ANTIMICROBIAL RESISTANCE AND GUIDELINE RECOMMENDATIONS: CONTEXTUALIZATION AND ADAPTABILITY

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By Rosa Stalteri, HBSc

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AUTHOR: Rosa Stalteri, HBSc. (University of Toronto)

SUPERVISOR: Holger J. Schünemann

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ABSTRACT

Antimicrobial Resistance and Guideline Recommendations: Contextualization and Adaptability

Master of Public Health, 2020, Rosa Stalteri, Department of Health Research Methodology, Evidence and Impact, McMaster University

BACKGROUND: Antibiotics are essential medicines and their effectiveness is under threat due to antimicrobial resistance. Guidelines are one way to conserve antibiotic effectiveness given that they are intended to modify clinician prescribing. Guidelines that provide antibiotic recommendations should make explicit contextual considerations that influence antimicrobial resistance and their downstream effects on resistance emergence. METHODS: We conducted a systematic review of tuberculosis, gonorrhoea, and respiratory tract infection guidelines and recommendations to examine how and to what extent they are considering contextual factors that influence antimicrobial resistance. We also investigated whether there are guidelines and recommendations that can be adopted or adapted to local contexts. RESULTS: We found that within 74 included guidelines, two thirds of recommendations considered antimicrobial resistance. Of which only five guidelines considered all factors required to consider local aspects such as values, resource use, acceptability, feasibility, and equity. As such, these five guidelines can be either adopted or adapted to Canadian and other contexts. We also found that 39% of guidelines met credibility scores of 60% or greater in AGREE II domains: scope and purpose, rigor of development, and editorial independence. CLINCAL IMPLICATIONS: There are very few Infectious disease guidelines for highly prevalent diseases that do not consider all important contextual factors may influence antimicrobial resistance. Our findings can support societies and organizations, public health policy, and health care stakeholders to develop and implement guidelines that are applicable to local contexts efficiently and resourcefully. Our antimicrobial resistance recommendation framework, used in addition to GRADE Evidence to Decision frameworks, is a start to having this come to fruition.

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Thesis outline

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LIST OF ABBREVIATIONS

AGREE II tool: Appraisal of Guidelines for Research & Evaluation II tool

AMR: Antimicrobial resistance

AWaRe: Access, Watch and Reserve (AWaRe)

BIGG: International database of GRADE guidelines.

CDC: The Centre for Disease Control and Protection

CI: Confidence interval

CPG infobase: Canadian Medical Association Clinical Practice Guideline Infobase

G-I-N: Guidelines International Network

GLASS: Glass Antimicrobial Resistance Surveillance System

GRADE: Grading of Recommendations, Assessment, Development and Evaluation

GRADE-ADOLOPMENT: Adoption, adaption and de-novo development

GRADE-EtD or EtD: Evidence to Decision

IDSA: Infectious Disease Society of America

IOM Standards for Developing Trustworthy Clinical Practice Guidelines: Institute of Medicine Standards for Developing Trustworthy Clinical Practice Guidelines

NCC-WCH: National Collaborating Centre for Women's and Children's Health

NICE: National Institute for Health and Care Excellence

NIH: National Institutes of Health

PICAR framework: the population, intervention, comparison, guideline attributes, and recommendation characteristics framework

PICO: Population, intervention, comparison and outcome

SD: Standard deviation

SIGN: The Scottish Intercollegiate Guidelines Network

TB: Tuberculosis

Trip: Turing Research Into Practice

WHO: World Health Organization

DECLARATION OF ACADEMIC ACHIEVEMENT

The following is a declaration that Rosa Stalteri, Dr. Holger J. Schünemann, Dr. Nancy Santesso, and Dr. Mark Loeb contributed to the study protocol, data analysis and interpretation, as well as reviewing, editing and writing the document. Dr. Thomas Piggott contributed to the study protocol. Dr. Thuva Vanniyasingam assisted with developing the data analysis plan. Dr. Lorenzo Moja was invited to review, edit and write the manuscript. Dr. Nancy Santesso revised and edited the systematic review search strategy, screening forms, and data extraction forms. Rosa Stalteri coordinated the systematic review, gathered reviewers, screened, collected, and analyzed data. Systematic reviewers included Dr. Antonio Bognanni, Dr. Andrea Darzi, Dr. Finn Schünemann Gian Paolo Morgano, Matthew Ventresca, Dr. Samer Karam, and Tejan Baldeh.

Chapter 1. Antimicrobial resistance and guidelines

Antibiotics are among the most essential medicines protecting human and animal health. Within the past century, many of the greatest public health achievements were due to antibiotics. About a decade post-discovery, antibiotics cured previously incurable bacterial illnesses, and prevented death from streptococcal and staphylococcal infections, gonorrhea, syphilis, and others.(1) Prophylactic doses of antibiotics enabled doctors to perform successful life-saving and essential surgeries by minimizing post-surgical hospital infections. Further, widespread use of antibiotics for the domestication of animals and agriculture improved nutrition.

The use of antibiotics is a double-edge sword. While their use protects human health, their use can also be a detriment to human and public health gains by way of antimicrobial resistance.

1.1. Antimicrobial resistance and antibiotic development

Antimicrobial resistance (AMR) is defined as the mechanistic ability for microorganisms to survive exposure to antimicrobials or antimicrobial-producing organisms.(2-4) Antimicrobials include a wide-range of agents — antibiotics, antifungals, antivirals, antimalarials and anthelmintics — targeting either bacteria, fungi, viruses, and parasites.(5) This paper will focus on antibiotics, and treatment of bacterial infections.

Antibiotic development in the mid-twentieth century enabled continuous management of infectious diseases despite AMR.(6) However, since the 1980s, drug-development and discovery significantly decreased. Given the move towards their conservation(7), their naturally short lifespans, and scientific challenges to antibiotic discovery,(6) antibiotics are viewed as unprofitable compared to other medicines.(8, 9)

To date, pharmaceutical companies committed to scale up production and prioritization of antibiotics.(7) Still, pharmaceutical investment in new antibiotics and discovery is suboptimal.(6, 10, 11)

Continuous antibiotic development and using antibiotics sparingly are both necessary for managing AMR, protecting human health, and conserving current and future regimens.(6)

1.2. What exacerbates AMR: historic and current issues regarding misuse

The misuse of antibiotics by humans is well documented in the human, animal, and environmental domains. Inappropriate use in humans includes: prescribing antibiotics for viral infections, prescribing unsuitable lines of antibiotics, unnecessary long prescribing durations, and self-medicating. Over-the-counter use of antimicrobials (which is still permitted in some countries) is associated with inappropriate choice of antibiotics and also a contributor to the rise of resistance in community settings.(12, 13)

Similarly, antibiotics are used to treat bacterial infections in animals. They are also used to increase yield and returns on investment: small prophylactic doses are given to support animal growth, and prevent sickness while living in compact conditions.(12, 14)

Pharmaceutical disposal of antimicrobials in water, and the use of manure from animals given antibiotics, provides additional opportunities for the emergence and spread of resistance by way of the environment.(15, 16)

Although this thesis focuses on antibiotic use for human treatment, addressing AMR requires coordinated actions within the all three domains: human, animal, and environmental.(14, 17)

1.3. Tuberculosis in the context of AMR

Tuberculosis (or TB) was the second most common cause of death in the early 20th century, ranking slightly below pneumonia or influenza in the United States of America.(18)

Today, it kills millions of people annually: it is among the top ten causes of death globally and is number one killer in terms of infectious causes. Majority of new cases in 2019 occurred in low-income countries.(19)

Tuberculosis is no longer among the top causes of death among high-income countries, but most prevalent among vulnerable populations. However, such countries are not insusceptible. Air travel and migration fuels the spread of bacterial infections from one country to another. In 2019, the Centre for Disease Control and Protection (CDC) classified *Mycobacterium* tuberculosis as a serious threat to public health in the United States of America.(15)

Drug-resistant tuberculosis imperils global health goals to 'End' this preventable and curable disease. Multidrug-resistant tuberculosis, defined as resistance to at least two first-line anti-tuberculosis therapy (isoniazid and rifampicin),(20) is challenging to treat. Treatment of drug-resistant strains is complex, costly, and toxic.(21) Inappropriate use is prevalent and is associated with the development of multidrug-resistant TB.(22, 23) Sometimes, patients develop a serious and deadly form — extensively drug-resistant tuberculosis — where resistance expands to fluoroquinolones and at least one of three second-line therapy.(20)

1.4. Gonorrhoea in the context of AMR

Gonorrhoea is a sexually transmitted disease caused by the microorganism, *Neisseria* gonorrhoea. It triggers negative and lasting health implications in women and, less so in men, especially when untreated.(15) Classified as an urgent public health threat, *Neisseria* gonorrhoea

rapidly developed resistance to all but one antibiotic therapy, ceftriaxone, in many settings.(15, 24)

The last recommended dual combination therapy is also under threat given the spread of ceftriaxone and azithromycin resistant strains related to travel.(25) The prospect of future treatment capabilities is concerning. The World Health Organization (WHO) classified cephalosporin-resistant and fluoroquinolone-resistant Neisseria gonorrhoeae as a high priority for research and development of new antibiotics.(6) Still, guidelines are recommending first-line therapies amid their growing ineffectiveness and slow to update based on resistance patterns.(26, 27)

1.5. Respiratory tract infections in the context of AMR

Respiratory tract infection is any infectious disease of either the upper or lower respiratory tract.(28) Some include, pharyngitis, sinusitis, otitis media and community-acquired pneumonia, and are mainly caused by microorganism, *Streptococcus* pneumoniae. All these syndromes have been prioritized by the WHO as part of Access, Watch and Reserve (AWaRe), the new classification system that supports a nuanced approach to target inappropriate use of broad spectrum Watch antibiotics.(29) In 2019, the CDC classified *Streptococcus* pneumoniae as a 'serious' threat to public health,(15) and among the WHO's priority list for research and development of new antibiotics.(6)

Most antibiotics are prescribed for respiratory tract infections, especially in outpatient settings. However, many, (including otitis media, sinusitis and pharyngitis), are self-limiting and viral in nature, meaning that they can resolve without antibiotics.(28, 30)

For the above reasons, this thesis focuses on three types of infection: tuberculosis, gonorrhoea, and respiratory tract infections (specifically: otitis media, pharyngitis, sinusitis, and community-acquired pneumonia).

1.6. Definition of guidelines

The 2015 United Nations General Assembly focused on the need for well-coordinated action plans to tackle AMR across the human, animal, and agricultural sectors — also known as the 'One Health Approach'. This was the fourth time that a health topic was discussed. All 194 member states committed to manage AMR by implementing national action plans (within two years) that align with five objectives developed by the WHO.(12, 31) The fourth objective is to optimize the use of antimicrobial medicines in human health through the development of national and hospital treatment guidelines.

Guideline development rapidly evolved over the last 30 years. Past and present research in this field ameliorated guideline development methodology, research, and implementation. Emphasis for better quality guidelines and recommendations based on the best available evidence has, for the most part, moved away from recommendations based solely on expert opinion, and 'cherry-picked' research evidence.(32) The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group has addressed shortcomings of distilling scientific evidence to recommendation development through a transparent approach to grading the certainty of evidence in systematic reviews and strength of recommendations.(33)

A practice guideline (or simply put a guideline), "is any document containing recommendations for clinical practice or public health policy".(34) A guideline contains one or more recommendations. Recommendations focusing on AMR intend to inform health care providers and recipients about best management options in relevant contexts. As a result, recommendations are the cornerstones for guiding antibiotic use, and for achieving the best

health outcomes in specific situations. Guidelines translate a wealth of scientific evidence and contextual considerations into actionable statements.(35) When adhered to, recommendations can modify clinician behavior by guiding the selection, duration, and dosage of antibiotics. Adherence to antibiotic prescribing guidelines has been associated with reductions in mortality,(36) length of hospital stay,(37) elderly comorbidity,[25] and resistance.(38)

1.7. The problem with guidelines in the context of AMR

Plenty of scientific societies, organizations, national agencies and institutions have built capacity within countries to develop practice guidelines. Widespread development brought issues with guideline trustworthiness given variations in methodology, addressing conflict of interests among panel members and funders, and transparency. In response, societies and organizations employed mutually agreed basic elements of guidelines (in designated handbooks) in efforts to standardize guideline development processes.(35) Despite these efforts, two major concerns about guideline and recommendation development in the context of AMR still lingers.

First, the preservation of antibiotics requires the consideration of how, and under what conditions, is it appropriate to prescribe antibiotics. Unfortunately, only a scant minority of recently published guidelines considered epidemiological and resistance pattern data.(39) This is likely related to the current lack of formal guidance for developing recommendations in a manner that considers AMR.

Oftentimes, guidelines also fail to consider other information required for contextualization to unique settings.(40, 41) These include: patient values, resource use, acceptability, feasibility, and equity. For example, guidelines that account for resistance burden, public health infrastructure and policies, and equitability of antibiotic regimens, supports effective use.(41-43) However, inclusion of AMR in guidelines is a difficult task. Evidence on the relationship between empiric treatment regimens for specific infectious syndromes, underlying diseases, clinical severity at presentation, pathogen resistance by phenotype and genotype, and associated clinical benefits

and harms (i.e. 28 days), are limited. Research is still in its infancy and it is likely that most guidelines will not incorporate such evidence in a short timeframe. Once new knowledge becomes available, it is important that it is efficiently transferred to guidelines, keeping the time lag between evidence creation and recommendations at a minimal.(39)

From the perspective of guideline developers or endorsers of guidelines for use, the lack of transparency is one important contributor to guideline inefficiencies. Oftentimes, existing guidelines do not report information required for later use by other guideline developers.(40, 41) Faulty reporting and the 'develop from scratch' mentality, results in duplication of work, as well as confusion and loss of confidence by clinicians.(42, 44) In many cases, de-novo development is unrealistic, overly burdensome, and a waste of finite resources — a single guideline can cost as much as $200,000 USD.(45)

Rather than creating guidelines from scratch, societies and organizations can develop recommendations efficiently and economically by using previous work done by other guideline groups. GRADE-ADOLOPMENT (or ADOLOPMENT) is a process that allows developers to use existing credible guidelines and recommendations by either adopting the recommendation without making any modifications (adoption), adapting the recommendation by making a few adjustments (adaption), or making new recommendations all together (*de novo* development).

Adoption or adaption of guideline recommendations requires careful consideration. First, the benefit of guidelines to end-users is correlated with their quality. Methodological rigor varies across guideline development, resulting in differences in the quality of guidelines and recommendations. Second, guideline development should transparently report the relation of evidence to recommendations, and the decisions made by panel members.(35, 46, 47)

1.8. GRADE-ADOLOPMENT and contextual considerations

ADOLOPMENT uses GRADE Evidence to Decision (or EtD) Frameworks to create guidelines and recommendations that are suitable for unique settings, and to facilitate transparency and clear reporting.(42) Evidence to Decision frameworks include explicit dimensions (to be considered in recommendations) including: values, resource use, acceptability, feasibility, and equity. These dimensions allow developers to account for resistance burden, public health infrastructure, and equitability of antibiotic regimens.(41-43)

Considering patient values in recommendations supports patient health goals and desirable health outcomes.(41, 42) Resource use considers the cost-effectiveness or cost-benefit of an antibiotic treatment, with other human and infrastructural resources required. Equity is concerned with whether certain interventions pose a disadvantage to particular groups. Acceptability focuses on the receipt of an intervention by stakeholders, while feasibility focuses on the sustainability, and potential barriers to implementation of an intervention.(42) Considering Evidence to Decision dimensions in recommendations is ethically and scientifically essential for better decision-making, and incorporating AMR.

1.9. Objectives

The aim of this thesis was twofold. The first was to conduct a retrospective analysis on how, and to what extent, broader contextual factors, including AMR, values, resource use, acceptability, feasibility, and equity are being considered in recommendations. To our knowledge, there is currently no guidance on how recommendations should appropriately consider AMR. We compiled ways that guidelines are considering AMR at the population, and outcome level.

The second was to assess whether guidelines report enough information for later adoption or adaption to the Canadian and other contexts. Our goal was to provide a framework as a starting

point to assist in the consideration of resistance in recommendations and to create efficiency in local development of infectious disease guidelines.

Chapter 2. Recommendations for antibiotics: the need to incorporate antibiotic resistance and reduce research waste

2.1. ABSTRACT

Objective(s): Antimicrobial resistance is a global health threat that can be managed through antimicrobial stewardship. Guidelines that provide antibiotic recommendations should make explicit considerations of contextual factors that influence antimicrobial resistance and their downstream effects on resistance emergence. Our objective was to conduct a retrospective analysis on how, and to what extent, guidelines are considering broader contextual factors including antimicrobial resistance and reporting enough information for later adoption or adaption of guidelines.

Methods: We performed a search in electronic databases: Ovid MEDLINE and Embase from inception to June 7 2019 for guidelines published since 2007 that focus on tuberculosis, gonorrhoea, and respiratory tract infections. To complement, we searched guideline databases TRIP (https://www.tripdatabase.com), G-I-N (https://www.g-i-n.net/home), BIGG (http://sites.bvsalud.org/bigg/en/biblio/), and the Canadian Medical Association PG Infobase (https://joulecma.ca/PG/homepage), key websites, and reference lists.

We screened and abstracted data in duplicate. We identified guidelines and recommendations that considered contextual factors including antimicrobial resistance, values, acceptability, feasibility, and equity. We assessed credibility of the guidelines using the Appraisal of Guidelines for Research & Evaluation II (AGREE II) tool.

Results: We screened 10,365 records. After screening, we retrieved 78 guidelines that provided sufficient information for data extraction. Among these, 74 guidelines had at least one recommendation that considered antimicrobial resistance. In total, approximately two thirds of recommendations considered antimicrobial resistance at the population- and/or outcome-level. Of these 74 guidelines, 39% (n = 29/74) had scores of 60% or greater in scope and purpose, rigour of development, and editorial independence. In addition, only 5 of the 29 guidelines reported all factors required for recommendation contextualization: values, resource use, acceptability, feasibility and equity. Resource use and values were the most considered, acceptability and feasibility were moderately considered, and equity was the least considered, across guidelines.

Conclusion(s): These results indicate that relatively few guidelines were published over a 13 year period for highly prevalent diseases that require recommendations that consider local aspects such as resistance. Additionally, there is a need to improve the development of regional guidelines, as most are of suboptimal quality. This study provides a snapshot of how current infectious disease guidelines are considering contextual factors necessary for appropriate antibiotic use. We also present an initial start to an antimicrobial resistance framework to improve recommendations influencing antibiotic use.

2.2. INTRODUCTION

Antibiotics are essential to protecting human health. Their effectiveness is under threat due to antimicrobial resistance (AMR) generated by well documented excessive misuse of antibiotics over several decades.

At the 2015 United Nations General Assembly, member states committed to address AMR by adopting national action plans centered on five strategic objectives outlined in the WHO's Global Action Plan.(48, 49)

The forth objective of this plan is to implement national and hospital treatment guidelines for the optimization of antimicrobial medicines use.(49) Guidelines are within a package of AMR stewardship interventions intended to modify clinician behavior by providing guidance on when, and how, to prescribe antibiotics, complementing antibiotic consumption, resistance surveillance, research & development, and burden of resistance.(50-53)

Concerns with guidelines in the context of AMR include: the lack of considering important contextual factors that influence AMR and duplication of work across guideline societies and organizations.

Preservation of antibiotics requires the consideration of how, and under what conditions, is it appropriate to recommend antibiotics. Unfortunately only a scant minority of recently published guidelines considered epidemiological and resistance pattern data.(39) This is likely related to the current lack of formal guidance for developing recommendations in a manner that considers AMR.

Oftentimes, guidelines also fail to consider other information required for contextualization to unique settings.(40, 41) These include: patient values, resource use, acceptability, feasibility, and equity. For example, guidelines that account for resistance burden, public health infrastructure and policies, and equitability of antibiotic regimens supports effective use.(41-43) However, inclusion of AMR in guidelines is a difficult task. Evidence on relationship between empiric treatment regimens for specific clinical infection syndromes, underlying disease (i.e. human immunodeficiency viruses) , clinical severity at presentation, pathogen resistance by phenotype and genotype, and associated clinical benefits and harms (i.e. 28 days) are limited. Research is still in its infancy and it is likely that most guidelines will not incorporate these evidence in a short

timeframe. Once new knowledge becomes available, it is important that it is efficiently transferred to guidelines, keeping the time lag between evidence creation and recommendations minimal.(39)

Faulty reporting and the 'develop from scratch' mentality results in guideline societies and organizations duplicating the same research. Having multiple guidelines on the same topic may lead to confusion and loss of confidence by clinicians,(42, 44) as well as research waste. Through transparent reporting, and proper inclusion of AMR as new research becomes available, information can be effectively used in recommendations by others. Processes, including GRADE-ADOLOPMENT, permits societies and organizations to capitalize on existing evidence evaluation and interpretation by considering important contextual factors that include AMR and reduce cost and redundancy.(42, 43)

When adhered to, guidelines can optimize antibiotic use through explicit consideration of contextual factors that influence AMR. As a necessary step towards ameliorating antibiotic guidelines and recommendations, our objective was to conduct a retrospective analysis on how, and to what extent, broader contextual factors including AMR are being considered and that provide enough information for later adoption/adaption. We hypothesized that few infectious disease guidelines consider and report important contextual factors in recommendations that influence AMR, and reduce research waste.

2.3. METHODS

2.3.1. Search strategy and selection criteria

We selected three types of infection: tuberculosis, gonorrhoea, and respiratory tract infections (specifically: otitis media, pharyngitis, sinusitis, and community-acquired pneumonia) as they are becoming increasingly harder to treat due to AMR. Harder to treat drug-resistant tuberculosis strains are increasing and projected to account for a quarter of all deaths by 2050.(54) Neisseria

gonorrhoea is an urgent public health threat.(15) The international spread of resistance to the last effective therapy, ceftriaxone and azithromycin, threatens sustained treatment of gonorrhoea.[17,18] Otitis media, pharyngitis, sinusitis, and community-acquired pneumonia are prevalent and *Streptococcus pneumoniae* (the main causal microorganism), was classified as a serious public health threat due to resistance.(15) All these syndromes have been prioritized by WHO as part of Access, Watch, and Reserve (AWaRe), the new classification system that support a more nuanced approach to target inappropriate use of broad spectrum Watch antibiotics.(29)

We included English language guidelines published between 2007 and 2019 on the above selected infections. We marked the 2007 WHO decision to update its guideline development as a major change in methodology, representing a division of two eras.(55) We limited the focus of our analyses to the era following this change. Table 1 outlines our research question.

We included guidelines with clearly articulated recommendations as defined by the *Institute of Medicine (IOM) Standards for Developing Trustworthy Clinical Practice Guidelines*.(35) After contacting guideline developers, we excluded guidelines with unobtainable supplementary materials required for analysis.

We searched Ovid MEDLINE and Embase from inception to June 7, 2019 (detailed search strategies in the Appendix). We conducted a second search in four guideline databases: TRIP (https://www.tripdatabase.com), G-I-N (https://www.g-i-n.net/home), BIGG (http://sites.bvsalud.org/bigg/en/biblio/), and the Canadian Medical Association PG Infobase (https://joulecma.ca/PG/homepage). We finally searched key international websites and reviewed references of included guidelines.

Table 1: PICAR framework guiding search for guidelines and recommendations

PICAR item	
P: Population, clinical indications(s), and condition(s)	1) Tuberculosis; 2) Gonorrhoea; and 3) Respiratory tract infections: otitis media, pharyngitis, sinusitis, and community acquired pneumonia.
I: Intervention(s)	Any intervention that treats tuberculosis, gonorrhoea, and respiratory tract infections.
C: Comparator(s), Comparison(s), and (key) content	Any comparator.
A: Attributes of eligible guidelines	**Publication year:** 2007 and above. **Language of publication:** English. **Scope: International and regional** guidelines. **Purpose:** provide a recommendation on antibiotic selection and prescribing. **Format:** any. **Specific methodological standards: guidelines** that meet the AGREE II cut off score ≥ 60% in scope and purpose (domain one), rigor of development (domain three), and editorial independence (domain six).
R: Recommendation characteristics	At least one recommendation considers AMR. **Location of recommendation:** anywhere within the guideline text, tables, and/or decision paths.

Independently and in pairs, reviewers (RS, AB, AD, MV, GPM, SK, and TB) screened titles and abstracts and the full text of potentially eligible guidelines. Disagreements were resolved by discussion or with a third reviewer.

2.3.2. Data extraction and quality assessment

We extracted data from guidelines, retrievable supplementary materials, and guideline development documents facilitated by pilot-tested forms and distillerSR (https://www.evidencepartners.com). Extractors (RS, AB, AD, FS, GPM, MV, and SK) recorded data independently and in pairs, and resolved disagreements.

Reviewers screened through recommendations classifying them as either considering AMR or not according to AMR dimensions. Although guidelines may have adopted different approaches to considering resistance with varying level of technicalities and detail, our operational definitions for considering a guideline "compliant" were inclusive. We assumed that for each recommendation, there would be an opportunity to consider information pertaining to AMR at the population- and outcome-level, given that formulation of specific recommendations are guided by PICO (population, intervention, comparison and outcome) frameworks. Population-level considerations include recommendations for populations with some level of resistance, considerations of local resistance patterns, recommending the use of narrow-spectrum antibiotics and recommending the watchful-waiting approach to prescribing. Outcome-level dimensions included considering future prospects of AMR or the emergence of resistance as a consequence of antibiotic use (examples provided in table 2).

We considered a guideline that reports information on any of the above dimensions in either the recommendation, accompanying evidence summaries or PICO framework would be considered satisfactory. Whereas guidelines that generally discussed AMR as an issue, without linking information pertaining to AMR to each recommendation were considered unsatisfactory.

We assessed a guideline's credibility using the Appraisal of Guidelines for Research & Evaluation (AGREE) II Instrument focusing on three relevant domains: a well-defined scope and purpose (domain one), rigorous development including a systematic search for evidence, transparent reporting of methods, links between evidence and recommendations, external review, and procedures for update (domain three), and editorial independence (domain six).(56) Satisfactory quality guidelines scored 60% or greater in these domains.(50)

We also abstracted information on values, resource use, acceptability, feasibility, and equity from guidelines that met our satisfactory cut-off (i.e. 60%). Briefly, regions may differ in the accessibility of antibiotics, the cultural view towards the use of antibiotics, pharmaceutical costs, and health care structures. We selected these dimensions as the transparent reporting of these factors is creditable: in appraising the evidence for antibiotics, guideline developers should be aware of the breadth of implications of their recommendations. Guidelines that ignore this wider agenda could provide narrow, misleading guidance.

2.3.1. Data synthesis and statistical analysis

We conducted descriptive statistics at the guideline and recommendation level, using counts and proportions (95%CI). We calculated the mean (SD) for AGREE II scores by region. We also compared the quality of guidelines from the WHO versus regional guidelines using scaled domain scores, mean difference, and a two-sided t-test. We calculated the frequency of guideline reporting of: values, resource use, acceptability, feasibility, and equity. All analyses were conducted in Microsoft® Excel and R-studio (RStudio Team (2016). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA URL http://www.rstudio.com/.).

The study protocol was registered in PROSPERO (registration #CRD42020145235). This paper is reported according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines and internally funded by the Michael G. DeGroote Cochrane Canada and MacGRADE centres.

Table 2: Satisfactory recommendations that consider AMR dimensions

AMR dimension(s)	Recommendation	Evidence illustration
AMR population-level dimensions considered	Amoxicillin-clavulanate rather than amoxicillin alone is recommended as empiric antimicrobial therapy for ABRS in adults (weak, low).(57)	Local national surveillance data in the United States of America for amoxicillin and beta-lactamase-producing *H. influenzae* was narratively described in the evidence summary was clearly linked to the recommendation.
AMR outcome-level dimensions considered	In neonates with gonococcal conjunctivitis, the WHO STI guideline suggests one of the following treatment options: • ceftriaxone 50 mg/kg (maximum 150 mg) IM as a single dose • kanamycin 25 mg/kg (maximum 75 mg) IM as a single dose • spectinomycin 25 mg/kg (maximum 75 mg) IM as a single dose.(58)	The outcome of *'antimicrobial resistance'* was formally considered within a PICO framework within a supplementary appendix.
Population and outcome-level dimensions considered	Bedaquiline should be included in longer MDR-TB regimens for patients aged 18 years or more (strong recommendation, moderate certainty in the estimates of effect).(59)	The recommendation considers a multi-drug-resistant tuberculosis patients, and the outcome *'acquisition (amplification) of drug resistance'* (60) was formally considered within a PICO framework provided within a supplementary appendix.
	Alternative first choice of antibiotics for adults aged 18 years and over with pharyngitis and a penicillin allergy or intolerance: Clarithromycin 250 mg to 500 mg twice a day for 5 days.(61)	Summary of committee discussions show that population-level resistance data was considered: "based on evidence, clinical experience and resistance data, the committee agreed to recommend the following alternative first-choice antibiotics for use in penicillin allergy or for phenoxymethylpenicillin intolerance: clarithromycin or erythromycin (which is preferred in pregnancy)."(61) Additional formal outcome considerations include *'antibiotic resistance'* in a supplementary appendix.

2.4. RESULTS

Our initial search identified 10,365 records. After screening, we retrieved 79 guidelines that had at least one recommendation on antibiotic selection: (n = 28 tuberculosis, n = 13 gonorrhea, n = 38 respiratory tract infections). Of these, 78 guidelines had sufficient information for assessment—one gonorrhoea guideline was excluded because we were unable to retrieve supplementary materials (figure 1).(62)

2.1. *Contextualizing recommendations*

2.1.1. Guideline recommendations considering AMR

After classifying recommendations, we found that 74 guidelines had at least one recommendation that considered AMR and four guidelines without such considerations.(63-66) These were excluded from further assessment. Of the 74 guidelines, a majority were developed in North America (n = 29),(57, 62, 67-94) and Europe (n = 26).(28, 61, 84, 95-116) A smaller portion were from Asia (n = 7),(117-123) South America (n = 1),(124) Africa (n = 1),(125) and Oceania (n = 1).(126) Nine guidelines(58-60, 127-132) were internationally developed by the WHO.

Within these 74 guidelines, we found that approximately two thirds of recommendations (n = 808/1198) considered AMR; that figure was 55% for tuberculosis recommendations (n = 272), 85% for gonorrhoea recommendations (n = 150), and 75% for respiratory tract infection recommendations (n = 386). Majority of recommendations were regionally developed (n = 736) and the rest were internationally developed (figure 2).

Most recommendations considered either population-level or outcome-level AMR dimensions, while fewer considered both simultaneously.

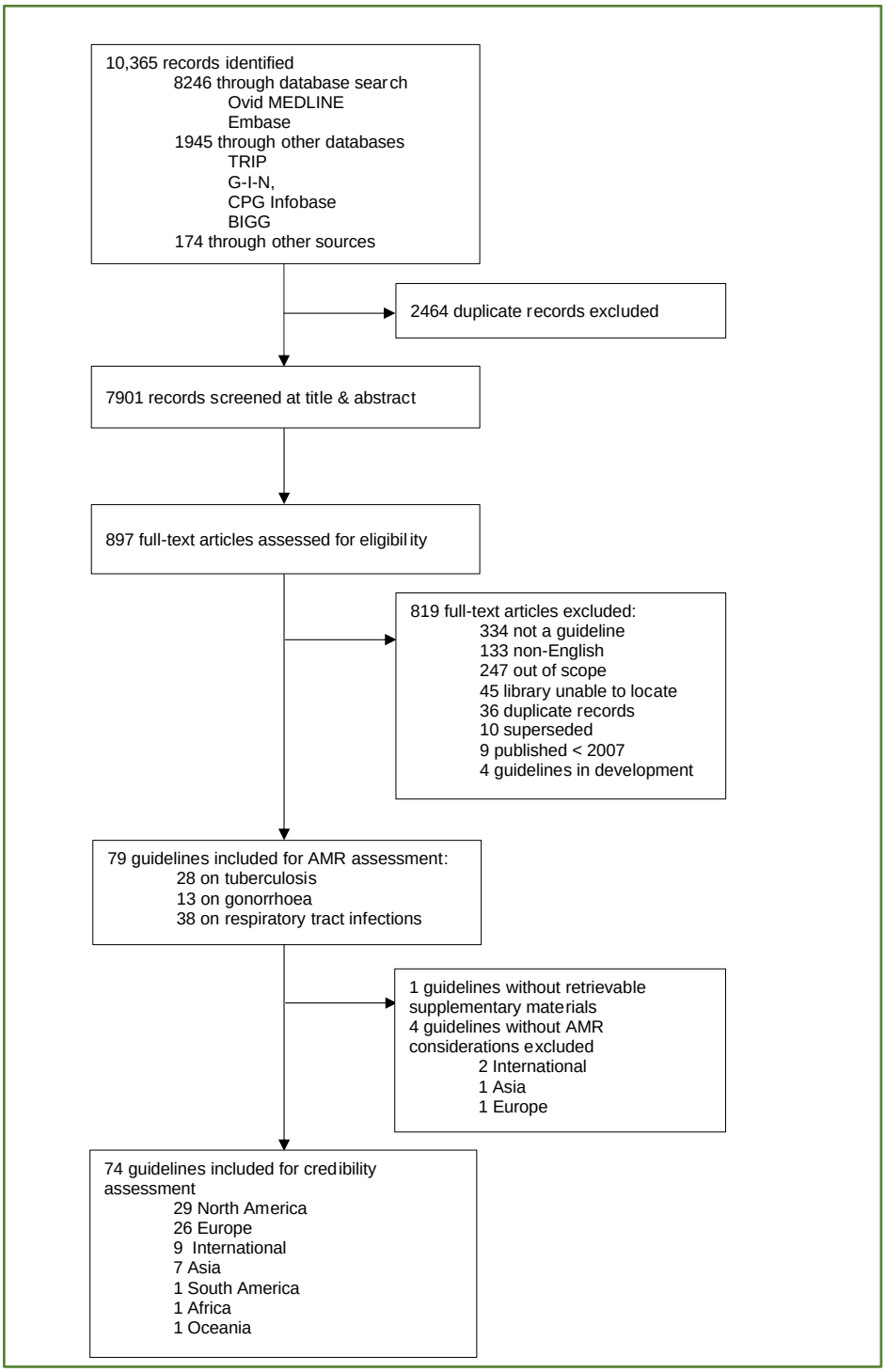

Figure 1: Flow diagram of the guideline selection process
Trip=Turing Research Into Practice. G-I-N=Guidelines International Network. CPG infobase=Canadian Medical Association Clinical Practice Guideline Infobase. BIGG=International database of GRADE guidelines. Out of scope=does not include recommendations on antibiotic selection or prescribing; does not have a significant section on tuberculosis, gonorrhoea, or respiratory tract infections.

Approximately 18% of recommendations (n=142/808) considered AMR at the population-level only. While 35% (n = 281/808) of recommendations considered resistance as an outcome only. Most notably, a majority of recommendations considering AMR as an outcome were not explicitly stated in PICO format, but rather buried within evidence summaries. Clearly stated outcomes formally considered in PICO frameworks included: 'acquired drug-resistance', 'antimicrobial in vitro resistance', 'bacterial antibiotic resistance', and 'emergence of drug-resistance'. Among respiratory tract infection recommendations, we found that 7% (n = 27/386) recommended no antibiotic or back-up antibiotic (i.e. the watchful waiting approach). This is a population-level dimension, i.e. recommendations for patients who likely have infections that are viral in nature.

Table 3: Guidelines and recommendations with AMR considerations*

Variable	Guidelines (N=78**)	Total number of recommendations (N=1198)	Number of recommendations with AMR consideration (N=808)	Proportion of recommendations with AMR consideration (95% CI)
Continent				
International***	11	93	72	0.77 (0.67, 0.85)
North America	29	503	321	0.64 (0.59, 0.68)
South America	1	26	7	0.27 (0.12, 0.48)
Europe	27	429	334	0.78 (0.74, 0.82)
Africa	1	24	8	0.33 (0.16, 0.55)
Asia	8	119	65	0.55 (0.45, 0.64)
Oceania	1	4	1	0.25 (0.01, 0.78)
Publication year				
2007	3	47	34	0.72 (0.57, 0.84)
2008	2	4	4	1.00 (0.40, 1.00)
2009	6	175	92	0.53 (0.45, 0.60)
2010	3	45	30	0.67 (0.51, 0.80)
2011	8	77	64	0.83 (0.72, 0.90)
2012	10	144	96	0.67 (0.58, 0.74)
2013	7	121	93	0.77 (0.68, 0.84)
2014	5	167	88	0.53 (0.45, 0.60)
2015	7	37	35	0.95 (0.80, 0.99)
2016	10	83	53	0.64 (0.53, 0.74)
2017	6	129	94	0.73 (0.64, 0.80)
2018	5	49	45	0.92 (0.80, 0.97)
2019	6	120	80	0.67 (0.57, 0.75)

*AMR = Antimicrobial resistance. ** 4/78 guidelines did not have recommendations that considered resistance ***International= World Health Organization

Figure 2: Number of regional guideline recommendations that consider AMR

Additionally, 48% (385/808) recommendations considered both population-level and outcome-level AMR dimensions simultaneously. Consider the following recommendation as an example: fully immunized infant or school-aged children with community-acquired pneumonia admitted to hospital are recommended to take ampicillin or penicillin G given that local epidemiologic data lack a substantial high-level of penicillin-resistance for invasive *S. pneumoniae*.(73) This recommendation is considering local resistance patterns (population-level dimension), and is also followed by a evidence summary the explains that lower costs of ampicillin or penicillin G need to be balanced by the increased possibility of emergence of resistance (outcome-level dimension) that may occur from prescribing a broad-spectrum antibiotic. About 23% (n = 182/808) of recommendations considered local resistance patterns in a similar manner.

We also found that not all recommendations consistently considered local resistance patterns, and that some put the onus on the clinicians consider these dimensions during decision-making.

2.1.2. Credibility of international and regional guidelines with recommendations that consider AMR

Overall, 39% (n = 29/74)(57-59, 61, 74-79, 82, 93, 103, 105, 106, 110-113, 118, 120, 127-134) of all international and regional practice guidelines had scores of 60% or greater in scope and purpose, rigor of development, and editorial independence.

Of the 29 guidelines that met our credibility cut-off, 10 were developed in North America(57, 74-79, 82, 93, 134), 9 in Europe(61, 84, 103, 105, 106, 110-113, 125), and 2 were developed in Asia.(118, 120) When we compared international and regional guidelines, majority of WHO guidelines performed significantly better than regional guidelines (table 4). Guidelines that did not meet our credibility cut-off score and excluded from further assessment included: nineteen from

North America, seventeen from Europe, five from Asia, and three guidelines from South America, Africa, and Oceania.

Table 4: Performance of World Health Organization versus regional guidelines with AMR considerations

AGREE II scores	World Health Organization guidelines (N=9)	Regional guidelines (N=65)	Mean difference (95%CI)	P
Domain 1: Scope and purpose				
Mean domain score (SD) as %	89(13)	71(22)	-18 (-0.28, -0.06)	0.004
Score range as %	69–100	17–100		
Scored 60% or greater as % (n)	100 (n = 9)	68 (n = 44)		
Domain 3: Rigor of development				
Mean domain score (SD) as %	81(24)	51(23)	-30 (-0.50, -0.11)	0.005
Score range as %	20–99	6–98		
Scored 60% or greater as % (n)	89 (n = 8)	37 (n = 24)		
Domain 6: Editorial independence				
Mean domain score (SD) as %	88(20)	56(30)	-32 (-0.48, -0.15)	0.001
Score range as %	38–100	0–100		
Scored 60% or greater as % (n)	89 (n = 8)	49 (n = 32)		

SD: standard deviation
AMR: antimicrobial resistance
P: p-value
AGREE II: Appraisal for Guidelines Research and Evaluation II

2.1.3. Guidelines considering values, resource use, acceptability, feasibility, and equity

Through our search, we found that only 5(58, 59, 128, 129, 131) of the 29 guidelines reported all factors required for broader recommendation contextualization: values, resource use, acceptability, feasibility and equity. The WHO was the only guideline developer to report all five factors in four tuberculosis guidelines and one gonorrhoea guideline.

Across all 29 guidelines, resource use was the most considered (n = 23 guidelines), followed by values (n = 16 guidelines) and acceptability (n = 12 guidelines) and feasibility (n = 12 guidelines). Equity was the least considered factor with only seven guidelines that made such considerations (figure 3): two were regionally and five were internationally developed. The WHO, the National

Institute for Health and Care Excellence (NICE), and the United States Preventative Task Force were the only organizations to consider equity.

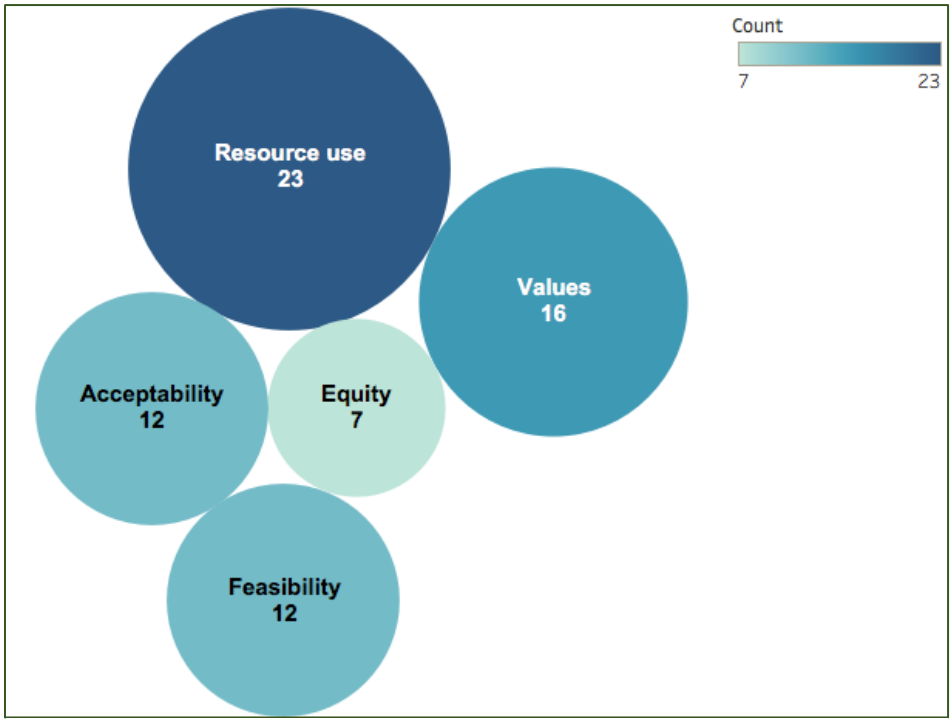

Figure 3: Contextualization of GRADE Evidence to Decision Frameworks in current infectious disease guidelines

Regional guidelines tended to consider values, resource use, acceptability, feasibility and equity less than internationally developed guidelines. Most regional guidelines considered one (n = 6/21) or two (n = 6/21) or three (n = 4/21) or none (n = 4/21) of the above contextual factors. Values and resource use was considered the most, while acceptability, feasibility and equity were less considered in regionally developed guidelines (figure 4).

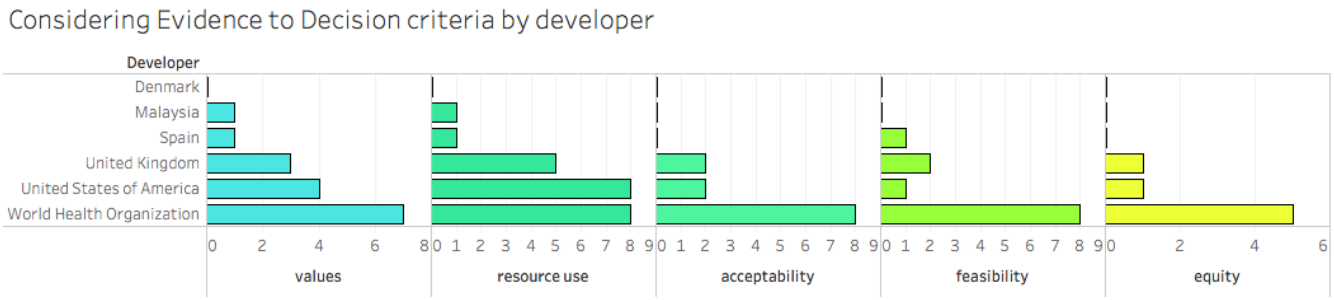

Figure 4: Number of internationally and regionally developed guidelines with considerations of GRADE Evidence to Decision Frameworks

2.2. DISCUSSION

Relatively few guidelines were published over a 13 year period for highly prevalent diseases that require recommendations that consider local aspects such as resistance. The compliance of recommendations is often unsatisfactory despite the emerging consensus that the reporting of Evidence to Decision dimensions is ethically and scientifically essential. Some of the proposed criteria seemed to be adopted by guideline developers (i.e. values and resource use), while others were less so: satisfaction rate was variable among guidelines and there were inconsistencies between regions and guidelines promoted/sponsored by different entities.

Frameworks including GRADE Evidence to Decision and it's enforcement by the WHO and NICE seem to positively influence guidelines with high proportion of guidelines containing complete information necessary to provide optimal guidance on how to use antibiotics in the considered syndromes.

Approximately 60% of regionally developed guidelines were of moderate and low quality, and tended to report less factors for contextualization of guidelines. As a result, we recommend regional guideline developers to polish their methodology including the processes used in evidence syntheses and recommendation formulation, transparency, and addressing potential

unduly biases with competing interests. As we have shown here, there are existing infectious disease guidelines that can be utilized to masterfully confront these shortcomings.

This is the first study to assess the extent to which guidelines are considering local dimensions such as AMR. We employed timely systematic methods to conduct our review and validated tools to measure quality of guidelines.(50, 56)

Arguably, using a credibility cut-off score of 60% or greater for three of the six AGREE II domains may be a limitation to our quality assessment. However, these restrictions parallel existing literature and methodology to assess quality of guidelines.(50, 135) In addition, we assessed reporting of GRADE Evidence to Decision Frameworks at the guideline level instead of the recommendation level to accommodate regional guidelines that do not report these criteria for every recommendation. We used dimensions that are fairly general as they apply to all interventions. These dimensions can be complemented with specific criteria related to the antibiotic field. For example, providing guidance on the appropriate threshold for escalating empiric guidance from narrower spectrum agents to broader spectrum agents. In other words, the real test for antibiotic guidelines is whether they facilitate making the potential implications of antibiotic prescribing on resistance available to the prescribers and the public, leading to virtuous and parsimonious prescribing and consumption habits.

Our results for a sample of guidelines in 2007–2019 are a snapshot from what has become a rapidly evolving field. It is likely we missed some national and international guidelines, as our search of grey literature was limited. The quality of the included guidelines might be slightly better when compare to that of guidelines that are not indexed.

A similar study discovered that about two thirds of respiratory tract infection recommendations on empirical antibiotic use did not consider country-specific resistance patterns.(39) The use of a broader framework and additional focus areas may have resulted in the larger number of

recommendations that considered AMR uncovered by this study. Aside from these findings, both studies support that there are inconsistencies in considering AMR in recommendation development and potential duplication of work among infectious disease guidelines.

In light of our research, we propose the following implications for future guideline development practice. Guideline development can be done efficiently and economically by using work done by other developers including the WHO. Rather developing guidelines from scratch, time and resources(45) may be shifted towards refining AMR surveillance systems that provide national resistance data to support recommendations and appropriate antibiotic use. Further, country-level participation of Global Antimicrobial Resistance Surveillance System (GLASS) enhances global monitoring of resistance trends and emerging resistance as well as the ability to evaluate the effectiveness of interventions.(136) As of 2020, 94 countries are participating in GLASS.(137)

However, surveillance systems depend on infrastructure, national laboratory capacities, and data management, which some countries are lacking.(39, 138) In 2018, there was at least one country within each WHO regions with the ability to collect national resistance data.(138) Regions facing unique challenges to antibiotic stewardship capacities,(139) may look to recommendations developed by other regions with similar resistance experiences.

Finally, as new antibiotic therapies and evidence become available, and the scientific community cumulates more evidence on resistance patterns and their implications for local prescribing, future infectious disease guideline recommendations may require more frequent updating than others.

Although we focused on recommendations in regards to antibiotic selection and prescribing, there are many players in appropriate use that should be assessed including rapid diagnostics to rule-out viral infections and resistant strains.(140) In addition, research should also explore whether recommendations are appropriately guided by evidence, resistance data, and the WHO's

Essential Medicines List and AWaRe Classification Database of Antibiotics updates.(141) Finally, future systematic reviews should focus on equity in the context of AMR.

2.3. CONCLUSION

Our study offers a snapshot of how current guidelines are considering contextual factors necessary to appropriately prescribe antibiotics. We also presented an initial start to an AMR framework used in combination with GRADE Evidence to Decision Frameworks to facilitate amelioration of the cornerstones that are guiding current antibiotic use. This may preserve the remaining and essential medicines we have left and the future of new classes of antibiotics.(16)

2.4. CONTRIBUTORS

RS, HJS, NS, and ML conceived the study. RS, HJS, NS, ML, and TP designed the study protocol. RS coordinated the study. RS, AB, AD, GPM, MV, SK, and TB assessed eligibility of records at title and abstract. RS, AD, and MV searched for unpublished guidelines in key websites. RS, AB, AD, GPM, MV, and SK assessed eligibility of full text articles. RS, AB, AD, FS, GPM, MV, and SK extracted data and assessed credibility using AGREE II. NS settled disputes. RS analyzed and interpreted the data with input from HJS, NS, and ML. RS and HJS drafted the manuscript, with writing contributions from NS, ML, and LM. All authors had a chance to interpret and make edits to the manuscript.

2.5. ACKNOWLEDGMENTS

We would like to thank Stephanie Sanger from the Health Science Library at McMaster University for assisting in the development our search strategy and biostatistician Dr. Thuva Vanniyasingam for assisting with developing an analysis plan for our protocol.

Chapter 3. Adaptability of infectious disease guidelines that consider AMR to the Canadian context: a systematic review

3.1. STUDY RATIONALE

In 2015 UN member states committed to fight against AMR's threat to global health and economic growth by developing and implementing national action plans. As outlined in the WHO's Global Action Plan, one way to address the misuse of antibiotics is through the development of trustworthy practice guidelines.

In 2017, the Pan-Canadian Framework for Action was developed to guide and coordinate Canada's efforts to fight AMR. The framework includes the establishment of pan-Canadian guidelines that could "improve and harmonize antimicrobial prescribing practices" among health care professionals.(142) It also calls on professional associations and licensing bodies in Canada to "establish standards and certification for prescribing guidelines".(142) Current challenges in antibiotic stewardship among Canadian clinicians include accessibility and consistency of guidelines, for example, finding relevant resources pertaining to AMR, and having multiple guidelines on the same topic available for different prescribing professionals.(143)

Instead of creating from scratch, Canadian guideline developers can use previous work done by other guideline groups that are both credible and that consider AMR. This would create efficiency and minimize costs required to create national and institutional guidelines that are applicable to unique contexts in Canada. GRADE-ADOLOPMENT (or ADOLOPMENT) is a process that allows developers to use existing credible guidelines and recommendations through adoption, adaption or making new recommendations altogether.(42) ADOLOPMENT uses GRADE Evidence to Decision Frameworks to create guidelines and recommendations that are contextualized, transparent, and clear.(42) Evidence to Decision frameworks enables guideline developers to incorporate evidence on values, resource use, acceptability, feasibility, and equity to recommendations,(42) that may influence AMR.

3.2. OBJECTIVE

The main objective was to investigate whether there are existing infectious disease guidelines that consider AMR, and that can be easily adopted or adapted to Canadian contexts. Our goal is to reduce duplication of work among guideline developers, conserve resources, and to create guidelines with efficiency.

3.3. HYPOTHESIS

We hypothesized that there exists trustworthy guidelines that provide important information required for later adoption or adaption to local Canadian contexts.

3.4. METHODS

This paper is formatted according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines.

3.4.1. Protocol and registration

The protocol for this systematic review was registered with PROSPERO (registration #CRD42020145235). The study was internally funded by the Michael G. DeGroote Cochrane Canada and McGRADE centres.

3.4.2. Eligibility criteria

We systematically reviewed the literature for guidelines that are both credible and contain recommendations that consider AMR. In conducting our search, we were guided by two frameworks: (1) the population, intervention, comparison, guideline attributes, and recommendation characteristics (PICAR) framework; and (2) a framework that we developed for assessing AMR consideration (table 1 and 2).

We selected three types of infection: tuberculosis, gonorrhoea, and respiratory tract infections (specifically: otitis media, pharyngitis, sinusitis, and community-acquired pneumonia) as they are becoming increasingly harder to treat due to AMR.

Tuberculosis is currently not among the top ten causes of death in Canada, however most prevalent in vulnerable indigenous populations, and could return. Harder to treat drug-resistant tuberculosis strains are increasing and projected to account for a quarter of all deaths by 2050.(54) Neisseria gonorrhoea is an urgent public health threat.(15) The international spread of resistance to the last effective therapy, ceftriaxone and azithromycin, threatens sustained treatment of gonorrhoea.[17,18] Otitis media, pharyngitis, sinusitis, and community-acquired pneumonia are prevalent and *Streptococcus pneumoniae* (the main causal microorganism*)*, was classified as a serious public health threat due to resistance.(15) All these syndromes have been prioritized by WHO as part of AWaRe, the new classification system that support a more nuanced approach to target inappropriate use of broad spectrum Watch antibiotics.(29)

We included English language guidelines published between 2007 and 2019 on the above selected infections. We marked the 2007 WHO decision to update its guideline development as a major change in methodology, representing a division of two eras.(55) We limited the focus of our analyses to the era following this change.

We included guidelines with clearly articulated recommendations as defined by the *IOM Standards for Developing Trustworthy Clinical Practice Guidelines*.(35) After contacting guideline developers, we excluded guidelines with unobtainable supplementary materials required for analysis.

3.4.3. Informational sources

We searched Ovid MEDLINE and Embase from inception to June 7, 2019. An information specialist specialized in systematic reviews at McMaster University, Hamilton, Ontario, Canada, developed our full electronic search strategy and the results were deduplicated in Ovid (Appendix).

We conducted a second search in four guideline databases: TRIP (https://www.tripdatabase.com), G-I-N (https://www.g-i-n.net/home), BIGG (http://sites.bvsalud.org/bigg/en/biblio/), and the Canadian Medical Association PG Infobase (https://joulecma.ca/PG/homepage) using key words: tuberculosis OR tuberculous OR TB OR gonoc* OR gonorr* OR pneumonia* OR otitis media OR pharyngitis OR sinusitis OR community acquired pneumonia. We searched key international and Canadian websites (list provided in Appendix, table 6) were used to identify guidelines that may not be published and reviewed references of included guidelines.

3.4.4. Guideline selection

Independently and in pairs, reviewers (RS, AB, AD, MV, GPM, SK, and TB) screened titles and abstracts and the full text of potentially eligible guidelines in a reference manager (EndNote X.9). Disagreements were resolved by discussion or with a third reviewer. All decisions were recorded in an Excel spreadsheet.

3.4.5. Data collection and quality assessment

We extracted data from guidelines, retrievable supplementary materials, and guideline development documents facilitated by pilot-tested forms and distillerSR (https://www.evidencepartners.com). Extractors (RS, AB, AD, FS, GPM, MV, and SK) recorded data independently and in pairs, and resolved disagreements.

Reviewers screened through recommendations classifying them as either considering AMR or not according to inclusive AMR dimensions. Although guidelines may have adopted different approaches to considering resistance with varying level of technicalities and detail, our operational definitions for considering a guideline "compliant" were inclusive. We assumed that for each recommendation, there would be an opportunity to consider information pertaining to AMR at the population- and outcome-level, given that formulation of specific recommendations are guided by PICO (population, intervention, comparison and outcome) frameworks. Population-level considerations include recommendations for populations with some level of resistance, considerations of local resistance patterns, recommending the use of narrow-spectrum antibiotics and recommending the watchful-waiting approach to prescribing. Outcome-level dimensions included considering future prospects of AMR or the emergence of resistance as a consequence of antibiotic use (examples provided in table 2).

We considered a guideline that reports information on any of the above dimensions in either the recommendation, accompanying evidence summaries, or PICO framework would be considered satisfactory. Whereas guidelines that generally discussed AMR as an issue, without linking information pertaining to AMR to each recommendation were considered unsatisfactory.

We assessed a guideline's credibility using the Appraisal of Guidelines for Research & Evaluation (AGREE) II Instrument focusing on three relevant domains: a well-defined scope and purpose (domain one), rigorous development including a systematic search for evidence, transparent reporting of methods, links between evidence and recommendations, external review, and procedures for update (domain three), and editorial independence (domain six).(56) Satisfactory quality guidelines scored 60% or greater in these domains.(50)

We also abstracted information on values, resource use, acceptability, feasibility, and equity from guidelines that met our satisfactory cut-off (i.e. 60%). Briefly, regions may differ in the accessibility

of antibiotics, the cultural view towards the use of antibiotics, pharmaceutical costs, and health care structures. We selected these dimensions as transparent reporting of these factors is creditable: in appraising the evidence for antibiotics, guideline developers should be aware of the breadth of implications of their recommendations. Guidelines that ignore this wider agenda could provide narrow, misleading guidance.

3.4.6. Data items

We extracted data from all included guidelines, retrievable supplementary materials, and guideline development documents in four phases.(42) We extracted details at the guideline-level (publication date, focus area, etc.) and recommendation-level (total number of recommendations and antibiotic prescribing recommendations, recommendation statements, etc.). Additional extractions included systematic review details (search strategies, risk of bias assessment, etc.), and reporting of values, resource use, acceptability, feasibility and equity. A detailed list of extracted data is provided in the Appendix.

We assumed that if guidelines made AMR, values, resource use, acceptability, feasibility and equity considerations, then it would be clearly reported in the guideline, supplementary material and/or guideline development document.

3.4.7. Synthesis of Results

We conducted descriptive statistics, including counts and proportions (95%CI) for guidelines and recommendations by year of publication. We examined distributions of the scaled domain scores using the Shapiro-Wilk normality test. We calculated the mean (SD) for AGREE II scores by region. We compared the quality of guidelines from Canada verses the rest of the world using scaled domain scores, mean difference, and a t-test. We calculated the frequency of guideline reporting of: values, resource use, acceptability, feasibility, and equity. All analyses were

conducted in Microsoft® Excel and R-studio (RStudio Team (2016). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA URL http://www.rstudio.com/.).

3.5. RESULTS

Our initial search identified 10,365 records. After screening, we narrowed this down to 78 guidelines with at least one recommendation that met our inclusion criteria (n = 28 tuberculosis, n = 12 gonorrhea, n = 38 respiratory tract infections), and that had sufficient information for assessment. We excluded one Canadian gonorrhoea guideline because we were unable to retrieve supplementary materials (figure 1).(62)

After classifying recommendations, we found that 74 guidelines had at least one recommendation that considered AMR and four guidelines without such considerations. These were excluded from further assessment. A total of six Canadian developed guidelines and 68 international guidelines were included for credibility assessment.

Within the 74 guidelines, we found approximately two thirds of recommendations (n = 808/1198) considered AMR; that figure was 55% for tuberculosis recommendations (n = 272), 85% for gonorrhoea recommendations (n = 150), and 75% for respiratory tract infection recommendations (n = 386).

3.5.1. Credibility of guidelines by geographic area

3.5.1.1. North America

We assessed 29 North American guidelines for credibility. Overall, only 34% (n = 10/29)(57, 74-79, 82, 93, 134) had scores of 60% or greater across all three AGREE domains. Mean scores were 70 (SD = 20) for scope and purpose, 54 (SD = 23) for rigor of development, and 62 (SD = 29) for editorial independence.

3.5.1.2. Europe

Of the 26 European guidelines, 35% (n = 9/26)(61, 84, 103, 105, 106, 110-113, 125) had scores of 60% or greater in the relevant AGREE domains. European guidelines performed well in scope and purpose, with a mean score of 74 (SD = 24), but fell short in rigor of development and editorial independence with mean scores of 52 (SD = 24) and 52 (SD = 32) respectively. We found poor reporting of financial and competing interests in 58% (n = 15/26) of European guidelines.

3.5.1.3. Asia

Only two of seven guidelines developed in Asia had scores of 60% or greater in each of the AGREE domains. The mean score was 76 (SD = 24) for scope and purpose, 44 (SD = 17) for rigor of development, and 54 (SD = 31) for editorial independence.

3.5.1.4. South America, Africa, and Oceania

The three guidelines from South America(124), Africa(125), and Oceania(126) did not meet our credibility cut-off across all three domains, and were therefore excluded from our study.

3.5.2. Canada versus rest of the world

Table 5 outlines the performance of Canadian vs. rest of the world guidelines by AGREE II domains. AGREE II scores for Canadian guidelines ranged from 22% to 75% for scope and purpose, 6% to 69% for rigour of development, and 0% to 71% for editorial independence. For rest of the world, AGREE II scores ranged from 17% to 100% for scope and purpose, 11% to 99% rigour of development, and 0% to 100% for editorial independence. Overall, we found that 29 guidelines (n = 29/74)(57-59, 61, 74-79, 82, 93, 103, 105, 106, 110-113, 118, 120, 127-134) of guidelines had scores of 60% or greater across all three domains and all of which were developed outside of Canada. Organizations that met our cut-off score included:

- World Health Organization (WHO)

- Infectious Disease Society of America (IDSA)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guidelines Network (SIGN)
- United States Preventative Task Force (USPTF)
- American Academy of Otolaryngology, American Academy of Pediatrics
- British Thoracic Society, Danish Health and Medicines Authority
- Institute for Clinical Systems Improvement,
- Malaysian Family Physician
- Ministry of Health Malaysia
- Society of Primary Care Physicians Spanish Society for Pulmonology and Thoracic Surgery.

We found that none of the Canadian developed guidelines (n = 0/6) met scores 60% or greater in all three domains. All mean scores for Canadian guidelines were below our cut-off in scope and purpose, rigor of development, and editorial independence. Sources of weakness included unspecific health questions and population of focus, lack of clear search strategies and eligibility criteria, lack of discussion on the balance between health benefits and harms, and poor reporting of financial and competing interests.

Table 5: Performance of Canadian vs. rest of the world guidelines with AMR considerations*

AGREE II Domain	Canadian guidelines (N=6); mean domain score (SD**) as %	Rest of the world guidelines (N=68); mean domain score (SD) as %	Mean difference (95%CI)	P***
Domain 1	57(19)	75(21)	-18 (-0.38, 0.02)	0.065
Domain 3	36(22)	56(25)	-20 (0.44, 0.03)	0.076
Domain 6	42(28)	62(31)	-20 (-0.42, 0.61)	0.161

*Antimicrobial resistance
**SD= standard deviation
***p-value

Figure 5 maps the variability in AGREE II domain scores within and across guidelines in Canada and the rest of the world. Boxplots show that there quality of guidelines vary on an international scale. However, Canadian guidelines performed particularly poorly in rigorous development and editorial independence.

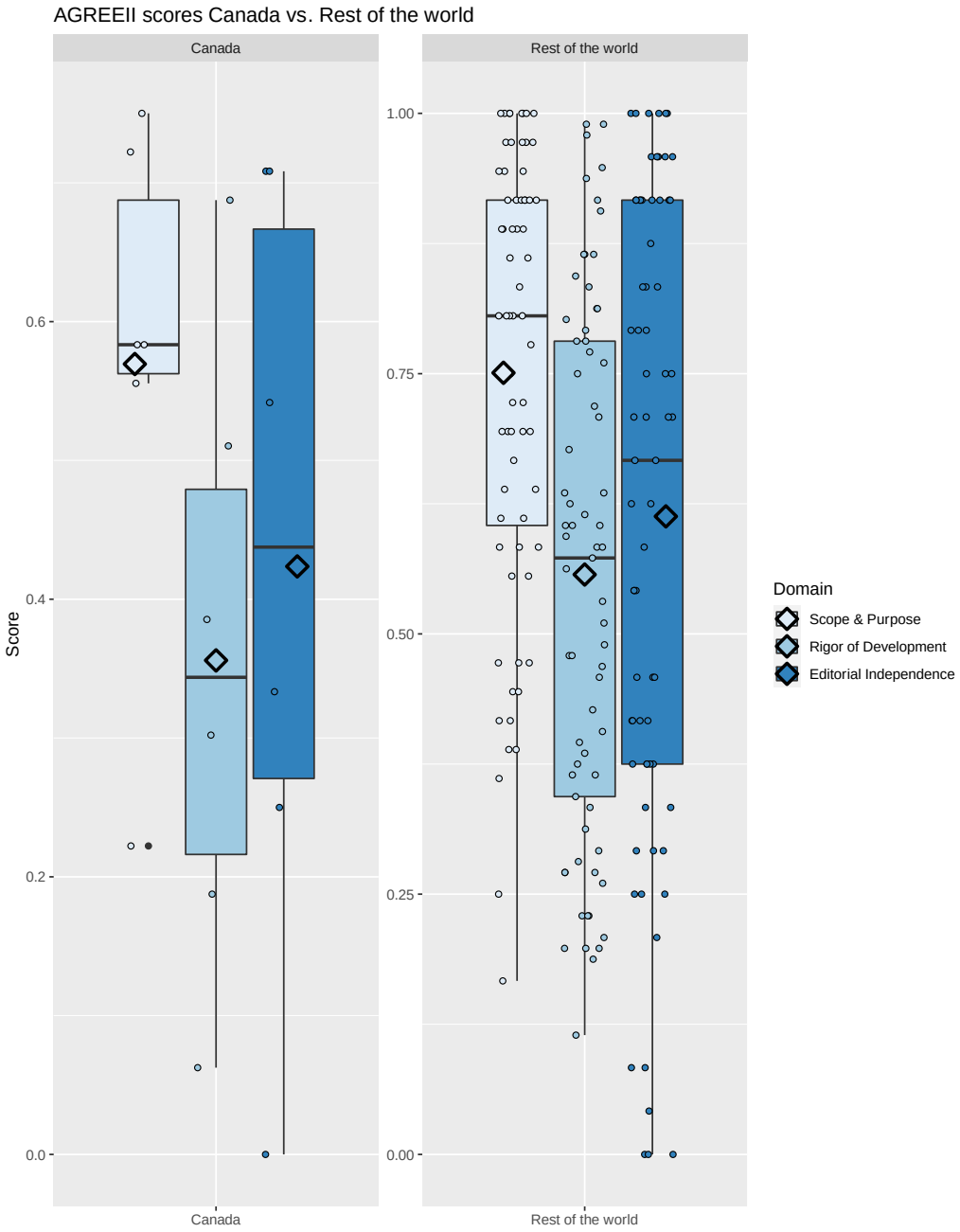

Figure 5: Boxplot of AGREE II scores comparing Canada and rest of the world guidelines
AGREE II = Appraisal of Guidelines for Research & Evaluation II Instrument; Scope and purpose = domain one; rigor of development = domain three; editorial independence = domain six; diamonds = mean AGREE II score; blue circles = individual guidelines.

3.5.3. Adoption/Adaption of guidelines

Given that none of the Canadian guidelines met our cut-off score, they were not eligible for adoption or adaption assessment. We therefore assessed all 29 guidelines (21 regionally developed, and 8 internationally developed) that met our cut-off score for adoption or adaption to the Canadian context.

3.5.3.1. Reporting Values, Resource Use, Acceptability, Feasibility, and Equity

We found that only 5 of the 29 guidelines can be adopted or adapted as they report all of the five Evidence to Decision criteria: values, resource use, acceptability, feasibility, and equity. The WHO was the only guideline developer to report all five criteria in 63% (n = 5/8) of their guidelines. Regionally developed guidelines tended to report less Evidence to Decision criteria. NICE was the only regional developer to report four criteria.

Among the 29 guidelines, 52% (n = 15/29) reported both values and resource use.(58, 59, 74-76, 82, 103, 106, 111, 118, 128-131) The remaining guidelines reported only values (n = 1/29), only resource use (n = 8/29), or neither values nor resource use (n = 5/29) in addition to other Evidence to Decision criteria.

When we compared WHO with regional guidelines, we found that 100% (n = 8/8) of WHO guidelines reported resource use, and 88% (n = 7/8) reported values. Conversely, those figures were only 71% (n = 15/21) and 43% (n = 9/21), for regional guidelines respectively (figure 6).

Overall, 24% of guidelines (n = 7/29) considered equity when formulating their recommendations. Compared to equity, acceptability (n = 12/29) and feasibility (n = 12/29) were considered more often in guidelines.

Among WHO guidelines, we found that acceptability and feasibility were considered in all eight guidelines (n = 8/8) eligible for adoption or adaption opportunities. However, equity was considered in a total of five guidelines (n = 5/8). By contrary, we found only two regional guidelines (n = 2/21) considered equity, and four guidelines with acceptability (n = 4/21) and feasibility (n = 4/21) considerations.

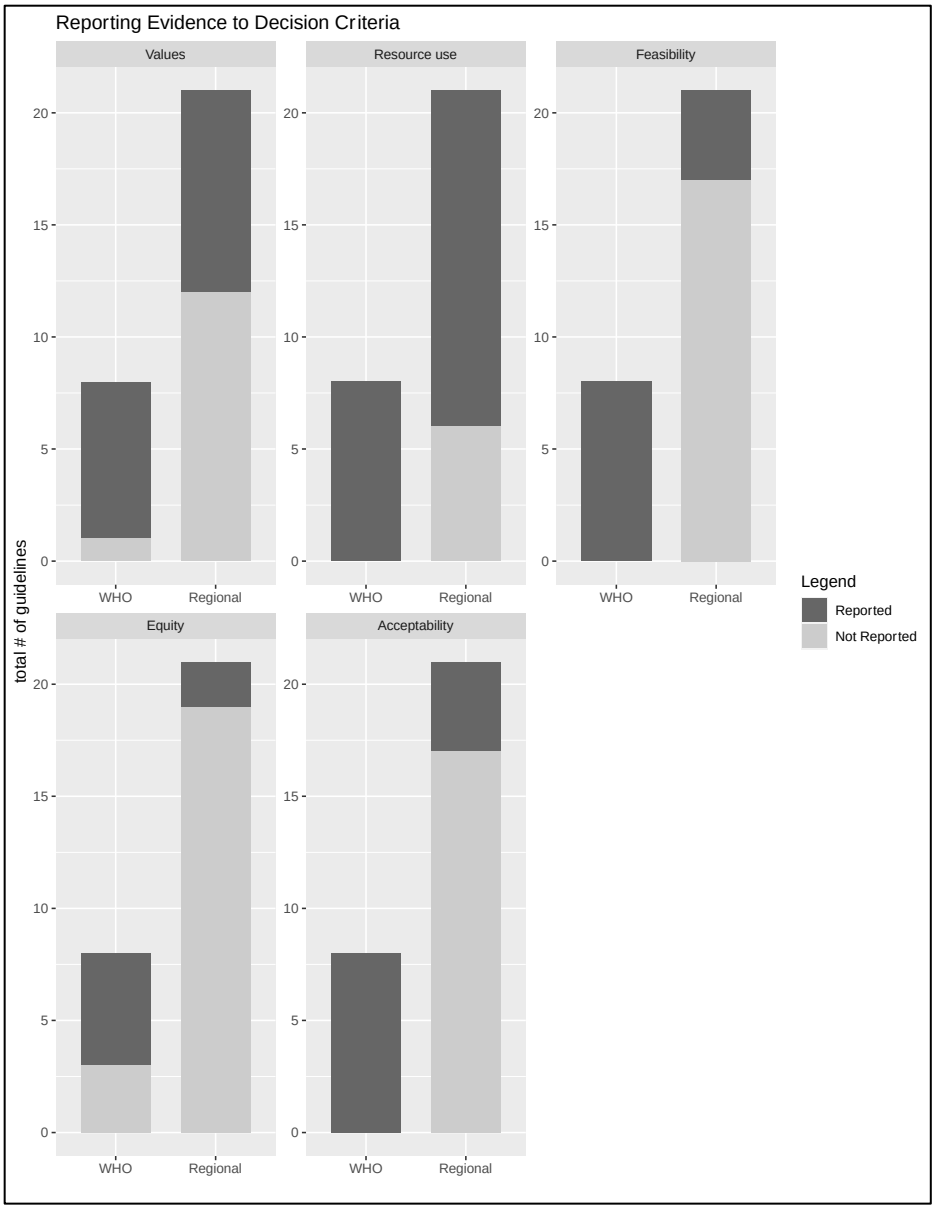

Figure 6: World Health Organization versus regional guidelines meeting AGREE II scores >/= 60% reporting GRADE Evidence to Decision Frameworks

3.6. DISCUSSION

3.6.1. Summary of the main results

This review highlights that there are 5(58, 59, 128, 129, 131) guidelines that can be adopted or adapted to the Canadian context given that they consider and report: AMR, values, resource use, acceptability, feasibility, and equity. All five guidelines were internationally developed by the WHO.

Canadian guidelines in our sample performed poorly in scope and purpose, rigorous development, and editorial independence. Compared to guidelines developed outside of Canada, Canadian guidelines were of lower quality.

3.6.2. Strengths and limitations

This is the first study to assess the quality of infectious disease guidelines with recommendations that consider AMR, and their adaptability to the Canadian context. We employed timely systematic methods to conduct our review and validated tools to measure quality of guidelines.(50, 56)

Arguably, using a credibility cut-off score of 60% or greater for three of the six AGREE II domains may be a limitation to our quality assessment. However, these restrictions parallel existing literature and methodology to assess quality of guidelines.(50, 135) In addition, we assessed reporting of Evidence to Decision criteria at the guideline level instead of the recommendation level, as recommended by GRADE methodology. The decision for assessment at the guideline-level was to accommodate regional guidelines that do not report these criteria for every recommendation. Furthermore, we used dimensions that are fairly general as they apply to all interventions. These dimensions can be complemented with specific criteria related to the antibiotic field.

3.6.3. IMPLICATIONS FOR PRACTICE

In light of our research, we propose the following implications for future practice. Canadian guideline developers can ameliorate their national and institutional guidelines in an efficient and economic manner by using work done by other developers.

Canadian guideline development methodology should be guided by standards including the Institute of Medicine (IOM), Guidelines International Network (G-I-N), and GRADE-Evidence to Decision Frameworks. Other tools that assist in dissemination of clear, specific, and transparent guidelines and recommendations include the Reporting Items for practice Guidelines in HealThcare (RIGHT) statement(144) and the Developing and Evaluating Communication strategies to support Informed Decisions and practice based on Evidence (DECIDE) project(145). To facilitate later adoption or adaption, developers should also report details linking evidence to decision and include all factors important to contextualizing recommendations that may influence AMR. Canadian guidelines, including all supporting materials, should also be easily accessible to others. These improvements will help reduce research waste from guideline development, and duplication of work across Canadian developers.

On an international level, future development of respiratory tract infection guidelines and recommendations should consider all Evidence to Decision that would help facilitate in their later adoption/adaption. We found that none of them report all relevant Evidence to Decision criteria for later adaption.(57, 74, 78, 79, 82, 84, 105, 110-113, 120)

3.6.4. CONCLUSION

Our study offers a way to refine infectious disease guidelines in Canada. We have highlighted that there are existing guidelines that can be adopted/adapted, and guidelines that may need improvement. While we wait for new classes of antibiotics, we can ameliorate the cornerstones guiding antibiotic use.(16) This may preserve the remaining and essential medicines we have left

by striking a balance between the use of appropriate methodology on one end, and keeping in mind the impact these recommendations may pose on AMR, on another.

Chapter 4. Conclusions

4.1. MAIN CONCLUSIONS

Guidelines are the cornerstones for appropriate antibiotic use, and are required to preserve our essential medicines for human and animal treatment. This thesis uncovered the need to ameliorate Canadian and regional infectious disease guidelines and antibiotic recommendations. Improvements needed include: better incorporation of contextual factors that influence AMR, rigorous development methodology, and transparency.

To date, there is a lack of guidance on how to incorporate AMR in recommendations. The development of an AMR recommendation framework may harmonize global efforts to address the misuse of antibiotics in human treatment through guidelines. This thesis presents an initial start to an AMR recommendation framework, and is described in detail in section 4.1.

However, an AMR recommendation framework alone is inadequate. Unique societal and structural factors (i.e. values, resource use, acceptability, feasibility, and equity) influencing AMR should also guide decision-making. There exists guidelines that can be adopted or adapted using ADOLOPMENT — a process facilitating recommendation contextualization, transparency, and that minimizes research waste from duplication of efforts across guideline developers with efficiency. Such a process would assist guideline developers to contextualize their recommendations.

4.2. AMR dimensions in recommendations

Guideline development advises that each recommendation answer a pre-determined and well-defined health care question that would later be turned into actionable statements.(35, 42, 47, 146) Formulating questions according to a well-known 'PICO' (population, intervention, comparator and outcome) framework facilitates careful specification of health care questions by both systematic review authors and guideline developers.(147) The following is a snapshot of how and, potentially why, current recommendations for antibiotics are considering AMR at the population- and outcome-level. We present this as an initial start to the development of an AMR recommendation framework, but appreciate that these dimensions can be complemented with specific criteria related to the antibiotic field.

4.2.1. *Population*: the recommendation is for a population that is infected with a resistant organism

Populations with resistant bacterial infections will require special antibiotic treatment depending on their susceptibility pattern. Antibiotic recommendations that are for specific populations consider resistance by selecting antibiotics that are effective at treating a particular strain of resistant bacteria. Such recommendations are usually supported by antimicrobial susceptibility testing to uncover if the bacteria is susceptible or resistant to one or more drugs and sequentially find (an) effective antibiotic(s).

4.2.2. *Population*: the recommendation is supported by country-specific resistance patterns

Resistance patterns differ within and across regions. Epidemiologic surveillance provides a description of resistance patterns, and identifies trends and outbreaks of resistant organisms.(138, 148)

Resistance patterns are essential to the use of antibiotics, as it tells us on a population-level, which antibiotics are effective, which ones are less susceptible, or which ones no longer are effective. As such, it helps to guide which antibiotics should be prescribed, especially for empirical use, i.e. when it is unclear of what type of pathogen we are dealing with, and when waiting for microbiological results.

When developing recommendations, guideline developers and associations should align antibiotic selection with what is experienced at the local-level, which is an opportunity to manage antibiotic resistance and cautiously use of antibiotics.(39) However, this principle cannot always be fulfilled as the ability to collect such data depends on surveillance infrastructure, national laboratory capacities, and data management, which some countries are lacking.(39, 138) Currently, within each WHO region, there is at least one country with the ability to collect national resistance data.(138)

4.2.3. *Population*: the recommendation is to prescribe narrow-spectrum antibiotics

Generally, narrow-spectrum antibiotics cover a select group of bacterial types. This differs from broad-spectrum antibiotics which generally cover a wide-range of bacterial types. Inappropriate use of antibiotics also occurs when broad-spectrum antibiotics are prescribed when a targeted narrow-spectrum antibiotic can be used.(149)

The WHO's Essential Medicines List Working Group classified antibiotics as either Access, Watch, and Reserve. Access antibiotics comprise of mostly narrow-spectrum antibiotics recommended for first or second-line empirical treatment.(150) Watch antibiotics are broader antibiotics only to be used for specific infectious diseases, given that they have a higher resistance potential and critically important to human health. Finally, Reserve antibiotics are to be saved for infections due to multidrug-resistant organisms.(151)

4.2.4. *Population*: the recommendation is for no antibiotic or back-up antibiotic or watchful waiting approach

Recommending no antibiotic or providing a back-up prescription is part of stewardship initiatives to prescribe antibiotics only when necessary.(152) It is also intended to limit the use of antibiotics for viral infections, especially for children with respiratory tract infections. The purpose of this approach, also known as 'watchful waiting', is to allow two to three days to pass before initiating antibiotics and to allow for symptoms to resolve on their own.(153)

4.2.5. *Outcome*: the recommendation considers resistance as an outcome

An outcome is a consequence (whether desirable or undesirable) of a particular action or decision that is made. Recommendations require consideration of important desirable or undesirable outcomes, which may vary across patients, health care providers, carers, cultures, and public health implications.(147)

Conservation of antibiotics and management of antibiotic resistance requires the consideration of the way we use of them today will influence how they will be used tomorrow. This is why, from a public health standpoint, it is important to consider the impact of our choice of interventions on antibiotic resistance. If our recommendations consider the potential for our current antibiotics to be no longer ineffective given how we use them, decision-makers would be better guided.

Here are examples of outcomes that current infectious disease guidelines are considering:

- 'resistance'
- 'resistant',
- 'drug-resistance',
- 'antibiotic resistance'
- 'antimicrobial resistance'
- 'antimicrobial in vitro resistance'
- 'acquired drug-resistance'

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APPENDIX

Search strategy: Ovid MEDLINE and Embase

Database: Embase <1974 to 2019 June 07>, 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 (tuberculosis or tuberculous or TB).mp. (510746)
2 (gonoc* or gonorr*).mp. (58460)
3 pneumonia*.mp. (557015)
4 strepto*.mp. (531324)
5 (pneumonia* adj2 strepto*).mp. (83649)
6 1 or 2 or 5 (648159)
7 exp clinical pathway/ (14358)
8 exp clinical protocol/ (252634)
9 exp consensus/ (72535)
10 exp consensus development conference/ (35258)
11 exp consensus development conferences as topic/ (26540)
12 critical pathways/ (14358)
13 exp guideline/ (32021)
14 guidelines as topic/ (375998)
15 exp practice guideline/ (526549)
16 practice guidelines as topic/ (381407)
17 health planning guidelines/ (93323)
18 (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt. (40981)
19 (position statement* or policy statement* or practice parameter* or best practice*).ti,ab,kf,kw. (71605)
20 (standards or guideline or guidelines).ti,kf,kw. (243012)
21 ((practice or treatment* or clinical) adj guideline*).ab. (90132)
22 (CPG or CPGs).ti. (12033)
23 consensus*.ti,kf,kw. (53111)
24 consensus*.ab. /freq=2 (52722)
25 ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf,kw. (47116)
26 recommendat*.ti,kf,kw. (85035)
27 (care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab,kf,kw. (142098)
28 (algorithm* adj2 (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti,ab,kf,kw. (16221)
29 (algorithm* adj2 (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti,ab,kf,kw. (22274)
30 or/7-29 (1489076)
31 6 and 30 (17406)
32 limit 31 to yr="2007 -Current" (11340)
33 (randomised or randomized or study or trial).ti. (3257255)
34 32 not 33 (10455)

35 limit 34 to (conference abstract or editorial or erratum or letter or tombstone or address or autobiography or biography or case reports or clinical trial, all or clinical trial protocol or clinical trial protocols as topic or clinical trial or comment or controlled clinical trial or interview or news or newspaper article or patient education handout or personal narrative or portrait or pragmatic clinical trial or randomized controlled trial) [Limit not valid in Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] (2878)
36 34 not 35 (7577)
37 limit 36 to yr="2014 -Current" (3831)
38 limit 36 to yr="2007 - 2014" (4415)
39 remove duplicates from 38 (3464)
40 remove duplicates from 37 (2937)
41 39 or 40 (5910)

Table 6: List of websites of organizations and associations that provide guidelines

International	Canada
The World Health Organization (WHO): https://www.who.int	The Public Health Agency of Canada (PHAC): https://www.canada.ca/en/public-health.html
The Centres for Disease Control and Prevention (CDC): https://www.cdc.gov	Public Health Ontario (PHO): https://www.publichealthontario.ca
The Scottish Intercollegiate Guidelines Network (SIGN): https://www.sign.ac.uk	Pan Canadian Public Health Network: http://www.phn-rsp.ca/index-eng.php
The Robert Koch Institute (RKI): https://www.rki.de/EN/Home/homepage_node.html	The Canadian Task Force on Preventative Health Care (CTFPHC): https://canadiantaskforce.ca
The National Institute for Health and Care Excellence (NICE): https://www.nice.org.uk	The College of Physicians and Surgeons of Ontario (CPSO): https://www.cpso.on.ca
The European Centre for Disease Prevention and Control (ECDC): https://ecdc.europa.eu/en/home	The Guidelines Advisory Committee (GAC): https://www.gacguidelines.ca
The Australian Government National Health and Medical Research Council (NHMRC): https://www.nhmrc.gov.au	The Canadian Agency for Drugs and Technologies in Health (CADTH): https://www.cadth.ca
Australian Clinical Practice Guidelines: https://www.clinicalguidelines.gov.au	Association of Medical Microbiology of Infectious Disease Canada: https://www.ammi.ca
New Zealand Guidelines Group: https://www.health.govt.nz/about-ministry/ministry-health-websites/new-zealand-guidelines-group	The Registered Nurses Association of Ontario's Best Practice Guidelines (NAOBPG): https://rnao.ca/bpg
United States Preventative Services Task Force: https://www.uspreventiveservicestaskforce.org	Canadian Paediatric Society: https://www.cps.ca
Infectious Diseases Society of America: https://www.idsociety.org	British Columbia (BC) Guidelines: https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines
American Academy of Family Physicians https://www.aafp.org	British Columbia Centre for Disease Control (BCCDC): http://www.bccdc.ca
The American Thoracic Society (ATS): https://www.thoracic.org	Towards Optimized Practice (TOP): http://www.topalbertadoctors.org/home/
	Winnipeg Regional Health Authority (WHRA): http://www.wrha.mb.ca

Details extracted and record from the guidelines and supplementary materials[1]:

1. Type of source.
2. Organization.
3. Document title.
4. Website link
5. Reference
6. The date of publication of guidelines/recommendations.
7. Year of planned update of the guideline/recommendations and the systematic review.
8. Recommendation that considers AMR.
9. What type of evidence did the recommendation that considers resistance consider?
10. The recommendation focus (i.e. tuberculosis, gonorrhoea, or respiratory tract infections)
11. The guideline question matched to the recommendation.
12. The number of recommendations on antibiotic use that consider AMR in each guideline.
13. The direction of the recommendations: for or against, or others variations.
14. The strength of the recommendations.
15. Type of infection.
16. Setting: hospital or community (i.e. primary, secondary, and tertiary care settings, low- or high-income settings, etc.).
17. Target population (i.e. people with cephalosporin resistant Neisseria gonorrhoeae).
18. The systematic reviews that support the recommendation. This includes systematic review that supports the certainty of the effect, and the systematic review conducted for the values and preferences of patients, equity issues and applicability.
    a. We will record the publication year.
    b. The research questions in PICO format.
    c. Risk of Bias assessment conducted.
    d. Analysis method (i.e. meta-analysis).
    e. Year of planned update.
19. Type of evidence summary methods (narrative, GRADE tables including the summary of findings (SoF) table, evidence profiles (EP) table, or other evidence tables).
    a. Assessment of the certainty of the evidence for each outcome.

[1] Details are informed by GRADE-ADOLOPMENT paper, appendix 1, step 5.

20. EtD available.

21. Criteria that influence the strength and direction of the recommendations are available or summarized. This includes:
    a. The problem and its importance;
    b. The certainty of the evidence;
    c. The values and preferences of patients. Are the patient's values and preferences described?: yes with search strategy available; yes – systematic review without search strategy, yes–narrative; no; other (specify).
    d. The balance between health benefits, harms and burden;
    e. The resources that are required. Is the cost effectiveness described?: yes–Cost-effectiveness analysis; yes–systematic review without search strategy; yes–narrative; no; other (specify).
    f. The increase or decrease in equity; where there health inequity considerations?
    g. Acceptability: are stakeholder acceptability to most it is to the users and the public described; and
    h. The feasibility of the recommendation: is the feasibility described?

22. Reporting or describing the following EtD criteria (yes/no): values, resource use, acceptability, feasibility, equity.
    a. How were they reported? Was the evidence buried within paragraphs, or easily found within the guideline through subheadings and tables?
    b. Was values, resource use, acceptability feasibility, or equity considerations part of their methodology? If so, the guideline/supplementary material actually report values, resource use, acceptability, feasibility, and equity?
    c. Type of evidence used to inform EtD criteria, i.e. research evidence or expert or expert opinion

Table 7: Number of GRADE Evidence to Decision framework criteria reported in guidelines

Author	Guideline developer	Year	Focus area	Number of EtD criteria reported	Values	Resource use	Acceptability	Feasibility	Equity
Chow AWB et al.	IDSA	2012	Sinusitis	1	Not reported	Reported	Not reported	Not reported	Not reported
Abdul Rahaman JAK et al.	Malaysian Family Physician	2012	Tuberculosis	2	Reported	Reported	Not reported	Not reported	Not reported
World Health Organization	WHO	2014	Tuberculosis	3	Not reported	Reported	Reported	Reported	Not reported
National Institute for Health and Care Excellence	NICE	2016	Tuberculosis	4	Reported	Reported	Reported	Reported	Not reported
World Health Organization	WHO	2019	Tuberculosis	5	Reported	Reported	Reported	Reported	Reported
British Infection Association	British Thoracic Society	2009	Community-acquired pneumonia	1	Not reported	Reported	Not reported	Not reported	Not reported
Spanish Society for Epidemiology, Spanish Society of	Spanish Society for Epidemiology, Spanish	2010	Tuberculosis	3	Reported	Reported	Not reported	Reported	Not reported

Primary Care, Physicians, etc.	Society of Primary Care, Physicians, etc.								
American Academy of Pediatrics	American Academy of Pediatrics	2013	Otitis media	2	Reported	Reported	Not reported	Not reported	Not reported
National Institute for Health and Clinical Excellence	NICE	2014	Community-acquired pneumonia	2	Reported	Not reported	Not reported	Reported	Not reported
World Health Organization	WHO	2015	Tuberculosis	5	Reported	Reported	Reported	Reported	Reported
Richard M. Rosenfeld et al.	American Academy of Otolaryngology—Head and Neck Surgery Foundation	2015	Sinusitis	3	Reported	Reported	Reported	Not reported	Not reported
World Health Organization	WHO	2015	Tuberculosis	5	Reported	Reported	Reported	Reported	Reported

Richard M. Rosenfeld et al.	American Academy of Otolaryngology—Head and Neck Surgery Foundation	2016	Otitis media	3	Reported	Reported	Reported	Not reported	Not reported
World Health Organization	WHO	2016	Gonorrhoea	5	Reported	Reported	Reported	Reported	Reported
P. Nahid et al.	IDSA	2016	Tuberculosis	0	Not reported	Not reported	Not reported	Not reported	Not reported
Institute for Clinical Systems Improvement	Institute for Clinical Systems Improvement	2017	Pharyngitis and sinusitis	1	Not reported	Reported	Not reported	Not reported	Not reported
Stanford T. Shulman et al.	IDSA	2012	Pharyngitis	1	Not reported	Reported	Not reported	Not reported	Not reported
Ministry of Health Malaysia	Ministry of Health Malaysia	2012	Otitis media	0	Not reported	Not reported	Not reported	Not reported	Not reported
Heidemann CL et al.	Danish Health and Medicines Authority and the Danish	2016	Otitis media	0	Not reported	Not reported	Not reported	Not reported	Not reported

	Society of Otorhinolaryngology, Head and Neck Surgery								
The Scottish Intercollegiate Guidelines Network	SIGN	2010	Pharyngitis	2	Reported	Reported	Not reported	Not reported	Not reported
World Health Organization	WHO	2011	Tuberculosis	4	Reported	Reported	Reported	Reported	Not reported
Richard M. Rosenfeld et al.	American Academy of Otolaryngology	2015	Sinusitis	2	Reported	Reported	Not reported	Not reported	Not reported
World Health Organization	WHO	2018	Tuberculosis	5	Reported	Reported	Reported	Reported	Reported
World Health Organization	WHO	2012	Otitis media	4	Reported	Reported	Reported	Reported	Not reported
The National Institute for Health and Care Excellence	NICE	2018	Pharyngitis	1	Not reported	Reported	Not reported	Not reported	Not reported
The National Institute for Health and Care Excellence	NICE	2019	Community-acquired pneumonia	0	Not reported	Not reported	Not reported	Not reported	Not reported

National Institutes of Health, Centers for Disease Control and Prevention, et al.	NIH, CDC	2013	Tuberculosis	1	Not reported	Reported	Not reported	Not reported	Not reported
The National Institute for Health and Care Excellence; National Collaborating Centre for Women's and Children's Health (NCC-WCH)	NICE, NCC-WCH	2008	Otitis media	3	Not reported	Reported	Reported	Not reported	Reported
United States Preventative Task Force	USPTF	2019	Gonorrhoea	2	Not reported	Not reported	Not reported	Reported	Reported

Table 8: Characteristics of excluded guidelines

Reference	Publishing year	Guideline developer	Continent	Setting	Focus area	Reason for exclusion
Gupta, D. et al.	2012	Indian Chest Society and National College of Chest Physicians	Asia	Secondary and tertiary	Community-acquired pneumonia	Had a scaled domain score of < 60%
Chow, A. et al.	2012	Infectious Disease Society of America (IDSA)	North America	Community and emergency department	Sinusitis	One EtD criteria reported: 1. Resource use
Bignell, C. et al.	2013	The European Branch of the International Union against Sexually Transmitted Infections (IUSTI Europe); the European Academy of Dermatology and Venereology (EADV); the European Dermatology Forum (EDF); the Union of European Medical Specialists (UEMS). The European Centre for Disease Prevention and Control (ECDC) and the European Office of the World Health	Europe	Primary care	Gonorrhoea	Had a scaled domain score of < 60%

		Organization (WHO-Europe)				
Centres for Disease Control and Prevention (CDC)	2013	Centre for Disease Control and Prevention (CDC)	North America	Secondary and tertiary	Tuberculosis	Had a scaled domain score of < 60%
Wald, E. R. et al.	2013	American Academy of Pediatrics	North America	Primary, secondary and tertiary care	Sinusitis	Had a scaled domain score of < 60%
Bignell, C.; Fitzgerald, M.	2011	British Association for Sexual Health and HIV (BASHH)	Europe	Tertiary care	Gonorrhoea	Had a scaled domain score of < 60%
Harris, M.	2011	British Thoracic Society	Europe	Primary and secondary care	Community-acquired pneumonia	Had a scaled domain score of < 60%
Migliori, G. B. et al.	2012	European Centre for Disease Prevention and Control (ECDC) and the European Respiratory Society (ERS)	Europe	Secondary and tertiary care	Tuberculosis	Had a scaled domain score of < 60%
Workowski, K. A.; Bolan, G. A.	2015	Centre for Disease Control and Prevention (CDC)	North America	Primary, secondary and tertiary care	Gonorrhoea	Had a scaled domain score of < 60%
Woodhead, M.;	2011	European Respiratory Society (ERS), in collaboration with The European Society for Clinical	Europe	Primary, secondary and tertiary care	Community-acquired pneumonia	Had a scaled domain score of < 60%

		Microbiology and Infectious Diseases (ESCMID)				
Spindler, C. et al.	2012	Swedish Society of Infectious	Europe	Secondary care	Community-acquired pneumonia	Had a scaled domain score of < 60%
Desrosiers, M et al.	2011	Canadian Society of Otolaryngology-Head and Neck Surgery	North America	Primary and secondary care	Sinusitis	Had a scaled domain score of < 60%
Mayor, M. T.; Roett, M. A.; Uduhiri, K. A.	2012	American Academy of Family Physicians	North America	Primary care	Gonorrhoea	Had a scaled domain score of < 60%
Thwaites, G.	2009	British Infection Society Guidelines	Europe	Secondary and tertiary	Tuberculosis	Had a scaled domain score of < 60%
Bignell, C.; Iusti/Who,	2009	IUSTI/WHO	Europe	Secondary and tertiary	Gonorrhoea	Had a scaled domain score of < 60%
Abdul Rahaman, J. A.; Ker, H. B.; Yusof, M.; Hanafi, N. S.; Wong, J. L.	2012	Malaysian Family Physician	Asia	Primary care but it should also be useful to those in the secondary/tertiary care.	Tuberculosis	Two EtD criteria reported: 1. Values 2. Resource use
World Health Organization (WHO)	2014	World Health Organization (WHO)	International	This document is targeted at national TB programmes, paediatricians and other health workers	Tuberculosis	Three EtD criteria reported: 1. Resource use

				in low- and middle-income countries		2. Acceptability 3. Feasibility
National Institute for Health and Care Excellence (NICE)	2016	The National Institute for Health and Care Excellence (NICE)	Europe	Primary, secondary and tertiary	Tuberculosis	Four EtD criteria reported: 1. Values 2. Resource use 3. Acceptability 4. Feasibility
Menendez, R. et al.	2010	Spanish Society of Pulmonology and Thoracic Surgery (SEPAR)	Europe	n/a	Community-acquired pneumonia	Had a scaled domain score of < 60%
Kaplan, J. E.; Benson, C.; Holmes, K. H.; Brooks, J. T.; Pau, A.; Masur, H.	2009	Centre for Disease Control and Prevention (CDC)	North America	Primary, secondary and tertiary settings; high-resource	Tuberculosis and CAP	Had a scaled domain score of < 60%
World Health Organization (WHO)	2007	World Health Organization (WHO)	International	Resource constraint primary, secondary and tertiary care	Tuberculosis	Had a scaled domain score of < 60%
National Institute for Health and Care Excellence (NICE)	2008	The National Institute for Health and Care Excellence (NICE)	Europe	Primary care	Otitis media, rhino sinusitis, pharyngitis	Had a scaled domain score of < 60%
British Thoracic Society	2009	British Thoracic Society	Europe	Primary, secondary and tertiary care	Community-acquired pneumonia	One EtD criteria reported:

						1. Resource use
Spanish Society for Epidemiology; Spanish Society of Primary Care Physicians; Spanish Society for Pulmonology and Thoracic Surgery, etc.	2010	Spanish Society for Epidemiology; Spanish Society of Primary Care Physicians; Spanish Society for Pulmonology and Thoracic Surgery, etc.	Europe	Primary care	Tuberculosis	Three EtD criteria reported: 1. Values 2. Resource use 3. Feasibility
Infectious Disease Society of America (IDSA)	2011	Infectious Disease Society of America (IDSA)	North America	Primary, secondary and tertiary care	Community-acquired pneumonia	Had a scaled domain score of < 60%
American Academy of Family Physicians	2013	American Academy of Pediatrics	North America	Primary care	Otitis media	Two EtD criteria reported: 1. Values 2. Resource use
National Institute for Health and Clinical Excellence (NICE)	2014	The National Institute for Health and Care Excellence (NICE)	Europe	Primary, secondary and tertiary	Community-acquired pneumonia	Two EtD criteria reported: 1. Values 2. Feasibility
American Academy of Otolaryngology	2015	American Academy of Otolaryngology—	North America	The guideline is intended for all clinicians who are likely to diagnose	Sinusitis	Three EtD criteria reported: 1. Values

		Head and Neck Surgery Foundation		and manage adults with rhinosinusitis and applies to any setting in which an adult with rhinosinusitis would be identified, monitored, or managed.		2. Resource use 3. Acceptability
American Academy of Otolaryngology	2016	American Academy of Otolaryngology—Head and Neck Surgery Foundation, the American Academy of Pediatrics, and the American Academy of Family Physicians	North America	Primary care	Otitis media	Three EtD criteria reported: 1. Values 2. Resource use 3. Acceptability
Infectious Disease Society of America (IDSA)	2016	Infectious Disease Society of America (IDSA)	North America	well-resourced; low-incidence settings	Tuberculosis	No EtD reported
The National Institute for Health and Care Excellence (NICE)	2017	The National Institute for Health and Care Excellence (NICE)	Europe	Primary, secondary and tertiary care	Sinusitis	Had a scaled domain score of < 60%
Institute for Clinical Systems Improvement	2017	Institute for Clinical Systems Improvement	North America	ambulatory care	Pharyngitis and sinusitis	One EtD criteria reported: 1. Resource use

The National Institute for Health and Care Excellence (NICE)	2018	The National Institute for Health and Care Excellence (NICE)	Europe	Primary and secondary care (For the treatment of acute uncomplicated otitis media in primary, secondary or other care settings (for example walk-in-centres, urgent care, and minor ailment schemes) either by prescription or by any other legal means of supply of medicine (for example Patient Group Direction).	Otitis media	Had a scaled domain score of < 60%
British Association for Sexual Health and HIV	2019	British Association for Sexual Health and HIV (BASHH)	Europe	The guidelines are primarily aimed at level 3 sexual health services within the United Kingdom (UK) although the principles of the recommendations could be adopted at all levels.	Gonorrhoea	Had a scaled domain score of < 60%
Ministry of Public Health/Qatar	2016	Ministry of Public Health of Qatar (MOPH)	Asia	primary care and secondary care settings	Community-acquired pneumonia	Had a scaled domain score of < 60%
Infectious Disease Society	2012	Infectious Disease Society of America (IDSA)	North America	healthcare providers who care for adult and pediatric patients	Pharyngitis	One EtD criteria reported:

of America (IDSA)				with group A streptococcal pharyngitis		1. Resource use
Ministry of Health Malaysia Ministry of Higher Education and private sector	2012	Ministry of Health Malaysia Ministry of Higher Education and private sector	Asia	Outpatient, inpatient and community setting	Otitis media	No EtD criteria reported
Borisov, A. S et al.	2018	Centre for Disease Control and Prevention (CDC)	North America	n/a	Tuberculosis	Had a scaled domain score of < 60%
Lee, M. S. et al.	2018	the Korean Society for Chemotherapy, the Korean Society of Infectious Diseases the Korea Academy of Tuberculosis and Respiratory Diseases, the Korean Association of Family Medicine, the Korean Medical Practitioners Association, and the National Evidence-based Healthcare Collaborating Agency	Asia	Primary care	Community-acquired pneumonia	Had a scaled domain score of < 60%

Pogany, L. et al.	2015	Canadian Family Physician	North America	Primary care	Gonorrhoea	Had a scaled domain score of < 60%
Stahl, J. P. et al.	2017	French Infectious Diseases Society (French acronym SPILF); National educational association for teaching therapeutics (French acronym APNET); French Society of Internal Medicine (French acronym SNFMI), etc.	Europe	n/a	Tuberculosis	Had a scaled domain score of < 60%
Heidemann, CH. et al.	2016	Danish Health and Medicines Authority and the Danish Society of Otorhinolaryngology, Head and Neck Surgery	Europe	primary health care	Otitis media	No EtD criteria reported
The Scottish Intercollegiate Guidelines Network (SIGN)	2010	The Scottish Intercollegiate Guidelines Network (SIGN)	Europe	Primary and secondary (general practitioners, nurses, paediatricians, pharmacists, otolaryngologists, anaesthetists, public health specialists)	Pharyngitis	Two EtD criteria reported: 1. Values 2. Resource use

World Health Organization (WHO)	2011	World Health Organization (WHO)	International	Resource constrained settings	Tuberculosis	Four EtD criteria reported: 1. Values 2. Resource use 3. Acceptability 4. Feasibility
American Academy of Otolaryngology	2015	American Academy of Otolaryngology	North America	(Primary, secondary and tertiary care) any setting in which an adult with rhinosinusitis would be identified	Sinusitis	Two EtD criteria reported: 1. Values 2. Resource use
Morbidity and Mortality Weekly Report	2009	CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics	North America	These guidelines are intended for use by clinicians and other health-care workers providing medical care for HIV-exposed and HIV-infected children in the United States.	Tuberculosis	Had a scaled domain score of < 60%
Public Health Agency of Canada	2014	Association of Medical Micro-biology and Infectious Disease Canada (AMMI Canada)	North America	Primary and secondary	Tuberculosis	Had a scaled domain score of < 60%

BC Centre for Disease Control	2014	British Columbia Centre for Disease Control (BCCDC)	North America	(Primary care) clinicians and public health professionals regarding care and treatment of STIs in British Columbia	Gonorrhoea	Had a scaled domain score of < 60%
Centres for Disease Control and Prevention	2019	Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America	North America	Primary, secondary and tertiary	Tuberculosis	Had a scaled domain score of < 60%
Infectious Disease Society of America (IDSA)	2011	Infectious Disease Society of America (IDSA)	North America	Secondary and tertiary	Community-acquired pneumonia	Had a scaled domain score of < 60%
The National Institute for Health and Care Excellence (NICE)	2018	The National Institute for Health and Care Excellence (NICE)	Europe	Primary, secondary and tertiary (in primary, secondary or other care settings (for example walk-in-centres, urgent care, and minor ailment schemes)	Pharyngitis	One EtD criteria reported: 1. Resource use
World Health Organization (WHO)	2016	World Health Organization (WHO)	International	low- and middle-income countries	Tuberculosis	Recommendations do not consider resistance

Public Health Agency of Canada (PHAC)	2014	Public Health Agency of Canada (PHAC)	North America	n/a	Gonorrhoea	Had a scaled domain score of < 60%
The National Institute for Health and Care Excellence (NICE)	2019	The National Institute for Health and Care Excellence (NICE)	Europe	Primary care settings (for example walk-in-centres, urgent care, and minor ailment schemes) either by prescription or by any other legal means of supply of medicine (for example patient group direction).	Community-acquired pneumonia	No EtD criteria reported
Centers for Disease Control and Prevention (CDC)	2013	National Institutes of Health, Centers for Disease Control and Prevention, the HIV Medicine Association of the Infectious Diseases Society of America and the Pediatric Infectious Diseases Society	North America	Primary care; high-resource settings	Tuberculosis	One EtD criteria reported: 1. Resource use
Ministry of Health Singapore	2016	Ministry of Health, Singapore	Asia	(primary secondary and tertiary) various (all healthcare practitioners)	Tuberculosis	Had a scaled domain score of < 60%
University of Michigan Health System	2013	Michigan Medicine. University of Michigan	North America	Primary care	Pharyngitis	Had a scaled domain score of < 60%

AHRQ - Agency for Healthcare Research + Quality,	2008	The National Institute for Health and Care Excellence (NICE); National Collaborating Centre for Women's and Children's Health (NCC-WCH)	Europe	Primary care and secondary care setting (including both community and hospital settings).	Otitis media	Three EtD criteria reported: 1. Resource use 2. Acceptability 3. Equity
British Columbia Centre for Excellence in HIV/AIDS	2015	British Columbia Centre for Excellence in HIV/AIDS	North America	Primary care	Tuberculosis	Had a scaled domain score of < 60%
Kawaguchi, R. et al.	2019	Japan Society of Obstetrics and Gynecology (JSOG) and Japan Association of Obstetricians and Gynecologists (JAOG)	Asia	Primary care (gynecological outpatient care.)	Gonorrhoea	Recommendations do not consider resistance
Mandell, L. A. et al.	2007	Infectious Disease Society of America (IDSA)	North America	Emergency medicine physicians, hospitalists, and primary care practitioners	Community-acquired pneumonia	Had a scaled domain score of < 60%
Public Health Ontario	2018	Public Health Ontario (PHO)	North America	Primary care	Gonorrhoea	Unable to provide supplementary materials
Wiersinga, W. J. et al.	2017	The Dutch Working Party on Antibiotic Policy or Stichting	Europe	This guideline is meant for the treatment of adult	Community-acquired pneumonia	Had a scaled domain score of < 60%

		Werkgroep Antibiotica Beleid (SWAB) and Dutch Association of Chest Physicians (NVALT)		patients who present themselves at the hospital, and are treated as outpatients, as well as for hospitalized patients up to 72 hours after admission, and is in full accordance with the 2011 NHG practice guideline for GPs2. The given recommendations are applicable to adult patients with a CAP in the Netherlands.		
U.S. Preventive Services Task Force	2019	United States Preventative Task Force (USPTF)	North America	primary care	Gonorrhoea	Two EtD criteria reported: 1. Feasibility 2. Equity
World Health Organization (WHO)	2012	World Health Organization (WHO)	International	primary care & low- and middle-income countries	Tuberculosis	Recommendations do not consider resistance
Athlin, S. et al.	2017	The Swedish Society of Infectious Diseases	Europe	These guidelines apply to the in-hospital treatment of adult non-immunocompromised patients with CAP.	Community-acquired pneumonia	Had a scaled domain score of < 60%

Boyles, T. H. et al.	2017	South African Thoracic Society (SATS) and the Federation of Infectious Diseases Societies of Southern Africa (FIDSSA).	Africa	Primary and secondary care	Community-acquired pneumonia	Had a scaled domain score of < 60%
Chaves NJ. et al.	2016	The Australasian Society for Infectious Diseases (ASID) National Tuberculosis Advisory Committee (NTAC) Royal Australasian College of Physicians (RACP) The Australasian Chapter of Sexual Health Medicine (AChSHM – RACP)	Oceania	Primary, secondary and tertiary intended for healthcare providers who care for people from refugee-like backgrounds, including general practitioners, refugee health nurses, refugee health specialists, Infectious Diseases (ID) physicians	Tuberculosis and gonorrhoea	Had a scaled domain score of < 60%
Chiappini, E. et al.	2013	Italian Society of Preventive and Social Pediatrics	Europe	Primary care (primary care pediatricians and general practice physicians)	Pharyngitis; sinusitis; community acquired pneumonia; otitis media	Had a scaled domain score of < 60%
Di Comite, A. et al.	2016	Italian Pediatric TB Study Group	Europe	primary and secondary care	Tuberculosis	Recommendations do not consider resistance

Jereb, J. A.; Goldberg, S. V.; Powell, K.; Villarino, M. E.; Lobue, P.	2011	Centre for Disease Control and Prevention (CDC)	North America	Primary and secondary care	Tuberculosis	Had a scaled domain score of < 60%
Ricardo de Amorim Corrêa. et al.	2009	Scientific Board and Respiratory Infection Committee of the Brazilian Thoracic Association	South America	Primary and secondary care	Community-acquired pneumonia	Had a scaled domain score of < 60%
Z.A. Memish. et al.	2007	THE GCC CAP WORKING GROUP (GCC-CAPWG)	Asia	Primary and secondary care	Community-acquired pneumonia	Had a scaled domain score of < 60%