improvement that required further antibacterial therapy; or lack of improvement in findings on the chest radiograph.
Nicolle, 1996	Worsening of clinical condition by day 3 or lack of improvement by day 5.
Norbby, 1998	All infection-related signs and symptoms unchanged or worsened; patient developed new clinical findings consistent with active infection which did not improve or disappear at clinical endpoint; patient died due to the infection; study drug discontinued due to clinical and/or bacteriological treatment failure; or one or more antibiotics were added to the study drug due to treatment failure.
Oh, 1996	Lack of resolution of clinical symptoms and signs at the end of treatment.
Ortiz-Ruiz, 2002	Not reported.
Ortqvist, 1996	Clinical failure and no radiological improvement.
Paladino, 2007	Persistence or progression of symptoms and signs of pneumonia; development of new pulmonary or extrapulmonary clinical findings consistent with active infection; persistence or progression of radiographic abnormalities; death due to pneumonia; inability to complete study antibiotic treatment because of adverse events; or treatment required with another antimicrobial regimen.

Pariente, 1988	Lack of improvement in signs and symptoms after 2 to 4 days.
Peng, 2006	Persistence or worsening in signs and symptoms.
Pertel, 2008	Symptoms and signs persisted or progressed; death; or the study therapy was stopped because of an adverse event.
Petermann, 2001	Persistence or progression of signs and symptoms of pneumonia; development of new pulmonary or extrapulmonary clinical findings consistent with active infection; persistence or progression of radiographic abnormalities at the long-term follow-up visit (14–21 days posttherapy); requirement for additional or alternative non-protocol anti-infective agents to treat pneumonia; rehospitalization due to clinical relapse of pneumonia caused by the baseline organism(s); or death due to the pneumonia present at admission.
Peterson, 1988	Lack of clinical response or worsening of respiratory infection with study drug resulting in addition of or change to another antibiotic; death; or need for additional or alternative antibiotic therapy to achieve clinical cure.
Phillips, 1993	Not reported.
Plouffe, 2000	Persistence or progression of signs and symptoms after 3 days of therapy; development of new findings consistent with active infection; persistence or progression of radiographic findings; death due to pneumonia; or inability to complete the study because of pneumonia-related adverse events.
Poirier, 1991	Not reported.
Poirier, 1999	Persistence without improvement of all clinical signs (fever, chills, chest pain, dyspnea) and radiologic anomalies present at inclusion.
Portier, 1996	Lack of resolution of signs and symptoms or improvement in radiographic signs.
Portier, 2005	Persistence or worsening of clinical symptoms requiring modification of the antibacterial regimen; or death attributed to pneumonia.
Rahlwes, 1988	Not reported.
Rizzato, 1992	Not reported.
Rizzato, 1993	Not reported.
Rizzato, 1995	Not reported.
Rizzato, 1997	Not reported.
Romanelli, 2002	No improvement or deterioration of signs and symptoms; or initial cure or improvement at the end of therapy, followed by a general decline and worsening of the clinical condition at follow-up.
Roson, 2001	Lack of improvement; superinfection; inability to complete treatment due to adverse events; or death by any cause.
Rossoff, 1995	Lack of significant improvement in signs and symptoms.
Samsonov, 2023	Lack of resolution or worsening of signs and symptoms; appearance of new signs and symptoms of pneumonia; requirement for additional antibiotic therapy; or lack improvement in chest roentgenograms (CT scans).
San Pedro, 2002	Persistence or progression of the signs and symptoms after at least 2 days of therapy; or administration of a potentially effective non-study antibiotic during treatment due to lack of efficacy.
Seki, 2009	Persistence of fever >37.5℃, chill, chest pain, cough and difficulty in Breathing.
Shao, 2008	Not reported.
Shlaes, 1994	Failure to improve in at least three clinical efficacy parameters; or requiring a change in antibacterial therapy.
Speich, 1998	No response to at least 48 h of antibiotic therapy; worsening of the clinical condition due to infection; death; or adequate initial response followed by a worsening of the clinical condition due to the occurrence of a bacterial or fungal infection within 7 days of stopping treatment.
Stets, 2019	No improvement or worsening of symptoms; requiring alternative (rescue) antibacterial treatment; or discontinuation of study drug due to adverse events.
Stille, 2000	Lack of improvement in clinical signs and symptoms, such as fever, cough, dyspnea, purulent discharge, and pleural pain.

Sturm, 1998	Not reported.
Tanaseanu, 2009	Persistence or worsening in signs and symptoms of the acute process with either failure to show improvement in the clinical findings, initial improvement in signs and symptoms followed by clinically significant worsening before the test-of-cure assessment; need for additional antimicrobial therapy, progression of chest radiograph abnormalities, or death after study day 2 because of pneumonia.
Thadepalli, 1991	Not reported.
Tieying, 2014	Persistence or progression of baseline clinical signs or symptoms of infection; partial improvement of baseline clinical signs and symptoms of infection but needed to change or add treatment options.
Torres, 2008	I.nsufficient lessening of the signs and symptoms of infection such that additional or alternative antimicrobial therapy was required
Tremolieres, 1998	Lack of resolution of chest radiograph findings, signs and symptoms, and/or requirement for additional antibiotics for inadequate response; clinical cure or improvement at treatment end with failure at a subsequent visit; or clinical cure or improvement at treatment end but receipt of additional antibiotic therapy for the primary disease before study end.
Vergis, 2000	Failure of symptoms and signs of pneumonia to resolve.
Vetter, 1997	No improvement in signs/symptoms.
Vetter, 2002	Death, worsening of signs and symptoms, emergence of new signs and symptoms of pneumonia, and/or treatment with additional antimicrobial therapy for pneumonia.
Vogel, 1991	Evidence of continued fever, or worsening of clinical signs, symptoms or radiographic findings after at least three full days of therapy.
Wallace, 1981	Not reported.
Wallace, 1982	Not reported.
Watanabe, 2010	No improvement in fever, X-ray findings, leucocytosis, or CRP level.
Weber, 1987	Death; progressive pulmonary infection; failure to improve after prolonged antibiotic administration (>10 days); or development of metastatic infection due to the initial pulmonary pathogen.
Williams, 1994	No significant improvement in signs and symptoms.
Wolff, 1997	Persistence or progression of symptoms of pneumonia or worsening of chest X-ray leading to replacement of study drugs by another antibiotic (switch); invasive superinfection; or death due to pneumonia or superinfection.
Xu, 2006	Insufficient lessening of signs and symptoms of infection, chest X-ray results showing bilateral or multilobe involvement, such that additional or alternative antimicrobial therapy was required.
Yamamoto, 2013	Not reported.
Yanagihara, 2006	Persistence of chest pain, cough and sputum, and difficulty breathing.
Yang, 2007	Not reported.
Yang, 2009	Persistence or worsening in signs and symptoms; or death.
Yang, 2009	No significant improvement or aggravation of signs and symptoms after 72 hours of treatment.
Yaqub, 2005	Incomplete resolution of signs and symptoms
Zervos, 1998	Failure to resolve signs and symptoms of pneumonia or progression of infection on chest radiography.
Zervos, 2004	Lack of resolution or deterioration of any of the signs/symptoms of pneumonia and a need for additional antibiotic(s).
Zhong, 2014	Persistence, incomplete clinical resolution, or worsening in signs and symptoms of that required alternative antimicrobial treatment; treatment-limiting adverse events that led to discontinuation of the study drugs; requiring alternative antimicrobial treatment for community-acquired pneumonia; or death by any cause within 28 days of the end of treatment.
Zuck, 1990	Clinical infection and the chest X-ray remained unchanged or worsened.

Supplement 17. Secondary analysis of treatment failure with individual antibiotic regimens as separate nodes (N=129 RCTs)

| Ceftaroline | | |

Supplement 18. Pairwise comparisons of reported effects on the risk of acute kidney injury

Comparisons		RR (95% CI)	Certainty of evidence
5th generation cephalosporins vs 3rd generation cephalosporins			
File (2011)	Ceftriaxone vs Ceftaroline	6.77 (0.35, 125.00)	
Low (2011)	Ceftriaxone vs Ceftaroline	0.51 (0.05, 5.62)	
Overall		1.60 (0.13, 19.61)	Very low [b]
Tetracyclines vs respiratory fluoroquinolones			
Stets (2019)	Omadacycline vs Moxifloxacin	0.20 (0.01, 4.14)	Very low [b]
β-lactam/β-lactamase inhibitors vs 3rd generation cephalosporins			
Watanabe (2010)	Piperacillin-tazobactam vs Ceftazidime	3.04 (0.12, 71.43)	Very low [a, b]
β-lactam/β-lactamase inhibitors vs macrolide			
Genne (1997)	Amoxicillin-clavulanate vs Clarithromycin	3.00 (0.12, 72.10)	Very low [a, b]
Respiratory fluoroquinolones vs penicillins			
Carbon (1992)	Temafloxacin vs Amoxicillin	2.92 (0.12, 71.43)	Very low [b]
A β-lactam/β-lactamase inhibitor plus an aminoglycoside vs β-lactam/β-lactamase inhibitor alone			
Speich (1998)	Amoxicillin-clavulanate plus an Aminoglycoside vs Piperacillin-tazobactam	4.89 (0.24, 99.08)	Very low [a, b]
3rd generation cephalosporins vs teicoplanin plus other fluoroquinolones			
Rizzato (1997)	Ceftriaxone vs Teicoplanin plus Ciprofloxacin	3.05 (0.12, 74.13)	Very low [a, b]
A carbapenem plus a macrolide vs a β-lactam/β-lactamase inhibitor plus a macrolide			
Ito (2010)	Imipenem plus Erythromycin vs Piperacillin-tazobactam plus Erythromycin	2.96 (0.12, 71.70)	Very low [a, b]
Comparisons with the same treatment nodes			
Horcajada (2019)	Moxifloxacin vs Delafloxacin	3.01 (0.12, 71.43)	Very low [b]
Poirier (1991)	Roxithromycin vs Clarithromycin	3.24 (0.13, 76.92)	Very low [a, b]
Wallace (1982)	Cefamandole vs Cefonicid	1.69 (0.04, 80.29)	Very low [a, b]

RR: relative risk; CI: confidence interval
a Due to serious risk of bias
b Due to extremely serious imprecision in effect estimate

Supplement 19. Network meta-regression analyses results

	RR vs respiratory fluoroquinolones (95% CI) for the interaction	Test of interaction p-value	Credibility of effect modification [a]
Severity of pneumonia (proportion with severe CAP)			
For both treatment failure and all-cause mortality, there was insufficient data to conduct the network meta-regression (see the subgroup analysis for severity of pneumonia).			
Risk of bias (high vs low for each domain)			
None of the comparisons with at least one study in each subgroup proved a test of interaction p-value of less than 0.05 for any of the outcomes.			
Study year			
None of the comparisons with enough variability in the data to conduct the network meta-regression proved a test of interaction p-value of less than 0.05 for treatment failure and all-cause mortality.			
Geographical region			
None of the comparisons with at least one study in each subgroup proved a test of interaction p-value of less than 0.05 for treatment failure and all-cause mortality.			
Follow-up time (days since end of treatment)			
Treatment failure			
5th generation cephalosporins alone	0.59 (0.41, 0.85)	0.005	Low; between trial comparison, lack of direct evidence, and the direction of the effect modification inconsistent with the hypothesis.
Other comparisons with enough variability in data to conduct the network meta-regression proved the test of interaction p-value of greater than 0.05.			
All-cause mortality			
None of the comparisons with enough variability in data to conduct the network meta-regression proved the test of interaction p-value of less than 0.05.			
Age (≤65 years versus >65 years)			
None of the comparisons with at least one study in each subgroup proved a test of interaction p-value of less than 0.05 for treatment failure and all-cause mortality.			

RR: relative risk; CI: confidence interval

[a] We evaluated the credibility of effect modification when the test of interaction p-value was less than 0.05.

Supplement 20. Subgroup analyses by severity of pneumonia (severe vs moderate) for critical outcomes

	N of trials	RR (95% CI)	Test of interaction p-value	Credibility of effect modification
Treatment failure				
Carbapenems alone vs 3rd generation cephalosporins alone			0.038	Low; between trial comparison, very small number of trials, and chance is a likely explanation of the effect modification.
Severe	2	0.35 (0.15, 0.85)		
Moderate	4	0.93 (0.69, 1.25)		
β-Lactam/β-lactamase inhibitors alone vs carbapenems alone			0.878	NA
Severe	1	0.75 (0.02, 32.68)		
Moderate	2	0.55 (0.23, 1.31)		
3rd generation cephalosporins alone vs 4th generation cephalosporins alone			0.855	NA
Severe	1	0.95 (0.59, 1.50)		
Moderate	4	1.01 (0.58, 1.75)		
3rd generation cephalosporins alone vs 5th generation cephalosporins alone			0.875	NA
Severe	1	1.35 (1.08, 1.69)		
Moderate	4	1.71 (0.09, 32.93)		
A 3rd generation cephalosporin plus a macrolide vs respiratory fluoroquinolones alone			0.942	NA
Severe	1	1.31 (0.68, 2.50)		
Moderate	7	1.27 (0.90, 1.80)		
Respiratory fluoroquinolones alone vs tigecycline			0.855	NA
Severe	1	1.50 (0.05, 49.07)		
Moderate	2	1.08 (0.79, 1.49)		
All-case mortality				
Carbapenems alone vs 3rd generation cephalosporins alone			0.102	NA
Severe	1	0.38 (0.11. 1.35)		
Moderate	3	1.39 (0.57, 3.34)		
A 3rd generation cephalosporin plus a macrolide vs respiratory fluoroquinolones alone			0.206	NA
Severe	1	0.58 (0.26, 1.28)		
Moderate	6	1.14 (0.57, 2.25)		

RR: relative risk; CI: confidence interval, N: number; NA: not applicable (we evaluated the credibility of effect modification when the test of interaction p-value was less than 0.05)

Supplement 21. Sensitivity analyses – excluding trials in which at least 80% of participants had severe CAP

Antibiotic regimen vs respiratory fluoroquinolones alone	Treatment failure		All-cause mortality	
	RR (95%CI)	RD (95%CI)	RR (95%CI)	RD (95%CI)
Baseline risk [a]	132 per 1000 patients		23 per 1000 patients	
Minimal important difference [b]	20 per 1000 patients		5 per 1000 patients	
Lefamulin	0.98 (0.67, 1.44)	-3 (-44, 58)		
β-Lactam/β-lactamase inhibitors alone	1.13 (0.86, 1.47)	17 (-18, 62)	1.00 (0.53, 1.9)	0 (-11, 21)
A β-lactam/β-lactamase inhibitor plus a macrolide	1.14 (0.84, 1.55)	19 (-21, 73)	1.52 (0.8, 2.86)	12 (-5, 43)
5th generation cephalosporins alone	1.04 (0.73, 1.49)	6 (-36, 64)	0.98 (0.47, 2.03)	0 (-12, 24)
Carbapenems alone	1.22 (0.82, 1.83)	29 (-24, 109)	1.12 (0.51, 2.45)	3 (-11, 33)
Penicillins alone	1.26 (0.94, 1.69)	34 (-8, 91)	1.12 (0.54, 2.34)	3 (-11, 31)
3rd generation cephalosporins alone	1.34 (1.00, 1.80)	45 (0, 106)	1.01 (0.64, 1.59)	0 (-8, 14)
A 3rd generation cephalosporin plus a macrolide	1.31 (0.92, 1.9)	35 (-10, 116)	1.14 (0.57, 2.25)	3 (-10, 29)
2nd generation cephalosporins alone	1.42 (0.93, 2.16)	55 (-9, 153)	1.35 (0.55, 3.32)	8 (-10, 53)
Tetracyclines alone [c]	0.77 (0.46, 1.27)	-31 (-71, 35)	2.08 (0.66, 6.59)	25 (-8, 128)
A 2nd generation cephalosporin plus a macrolide	1.07 (0.76, 1.5)	10 (-31, 66)	0.59 (0.23, 1.51)	-9 (-18, 12)
4th generation cephalosporins alone	1.17 (0.75, 1.85)	23 (-33, 112)	1.22 (0.59, 2.52)	5 (-9, 35)
A 3rd generation cephalosporin plus a respiratory fluoroquinolone	0.79 (0.53, 1.18)	-27 (-62, 24)	0.67 (0.33, 1.38)	-8 (-15, 9)
A carbapenem plus a macrolide	1.06 (0.61, 1.85)	8 (-52, 112)	2.49 (1.01, 6.18)	34 (0, 119)
Third generation cephalosporin/β-lactamase inhibitors alone	0.37 (0.13, 1.01)	-84 (-114, 1)	0.97 (0.02, 48.96)	-1 (-23, 1000)
A 2nd generation cephalosporin plus a tetracycline	1.08 (0.53, 2.19)	10 (-62, 158)		

	Among the best	Not different from respiratory fluoroquinolones alone	Among the worst
High / Moderate certainty	(Probably) better than respiratory fluoroquinolones alone and some alternatives	(Probably) results in little or no difference compared with respiratory fluoroquinolones alone	(Probably) inferior to respiratory fluoroquinolones alone and some alternatives
Low certainty	May be better than respiratory fluoroquinolones alone and some alternatives	May result in little or no difference compared with respiratory fluoroquinolones alone	May be inferior to respiratory fluoroquinolones alone and some alternatives
Ver low certainty	We are very uncertain regarding the effect of the antibiotic		
No evidence			

RR: relative risk; RD: risk difference; CI: confidence interval. Numbers in the colored cells are the estimated risk differences and 95% CI per 1000 patients comparing each antibiotic regimen versus respiratory fluoroquinolones alone.

[a] The baseline risks was derived from the median of risk of event across the arms that randomized patients to the respiratory fluoroquinolones alone.

[b] We decided on the minimal important difference thresholds based on a consensus among the clinical experts in the team.

[c] The network estimates on the effects of tetracyclines alone versus respiratory fluoroquinolones alone were dominantly informed by the direct evidence which came from a single trial that used omadacycline.

Chapter 6: Discussion and Conclusion to the thesis

This thesis presents a systematic survey addressing the extent to which the trustworthiness of treatment guidelines has changed since the introduction of IOM standards [1] and describes the development of the modified NEATS instrument [2], which was applied in our systematic survey to assess the trustworthiness of guidelines. The subsequent chapters of this thesis present two systematic reviews with NMAs – one to inform empiric antibiotic therapy of adults with HAP [3] and another for moderate to severe CAP [4] – which serve as examples of evidence synthesis conducted in adherence to the trustworthiness standards.

Addressing methodological challenges

Within the context of our systematic survey to explore the extent to which the trustworthiness of treatment guidelines has improved after the introduction of IOM standards [1], we encountered two main challenges. The first challenge was to obtain a representative sample of treatment guidelines.

Many prominent guideline developing organizations, such as the World Health Organization, the National Institute for Health and Care Excellence, and the Scottish Intercollegiate Guidelines Network, do not publish their guidelines in medical journals. To retrieve these guidelines, we could either search each organization's website or use guideline-specific databases. The latter was more feasible, but it raised another challenge: selecting the optimal database within the context of our study. Several guideline-specific databases are available, and each has limitations. For example, GIN library [5] only includes guidelines published or endorsed by GIN member organizations; BIGG database

[6] provides a repository of guidelines developed using the GRADE methodology; ECRI database [7] only includes guidelines published within the last 5 years.

TRIP database [8] is more inclusive than other guideline-specific databases and provides a representative sample of guidelines regardless of the rigor of the methodology and publication time. Therefore, as Chapter 2 described, we hand searched TRIP database to identify guidelines that are only available from the developers' website and systematically searched bibliographic databases to retrieve guidelines published in medical journals. Using stratified sampling, we ensured inclusion of both journal and non-journal guidelines in our study sample.

The second challenge was the limitations of the available instrument capturing IOM trustworthiness criteria, NEATS [9], to adequately address the guideline development process and to provide explicit instructions for reproducible assessment of guidelines.

To address these limitations, as described in Chapter 3, our team – including experts in guideline methodology who participated in multiple discussions – developed modifications to the NEATS instrument [2]. Initially, we modified the wording of the items to capture trustworthiness rather than reporting quality. For example, in evaluating the disclosure and management of conflict of interest (COI) of guideline development group (GDG) members, the NEATS instrument addresses whether the authors have taken any steps to manage COIs [9]. Our modifications instead address whether COIs were appropriately managed; that is, appointing at least one co-chair without COIs to lead the GDG and excluding conflicted members from participating in the decision/voting specific to the direction and strength of recommendations related to their COIs [2].

Additionally, we created algorithms for the assessment of each item. This step involved the challenge of deciding on the structure of each algorithm. Based on consensus among our team members, we ranked criteria relevant to each item consistent with their potential impact on the appropriateness of the underlying process and developed hierarchical algorithms starting with a question about a criterion deemed most fundamental, where the answer "No" or "No information / unclear" means the lowest adherence to the given item. The algorithms progress toward addressing criteria with lower potential impact in subsequent steps that map to increasing levels of adherence to the items. For example, the algorithm specific to the search strategy item starts with the most influential element of a systematic search, the relevancy of search terms to the recommendation question. Subsequently, the algorithm addresses whether the search was comprehensive and up to date [2].

Moreover, in each algorithm, we addressed the criteria using prompting questions that were agreed on for less subjectivity in interpretation. For example, the prompting question evaluating the comprehensiveness of the systematic search explicitly states, "Were both MEDLINE (PubMed) and EMBASE searched, or if not, was any database in addition to MEDLINE (PubMed) or EMBASE searched?" [2] , or to assess whether the search was up-to-date, the prompting question explicitly states, "Was the time from last search to publication of the guideline shorter than 12 months if the evidence accrual for the topic is rapid or shorter than 18 months if not" [2].

In conducting the evidence synthesis of this thesis, we faced several challenges, as Chapters 4 and 5 describe. In defining eligibility criteria, we dealt with three main issues.

First, most of the trials conducted in the 1970s to 1990s included patients with a variety of respiratory tract infections, including pneumonia, chronic obstructive pulmonary disease, and bronchitis. To deal with these studies and avoid excluding them from the reviews, unless trials reported outcomes of interest separately for eligible participants, we prespecified a threshold for including studies [10] if at least 80% of enrolled participants were diagnosed with HAP or CAP [3, 4].

Second, we initially decided to conduct two separate NMAs for inpatient and outpatient CAP. However, reviewing inpatient trials showed in some trials more than 50% of enrolled patients had mild CAP and thus may show different effects compared with trials in which most cases had moderate to severe CAP. This highlighted the variability in the hospital admission criteria for CAP treatment. To deal with this issue and avoid relying on site of care for inclusion of trials, as illustrated in Chapter 5, we classified trials as mild versus moderate to severe CAP based on the severity data reported in the trials [4]. In this thesis, we only focused on moderate to severe CAP and included trials in which at least 50% of enrolled participants had moderate to severe CAP.

Third, trials on CAP and HAP were published as early as 1971 [3, 4], and some of the antibiotic regimens administered in these trials are no longer used in practice. We therefore had to address whether we should restrict the eligibility criteria for the interventions and comparators to the currently used antibiotic regimens. Our methods team agreed that these antibiotics may provide important indirect evidence for comparisons of interest, particularly because five trials or fewer informed most direct comparisons in our

NMAs, and thus excluding them would further compromise the precision of our estimates [11, 12].

In the synthesis of evidence stage of the NMAs, we experienced three main challenges. First, in the CAP NMA [4], 5 out of 19 trials included in the primary analysis of duration of hospitalization did not report on variability of the outcome. To avoid excluding these trials from the NMA, we imputed standard deviations (SD) based on the prognostic method proposed by Ma et al [13]. This approach uses the weighted average of observed variances to predict missing variability information, under the assumption that the participants of trials were randomly selected from the same population. As an adaptation of the prognostic approach, we predicted missing SDs using a linear regression with robust standard error, incorporating available SDs as a dependent variable and the logarithm of associated sample sizes as an independent variable. This approach, compared to the traditional approach of using a common average of observed SDs, provides the advantage of accounting for sample size in estimating missing variances, which in turn can enhance the accuracy of weighting contribution of studies with missing variability information in the estimation of direct estimates and thus improve reliability of network estimates.

The second issue we encountered during the synthesis of evidence was that, in some of the included trials, investigators allowed the administration of antibiotics different from study antibiotics based on the discretion of the treating physician. In the HAP NMA, we dealt with this issue by conducting network meta-regression for co-interventions with coverage against *P. aeruginosa* or Methicillin-resistant *S.* aureus [3]. For the CAP NMA,

we included co-administered antibiotics in our characterization of treatment nodes if more than 20% of participants of a study arm received the antibiotics [4].

Third, because the severity of disease in HAP and CAP may modify antibiotic effects [14, 15], we prespecified a hypothesis to conduct network meta-regression by the proportion of participants with severe disease for the NMAs [3, 4]. The challenge was that trials reported on severity differently: the proportion of participants with severe disease or the mean or median of a severity score. To obtain proportion from mean or median, when the proportion of participants with the severe disease was not identified in the trials, as the scores were approximately normally distributed in the trials, we calculated a z-value from mean, SD, and threshold of severity for that specific score and subsequently used the z-value to estimate the proportion of participants that fell above the threshold of severity for the score.

The last important issue we faced in these reviews was drawing conclusions from our NMAs. The CIs for the effects of almost all antibiotic regimens versus the reference crossed the threshold of no effect, and thus, with the GRADE approach [16], we were unable to capture potentially important differences between regimens. To address this challenge, we focused on the point estimate comparing an antibiotic regimen versus the reference rather than the CI around the point estimate [3, 4].

With this modification, we classified an antibiotic regimen as among the best if the point estimate comparing the antibiotic regimen versus the reference and two other alternatives showed important beneficial effects. We classified an antibiotic regimen as among the worst if the point estimate comparing the antibiotic regimen versus the reference

and two other alternatives showed important harmful effects. We classified an antibiotic regimen as intermediate (i.e., not different from the reference) if the point estimate comparing the antibiotic regimen versus the reference showed an unimportant effect. Clinical experts in our team reached a consensus on the thresholds for important effects.

Strengths and Limitations

The main strength of this thesis lies in the rigor of the methods applied in assessing the trustworthiness of guidelines and summarizing available evidence to inform comparative effects of empiric antibiotic regimens in the management of HAP and moderate to severe CAP. Rather than using existing instruments that have important limitations in addressing the appropriateness of the guideline development process to assess the trustworthiness of guidelines, we modified an existing instrument and developed a structured framework for appropriate and more reproducible assessments of the trustworthiness of guidelines. Moreover, the evidence synthesis of this thesis benefited from a comprehensive and up-to-date search, adequate study selection and data extraction process, efficient analysis using a rigorous NMA approach, rating the certainty of evidence using the GRADE methodology and drawing informative conclusions using a modification of the GRADE approach.

Nonetheless, this thesis has limitations, which were described in detail in previous Chapters. The main limitation of this thesis results from the limitations of the underlying evidence. Limitations in reporting on the guideline development process remain a challenge in assessing the trustworthiness of guidelines that may have undermined the appropriate and fair evaluation of trustworthiness, particularly for pre-IOM guidelines,

which are less transparent. With respect to the NMAs, few trials per direct comparison, concerns with risk of bias, failure to address all patient-important outcomes, and lack of data on potential effect modifiers resulted in uncertainty in the effects for most antibiotic regimens for HAP and moderate to severe CAP and limited usefulness of the findings for decision-making.

Moreover, although we developed the modified NEATS instrument to better capture the trustworthiness of guidelines and improve the reproducibility of trustworthiness assessment, its use was confined to a relatively small number of users and guidelines. To demonstrate the advantages of modified NEATS to existing instruments, there remains a need for a formal validation process.

Additionally, while this thesis offers useful examples of rigorous conduct of systematic reviews of interventions to inform treatment guidelines, the methods applied in these systematic reviews may not be generalizable to other clinical areas. For instance, in systematic reviews of interventions in which insufficient direct evidence is available for patient-important outcomes from RCTs, inclusion of indirect evidence from surrogate outcomes or direct evidence from non-randomized studies may be necessary [17].

Implications and future directions

This thesis highlights important opportunities for strengthening the appraisal and development of treatment guidelines. The modified NEATS instrument developed in this thesis by addressing methodological aspects of the guideline development process can distinguish a trustworthy guideline from a well-reported one. The straightforward structure of the instrument provides an ideal framework for users without extensive experience in

guideline methodology. Future studies can investigate the reliability of the modified NEATS assessments when applied by users with different levels of expertise in guidelines methodology.

Moreover, this thesis increases awareness among guideline users regarding the limitations in the trustworthiness of current guidelines and importance of ascertaining the rigor of the guideline development process in considering a guideline for decision-making. Additionally, our findings can inform guideline developers on actionable opportunities to advance the guideline development process and emphasize the necessity of transparency in reporting their development process. Future studies should identify barriers to the adoption of trustworthiness standards among guideline developers and devise interventions to overcome these barriers.

Furthermore, the rigorous systematic reviews conducted in this thesis can serve as a basis for future guidelines to inform their recommendations on antibiotic selection for empiric therapy of HAP and moderate to severe CAP.

Conclusion

This thesis represents an effort to enhance trustworthiness and application of treatment guidelines. By developing modifications to the NEATS instrument, applying it to a random sample of treatment guidelines, and addressing common evidence synthesis limitations through rigorously conducted systematic reviews, the work provides both practical frameworks and empirical insights into persistent challenges in guideline development. While our findings highlight areas for improvement in the guideline development process, they also offer a path forward for refining guideline appraisal

methods and strengthening the systematic review process based on which guidelines are informed. To optimize patient care, further efforts for methodologically robust and more transparent guidelines are essential.

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