ANTIBIOTIC PRESCRIBING RECOMMENDATIONS IN COVID-19: A SYSTEMATIC SURVEY

ANTIBIOTIC PRESCRIBING RECOMMENDATIONS IN COVID-19: A SYSTEMATIC SURVEY

By BRADLEY J. LANGFORD, BSC, BSC.PHM., PHARM.D.

A Thesis Submitted to the School of Graduate Studies in Partial Fulfilment of the Requirements for the Degree Master of Public Health

McMaster University MASTER OF PUBLIC HEALTH (2023), Hamilton, Ontario

TITLE: Antibiotic Prescribing Recommendations In COVID-19: A Systematic Survey

AUTHOR: Bradley J. Langford, BSc, BScPhm, PharmD (McMaster University)

SUPERVISOR: Holger Schunemann

NUMBER OF PAGES: lv, 70

LAY ABSTRACT

COVID-19 and antimicrobial resistance (AMR) are two serious threats to public health. Inappropriate use of antibiotics in patients with COVID-19 can worsen AMR and make future infections harder to treat. Practice guidelines can help healthcare providers prescribe antibiotics wisely. Using antibiotics carefully to reduce their harms is called antibiotic stewardship. This study evaluated the quality of practice guidelines for antibiotic prescribing in patients with COVID-19. It also assessed if the guidelines included principles of antibiotic stewardship. We searched for guidelines in a database called the eCOVID-19 living map of recommendations (RecMap). We found 28 guidelines with 63 recommendations. Identified guidelines differed widely in quality. Just over two-thirds of guidelines addressed antibiotic stewardship. Guidelines developed along with infectious disease experts and guidelines with higher recommendation quality scores were more likely to address antibiotic stewardship. Our findings can help guideline developers better address antibiotic stewardship in future recommendations.

ABSTRACT

Background

COVID-19 and antimicrobial resistance (AMR) are two intersecting public health crises. Antimicrobial overuse in patients with COVID-19 threatens to contribute to the growing threat of AMR. Guidelines are fundamental in encouraging antimicrobial stewardship. We sought to assess the quality of antibiotic prescribing guidelines and recommendations in the context of COVID-19, and if these guidelines incorporate principles of antimicrobial stewardship.

Methods

We performed a systematic survey which included a search using the concepts “antibiotic/antimicrobial” in September to November 2022 of the eCOVID-19 living map of recommendations (RecMap) which aggregates and summarizes guidelines across a range of international sources and all languages. Guidelines providing explicit recommendations regarding antibacterial use in COVID-19 from any jurisdiction were eligible for inclusion. Guideline and recommendation quality were assessed using the AGREE II and AGREE-REX instruments, respectively. We extracted guideline characteristics including panel representation and the presence or absence of explicit statements related to antimicrobial stewardship (i.e., judicious antibiotic use, antimicrobial resistance or adverse effects as a consequence of antibiotic use). We used logistic regression to evaluate the relationship between guideline characteristics including quality and incorporation of antimicrobial stewardship principles.

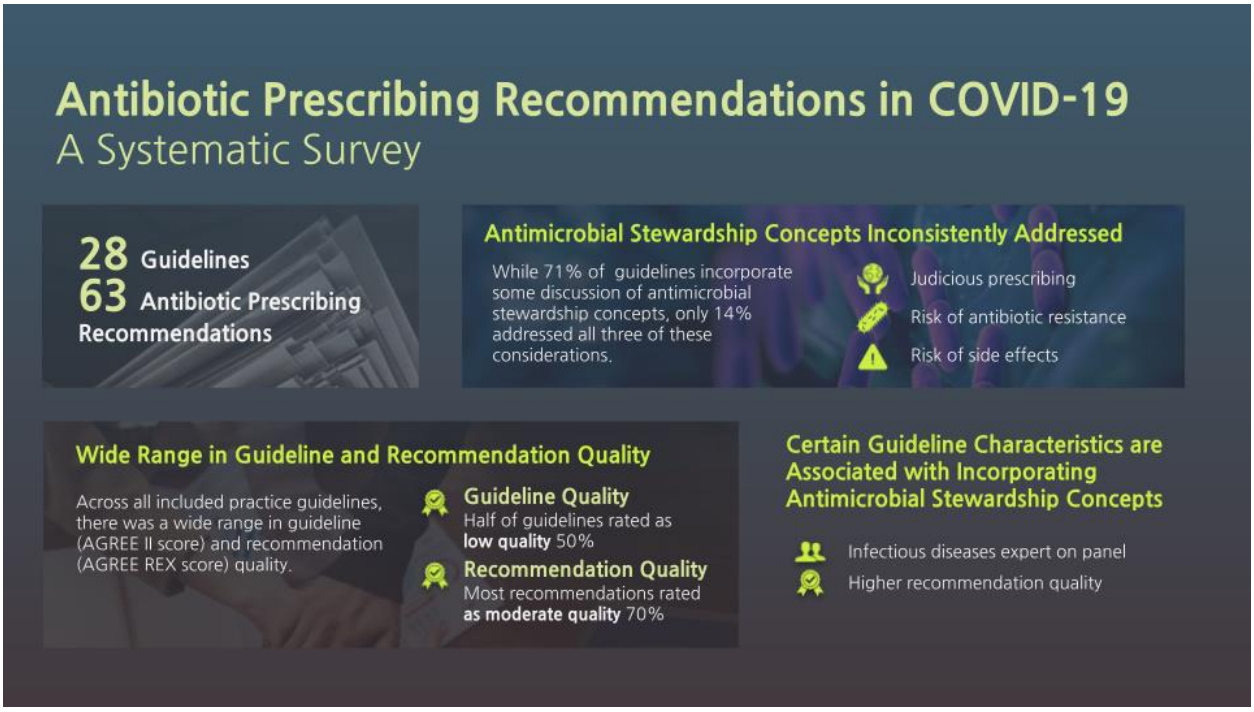
Results

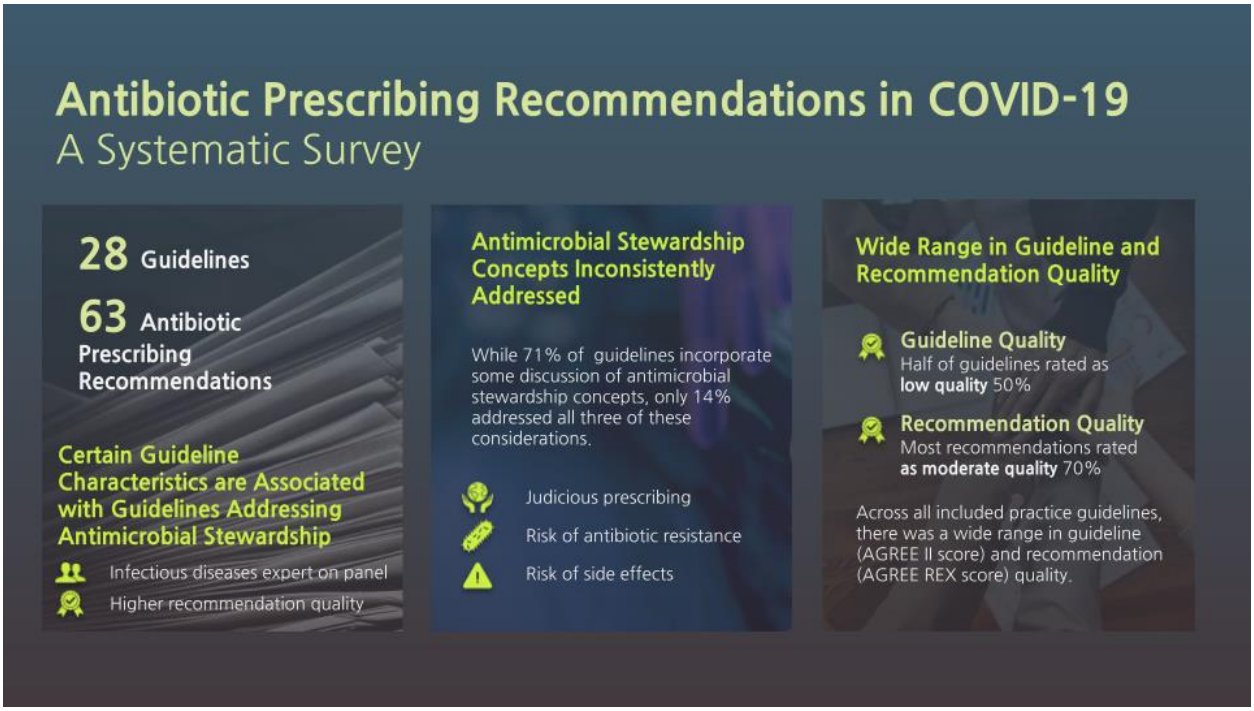
Twenty-eight guidelines with 63 antibiotic prescribing recommendations were included. Recommendations focused on antibiotic initiation (n=52, 83%) and less commonly antibiotic selection (n=13, 21%), and duration of therapy (n=15, 24%). Guideline and recommendation quality varied widely. Twenty (71%) guidelines incorporated at least one concept relating to antimicrobial stewardship. Including infectious diseases expertise on the guideline panel (OR 9.44, 97.5%CI: 1.09 to 81.59) and AGREE-REX score (OR 3.26, 97.5%CI: 1.14 to 9.31 per 10% increase in overall score) were associated with a higher odds of guidelines addressing antimicrobial stewardship.

Conclusion

There is an opportunity to improve antibiotic prescribing guidelines in terms of both quality and incorporation of antimicrobial stewardship principles. These findings can help guideline developers better address antibiotic stewardship in future recommendations beyond COVID-19.

VISUAL ABSTRACTS





ACKNOWLEDGEMENTS

I would like to thank Dr. Holger J. Schunemann for his exceptional guidance, leadership and support for this research project that met our mutual interests of antimicrobial stewardship and health research methods and guideline recommendations. Thank you to Dr. Elie Akl for thoughtful and constructive suggestions from seven time zones ahead! Thank you to Dr. Robby Nieuwlaat for his support, collaborative approach, and expertise. I am also grateful for the continued support from Dr. Tamara Lotfi and her patience with all of my questions. Special thanks to the antimicrobial stewardship and antimicrobial resistance team at Public Health Ontario for their ongoing collaboration and shared efforts to keep antibiotics working: Dr. Nick Daneman, Dr. Kevin Schwartz, Dr. Kevin Brown, and honorary team member and reviewer extraordinaire, Dr. Jennifer Lo. Huge thanks to Valerie Leung for her support during my post-graduate training and for her significant contributions to this project.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

AGREE II: Appraisal of Guidelines for REsearch & Evaluation II

AGREE-REX: Appraisal of Guidelines for REsearch & Evaluation Recommendation EXcellence

AMR: Antimicrobial Resistance

COVID-19: Coronavirus Disease 2019

RecMap: eCOVID-19 living map of recommendations

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

DECLARATION OF ACADEMIC ACHIEVEMENT

Bradley J. Langford and Valerie Leung contributed to study conceptualization, protocol development, screening, extraction, scoring, analysis and interpretation, and manuscript writing and editing. Jennifer Lo contributed to screening, extraction, scoring, analysis and interpretation, and manuscript writing and editing. Elie Akl, Robby Nieuwlaat , Valerie Leung, Nick Daneman, Kevin L. Schwartz, Kevin A. Brown contributed to study conceptualization, protocol development, analysis and interpretation, and manuscript writing and editing. Tamara Lotfi contributed to data curation, analysis and interpretation and manuscript writing and editing. Holger J. Schunemann contributed to study conceptualization, protocol development, analysis and interpretation, and manuscript writing and editing and supervision.

CHAPTER 1. INTRODUCTION

1.1 COVID-19 and Antimicrobial Resistance Are Two Intersecting Public Health Crises

COVID-19 and antimicrobial resistance (AMR) are two intersecting public health emergencies leading to devastating global consequences.[1,2] As of January 1, 2023, with over 6 million cumulative reported deaths and over 600 million reported cases, the COVID-19 pandemic has overwhelmed the public health and the healthcare systems.[3] While recent public health efforts have largely focused on mitigating the impact of COVID-19 on human health, another more insidious pandemic threatens similar societal harm.

Based on data from 2019, bacterial AMR is associated with an estimated 4.95 million deaths and 1.27 million directly attributable deaths each year, making it one of the leading causes of global mortality.[2] Antimicrobial use is the main driver for AMR. Antimicrobial exposure kills susceptible organisms, allowing resistant microbes to thrive and become more predominant in the population, a concept coined selective pressure.[4] Due to transmission of resistant organisms between individuals, antimicrobial use in individuals can alter the prevalence of drug resistance not only in those individuals but also across institutions and populations, making it a broad threat to public health.[5] Given that approximately 50% of antibiotic use is considered inappropriate across a range of healthcare settings,[6,7] antimicrobial resistance can be mitigated by systematic approaches to improve judicious antimicrobial prescribing and reduce unnecessary use, a concept called antimicrobial stewardship.[8]

1.2 COVID-19 Pandemic Impact on Antimicrobial Resistance is Multi-Factorial

The impact of COVID-19 on the AMR pandemic is still poorly understood. Public health interventions aimed at controlling the spread of SARS-CoV-2, such as masking, physical distancing, travel restrictions, and improved hand hygiene may have impeded the spread of drug-resistant organisms.[9] However these measures were inconsistently and sporadically applied, as well as temporary in nature. On the other hand, high healthcare resource utilization during the pandemic may have hampered infection prevention and control efforts and shifted resourcing to focus on COVID-19 and away

from mitigating the transmission of drug-resistant organisms (e.g., reduced screening and tracking of antimicrobial resistant organisms (AROs) in hospitals).[10,11] Importantly, high antimicrobial use in patients with COVID-19 may have also contributed to increasing rates of AMR.

1.3 Inappropriate Antibiotic Use in Patients with COVID-19 Hastens Antimicrobial Resistance

Similar to other infectious diseases, inappropriate antibiotic use also appears to be a common phenomenon in the setting of COVID-19. Despite the viral etiology and low bacterial co-infection rate in COVID-19,[12,13] early reports indicate a high prevalence of antibiotic prescribing in patients with SARS-CoV-2. A large systematic review performed by our team early in the pandemic found that antibiotics were used in about 75% of hospitalized patients with COVID-19[14] which may further contribute to the threat of antimicrobial resistance. Further, data from randomized controlled trials indicates a lack of benefit and possible harm associated with antibiotics, specifically azithromycin, for the treatment of COVID-19.[15] Despite this lack of benefit, antibiotic overuse is common due to initial uncertainty in etiology while awaiting test results and concerns about possible co-infection even once SARS-CoV-2 is identified.[16] Although antibiotic use in patients with COVID-19 may have improved as the pandemic progressed,[17] very high use early in the pandemic, coupled with shifts in infection control and antimicrobial stewardship resourcing, the prevalence of drug resistant organisms may have already been altered.[11,18] A recent systematic review performed by our team indicates that as many as 60% of patients that have bacterial infections and COVID-19 harbour an ARO.[19] Further, rates of AMR in patients with COVID-19 and changes to AMR prevalence in the population are highly variable between studies and across regions, suggesting some regions may be more impacted than others.[18,20]

1.4 Guidelines Can Support Appropriate Antibiotic Prescribing in COVID-19

Several guidelines aimed to support optimal prescribing of antibiotics in the context of COVID-19 but high antibiotic use in hospitalized patients persisted despite these recommendations.[21] A variety of factors may affect this knowledge-to-practice gap including local context such as the quality of guideline recommendations, feasibility of

implementation, and the incorporation of key values such as antimicrobial stewardship in guideline development. There is evidence that other infectious disease recommendations may not adequately address antimicrobial resistance implications which can compromise their impact.[22] But as COVID-19 continues to evolve, the applicability of guidelines to appropriate antibiotic prescribing in this context are not yet known. In addition, differing recommendation statements between guidelines are common in COVID-19,[23] including those for antibiotic prescribing.[24,25] Diverging recommendations associated with methodological differences can compromise the impact of their implementation into practice.

CHAPTER 2. OBJECTIVES & METHODOLOGY

2.1 Objectives

We aimed to assess the quality of antibiotic prescribing guidelines and recommendations in the context of COVID-19, and whether and the extent to which these guidelines incorporate principles of antimicrobial stewardship.

Table 1. PICAR Framework for Systematic Survey

P - Population	Patients with COVID-19 in any healthcare setting
I - Intervention	Antibiotic therapy for managing or preventing bacterial infection
C - Comparator	Any
A - Attributes of Eligible Guidelines	Publication year: any Language: any Scope: Regional, national, or international
R - Recommendation characteristics	Recommendation that pertains to antibiotic (antibacterial) prescribing to treat or prevent infections in the patients with COVID-19

2.2 Methodology

The methodology follows recommendations from the methodological guide for systematic reviews of clinical practice guidelines by Johnston et al.[26] The protocol was registered on Open Science Framework (OSF): https://osf.io/4pgtc.

2.3 Eligibility Criteria

Guidelines providing explicit recommendations regarding antibacterial use for prevention or management of infection related to COVID-19 from any jurisdiction at the regional, national, or international level are eligible for inclusion. Recommendations pertaining to any healthcare setting (including ambulatory and hospitalized patients) and any patient population (including children and adults) are eligible.

2.4 Data Source

The eCOVID-19 living map of recommendations (RecMap) was searched for eligible guidelines. COVID-19 RecMap aggregates globally published clinical, public health, and health policy guidelines to support contextualized decision making.[27,28] RecMap staff apply bibliographic searches for COVID-19 guidelines in Pubmed (search string: ((practice guideline[PT]) OR (practice guidelines as topic*[MH])) NOT (comment[pt] or editorial[pt] or letter[pt] or interview[pt] or case reports[pt] or news[pt]). Searches are also conducted across a number of databases including International Database of GRADE Guidelines, National Institute for Health and Care Excellence (NICE), World Health Organization, Guidelines International Network library, ECRI Clinical Guidelines, US Centers for Disease Control and Prevention (US CDC), Public Health Agency of Canada, COVID Network Meta-analysis initiative, and the European Centers for Disease Control.[28] The search also included automated web scraping via of Guidelines International Network (GIN)'s libraries. Guidelines were then screened manually for relevance to COVID-19 and appraised by two trained reviewers using AGREE II instrument. Searches are not limited by language. The unit of organization of RecMap is the individual guideline recommendation which is organized by topic area and population. Each recommendation includes the population, intervention,

comparator, outcomes (PICO) elements and links to summary of findings and evidence to decision tables if available.

2.5 Search Strategy

COVID-19 RecMap was searched using the terms ‘antibiotic’, ‘antibacterial’, ‘antimicrobial’, and ‘anti-infective’. Included in this strategy was an additional search for specific antibacterial agents (i.e., azithromycin, doxycycline) that may be prescribed in COVID-19. The searches were performed between September and November 2022.

2.6 Guideline Selection Process

Screening was performed by two independent reviewers (BL and VL) to assess guidelines for eligibility. The full-text and any supplementary/accompanying material for each search result was screened by each reviewer. Conflicts were resolved via consensus. In situations in which there are multiple guideline iterations from the same organization, the most recent guideline was selected for extraction, with any antibiotic-related changes documented.

2.7 Data Collection Process

One independent reviewer extracted data from eligible guidelines which was checked independently by a second reviewer. A spreadsheet was used for data extraction which was piloted and refined based on initial extraction of eligible guidelines. Additional relevant data that were previously extracted into RecMap were checked to ensure it was accurately extracted from RecMap.

2.8 Data Items

The following data items were extracted for each eligible guideline. Data already extracted by RecMap collaborators is identified with an asterisk:

Guideline

1. Country
2. Region
3. Date of publication
4. Organization, organization type* (e.g., academic, guideline society, governmental)
5. Expertise on panel (i.e., infectious diseases specialist, public health, pharmacist)
6. Guideline quality assessment using the AGREE II Framework*

Recommendation

7. COVID-19 severity (i.e., mild, moderate, severe/critical as per guideline authors)
8. Healthcare setting (i.e., outpatient, inpatient non-intensive care, inpatient intensive care)
9. Recommendation content, statements on appropriate: initiation (starting of antibiotics in various scenarios); selection (regimen and re-assessment of antibiotics); duration (length of therapy, when to stop) antibiotic therapy.
10. Level of evidence*[29]
    a. Certainty of evidence
        i. Very low: true effect probably markedly different from estimated effect
        ii. Low: true effect might be markedly different from estimated effect
        iii. Moderate: true effect is probably close to the estimated effect
        iv. High: true effect is very likely close to the estimated effect
    b. Strength of recommendation
        i. Conditional: course of action may be dependent on patient population
        ii. Strong: course of action applies to most individuals
11. Type of statement*
    - Recommendation: actionable guidance based on a structured evaluation
    - Additional guidance: actionable guidance not based on a structured evaluation

    - Good practice statements represent guidance without a formal evaluation.[30] Five criteria are required for Good Practice Statements: 1) clear and actionable; 2) message is necessary for healthcare practice; 3) it is impractical to systematically collect evidence; (4) summarizing the evidence would be a poor use of the panel's time; and (5) there is a statement linking clearly to the indirect evidence.
12. Explicit statements on judicious antibiotic use directly related to the recommendation (i.e., statement regarding careful antibiotic prescribing/antimicrobial stewardship in rationale or recommendation)
13. Explicit statements on antimicrobial resistance as an outcome (e.g., associated with antibiotic overuse)
14. Explicit statements on other antimicrobial associated harms as an outcome (e.g., adverse effects, super-infections).
15. Changes to recommendation over time, if any
16. Evidence to Decision (EtD) framework by study authors (values, resource use, availability of diagnostic and laboratory testing, equity, acceptability or feasibility)*
17. Recommendation quality appraisal using AGREE-REX Framework

2.9 Quality Appraisal

Two instruments were used to evaluate the quality of included guidelines: AGREE II and AGREE-REX.

2.10.1 AGREE II (Appraisal of the Guideline)

The Appraisal of Guidelines for REsearch & Evaluation (AGREE II) Instrument aims to assess guideline quality in terms of methodological rigour and transparency.[31] Three main goals of AGREE II include to 1) assess guideline quality, 2) provide a methodological outline for guideline development and, 3) inform which content should be included in guidelines and how it should be reported. AGREE II includes 23 questions, in addition to two global rating items, all using a seven-point ordinal scale. Items are categorized into six domains: Domain 1. Scope and Purpose; Domain 2.

Stakeholder Involvement; Domain 3. Rigour of Development; Domain 4. Clarity of Presentation; Domain 5. Applicability; Domain 6. Editorial Independence

Each guideline in RecMap has previously been appraised using the online AGREE II tool rating each of the 23 items, plus 2 global items, on the 7-point scale as per the AGREE manual. A score of 1 is given when there is no information relevant to that item, if the authors explicitly indicate that criterion was not met, or if the concept is very poorly reported. On the opposite end of the scale, a score of 7 is given if full criteria indicated in the AGREE II manual have been met. A score is tabulated based on the sum of at least two reviewers' score divided by the sum of the maximum possible score, providing a percentage rating. This rating was calculated for each of the six domains. Pre-existing AGREE II scores calculated by the RecMap team were used for each eligible guideline.

2.10.2 AGREE-REX (Appraisal of the Recommendation)

The AGREE-REX (Recommendation EXcellence) is a newly developed tool to accompany AGREE II aimed at assessing the quality of guideline recommendations across three domains: 1) credibility, 2) values and preferences, and 3) implementibility.[32] The tool considers the target users of the guideline, the context in which it will be implemented, the patient population, and any other relevant stakeholders. AGREE-REX includes nine items with 7-point ordinal scale across the three domains plus an overall rating.

The nine AGREE-REX items include:

Domain 1: Clinical Applicability:

1. Evidence;
2. Applicability to Target Users;
3. Applicability to Patients/Populations;

Domain 2: Values and Preferences:

4. Values and Preferences of Target Users;
5. Values and Preferences of Patients/Populations;
6. Values and Preferences of Policy/Decision Makers;

7. Values and Preferences of Guideline Developers;

Domain 3: Implementability:

8. Purpose;

9. Local Application and Adoption.

Three independent reviewers (BL, VL, JL) appraised each eligible antibiotic prescribing recommendation using the AGREE-REX tool rating each of the nine items on the 7-point scale as per the AGREE-REX checklist.[33] Multiple recommendations for the same guideline were graded with a single score. The 'suitability for use' optional item is less relevant in the context of COVID-19 management with antibiotics, as such it was not included in our analysis. Similarly, items 4 (Values and Preferences of Target Users), 5 (Values and Preferences of Patient/Population), and 9 (Local Application and Adoption) were deemed to be less relevant in to the use of antibiotics in COVID-19, as such guideline recommendations may have intentionally not addressed these aspects thoroughly. To account for this consideration, the AGREE-REX scoring team agreed to score each of these items at a minimum of 'neutral' (4 out of 7). As with AGREE II, a score is tabulated based on the sum of the reviewers' score divided by the sum of the maximum possible score, providing a percentage rating. This rating was calculated for each of the nine items, three domains (sum for each domain) and overall (sum of all scores).

2.11 Analysis

A descriptive approach was used to illustrate the content and quality of antibiotic recommendations in the context of COVID-19. The first summary table includes a list of guidelines and their key features (citation, year, location), antibiotic recommendations relating to initiation, selection, duration, and whether antimicrobial stewardship and AMR are considerations. The second summary table lists each guideline with its total AGREE II and AGREE-REX scores.

Guidelines were categorized as low quality if they scored <60% in two or more AGREE II domains and/or <50% in domain 3 (rigor of development), moderate quality if they scored ≥ 60% in 3 domains except domain 3, high quality if they scored ≥ 60% in at

least 3 domains including domain 3.[31,34] Guideline recommendations were categorized as high quality if the overall AGREE-REX score was above 70%, moderate quality if 30 to 70%, and low quality if less than 30%.[33]

To assess the extent of agreement between reviewers for the AGREE REX score, Krippendorff's alpha scores were calculated to determine inter-rater agreement for each item, domain, and for the total score. [35,36] Krippendorff's alpha, unlike Cohen's kappa, measures agreement for more than two observers and provides flexibility to evaluate agreement across nominal, ordinal, and continuous data. Similar to other measures of reliability, alpha ranges from -1 to +1. For item level AGREE REX scores, data were treated as ordinal, and for domain and total scores, data were treated as continuous.

To evaluate the association between guideline characteristics (e.g., guideline year, incorporation of expertise on guideline panel, and AGREE II and AGREE-REX scores per 10% increase) and inclusion of at least one antimicrobial stewardship element, we performed univariable generalized linear model (GLM) logistic regression to estimate odds ratio (OR) and 97.5% confidence interval. A more conservative confidence interval was selected given the research question addressing the association of both practice guideline elements and quality with antimicrobial stewardship incorporation. Analyses were carried out in using R for statistics (Vienna, Austria) version 4.2.2.

2.12 Ethics

Ethics approval is not required for this systematic survey as data were synthesized from published literature/guidelines.

CHAPTER 3. RESULTS

3.1 Characteristics of Guidelines

Of 470 guidelines in the eCOVID19 RecMap database as of October 2022, 30 were screened and 28 were eligible for inclusion (See Figure 1 for PRISMA Flow

Diagram).[37–64] Out of the 28 guidelines, 63 recommendations pertained to antibiotic prescribing in patients with COVID-19. The most common regions/countries represented were global (n=5, 18%), Europe (n=3, 11%), United States (n=3, 11%), Americas (n=2, 7%), Brazil (n=2, 7%), and one guideline (n=1, 4%) from each of the following: Australia; Canada (Ontario); China; Czech Republic; France; Germany; Italy; Mexico; Pakistan; Portugal; Spain; The Netherlands; and United Kingdom (Figure 2). Including international guidelines, low-and middle-income countries were represented in 15 guidelines (54%). The full list of guidelines and recommendations is available in Supplementary Table 1.

Guideline-producing organizations were commonly academic (n=16, 57%) guideline societies (n=12, 43%), governmental or inter-governmental (n=6, 21%), and not for profit (n=3, 11%). Years of publication were 2020 (n=7, 25%), 2021 (n=9, 32%), and 2022 (n=12, 43%). Three (11%) guidelines had substantial updates to the antibiotic prescribing recommendations during the pandemic with two guidelines removing recommendations that antimicrobial use was acceptable in the context of a clinical trial,[43,61] one guideline upgrading recommendations against azithromycin use from conditional to strong,[57] and one guideline adding antimicrobial recommendations that were not in a previous version.[43] Eight (29%) guidelines were described as ‘rapid’.

3.2 Expertise on Guideline Panel

Of the 28 eligible guidelines, 20 (71%) indicated there was infectious diseases specialist representation, 9 (32%) stated that there was public health expert on the panel, and 9 (32%) indicated a pharmacist representative participated on the panel.

Figure 1. PRISMA Flow Diagram

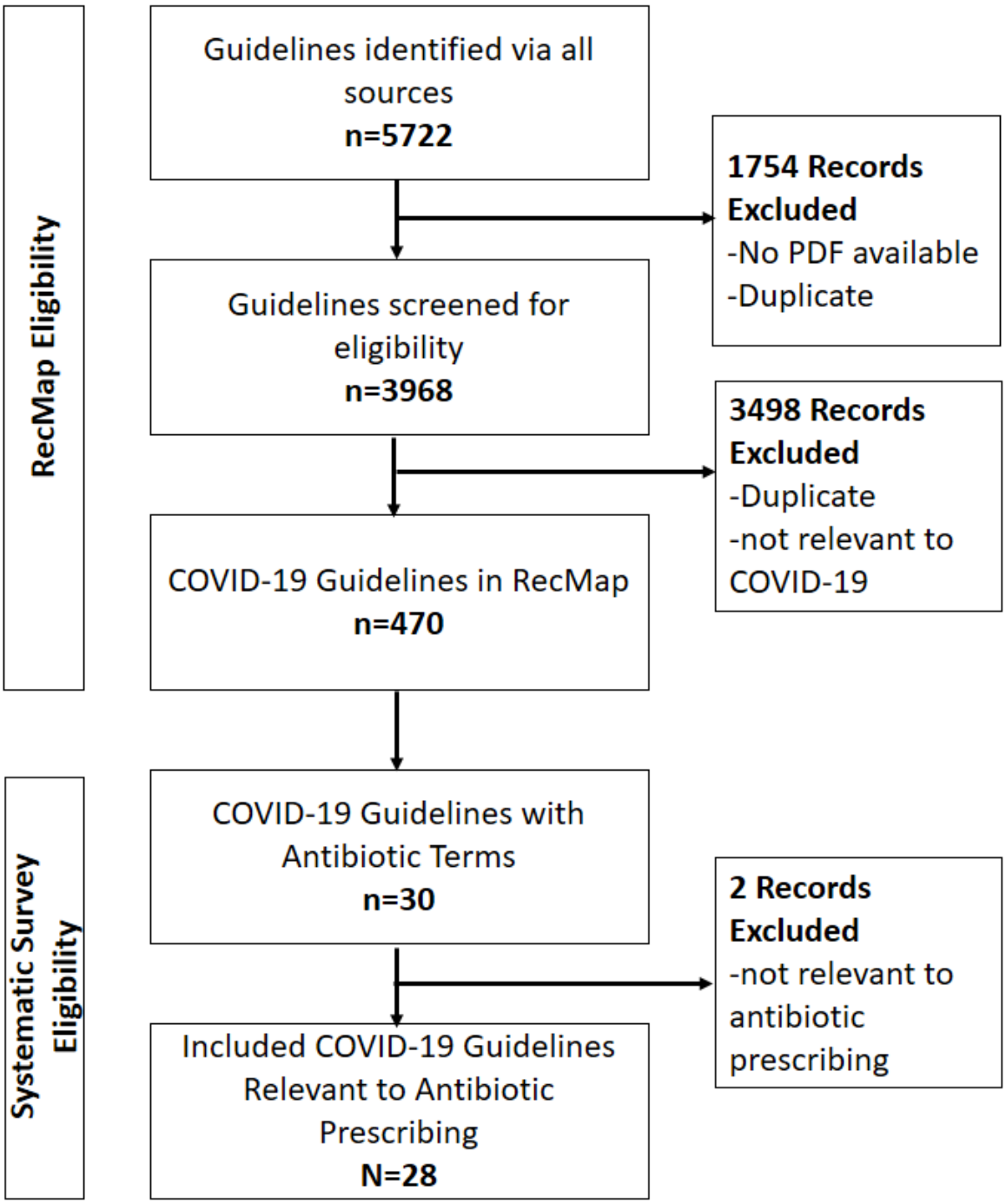
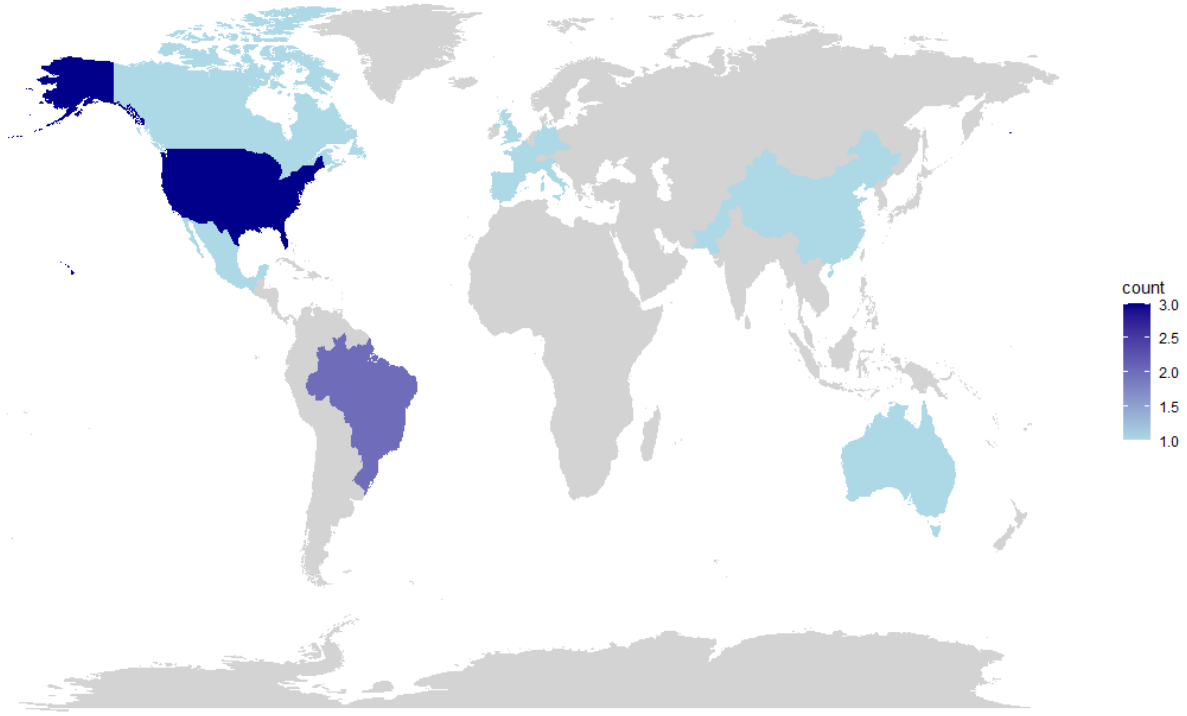


Figure 2. Count of Guidelines Pertaining to Antibiotic Prescribing in COVID-19 by Country



Map does not include multi-country/international guidelines

3.3 Characteristics of Recommendations

Of the 63 recommendations, 49 (78%) applied broadly to all antibiotics, whereas 14 (22%) specifically addressed azithromycin use in the context of COVID-19. Healthcare setting varied across recommendations; all patients (n=22, 35%); hospitalized only (n=19, 30%); ICU only (n=13, 21%); outpatient (n=5, 8%); inpatient non-ICU (n=3, 5%), and outpatient and inpatient non-ICU (n=1, 2%). The focus was largely on adult patients (n=40, 63%), both adults and children or not specified (n=22, 35%), or children only (n=1, 2%).

Certainty of evidence for recommendations pertaining to all antibiotics was generally very low (n=11), followed by low (n=4) or moderate (n=3). Recommendation strength for those pertaining to general antibiotic use was split between strong (n=14) and conditional (n=12).

However, for recommendations pertaining to azithromycin certainty of evidence ranged from high (n=3), moderate (n=4), low (n=3), to very low (n=3). The strength of

recommendation was higher than those focusing on all antibiotics, with 9 recommendations considered strong and 3 recommendations conditional for use of azithromycin.

Most guidelines (n=21, 75%), did not incorporate an evidence-to-decision framework as a structured and transparent approach to summarize how recommendations were formulated.

3.3.1 Aspects of Antibiotic Prescribing

Recommendations most commonly focused on antibiotic initiation (e.g., empiric use of antibiotics, diagnostic recommendations, timeliness of initiation, n=52, 83%) and less commonly antibiotic selection (e.g., empiric choice of agent based on local resistance rates or targeted based on culture and susceptibility results, use of institutional or local protocols to support selection, n=13, 21%), and duration of therapy (e.g., fixed duration of therapy or tailored to diagnostic and microbiological findings, n=15, 24%). Eleven (17%) recommendations pertained to use of microbiological methods to inform antibiotic use. The full list of guidelines and recommendations is available in Supplementary Table 1.

3.3.2 Antibiotic Initiation Recommendations

Of the 52 recommendations focusing on antibiotic initiation, the majority addressed empiric or prophylactic antibiotic prescribing in COVID-19 in the absence of proven bacterial infection (n=43). Six (14%) recommendations suggested empiric antibiotic therapy regardless of evidence of bacterial infection. All but one of these recommendations applied to critically ill patients with COVID-19. However, one guideline recommended “usual antimicrobial treatment” for pneumonia for all patients with COVID-19 regardless of evidence suggesting bacterial infection (e.g., with and without radiographic abnormalities, in all levels of severity). Five of these six recommendations suggest bacteriological microbiological sampling in order to rule out co-infection. Similarly, four of the above six guidelines recommend de-escalating or discontinuing antimicrobial on the basis of additional (e.g., microbiological) findings. A rationale was provided for 4 of 6 recommendations, which often mentioned the higher

prevalence of co-infection in critically ill patients and the risk of rapid deterioration/poor outcomes if severely ill patients develop co-infection.

Of the remaining 37 recommendations recommending avoiding empiric antibiotic therapy in patients without evidence of bacterial infection, all provided a rationale. A common reason to recommend avoiding prophylactic/empiric antibiotics was the low rate of co-infection in non-severe COVID-19, the lack of proven benefit of antibiotics (e.g., azithromycin), as well as the potential risk of harm including side effects and/or contribution to antimicrobial resistance.

Other initiation-focused recommendations endorsed prescribing antibiotics for patients with suspected or proven bacterial infection (n=5), collecting microbiological cultures prior to antibiotic initiation (n=3), and timely initiation of antibiotics once bacterial infection is identified (n=2).

3.3.2 Antibiotic Selection Recommendations

Of the 13 recommendations addressing antibiotic selection, common areas of focus included choosing antibiotic regimens in concordance with institutional/local guidelines (n=5), re-evaluating therapy for opportunities to modify treatment based on clinical response and diagnostic findings (n=6), specific antibiotic choice recommendations (e.g., avoidance of atypical coverage in most patients, n=2), selecting targeted therapy on the basis of culture results or likely co-infecting pathogens (n=2).

3.3.3 Antibiotic Duration Recommendations

Of the 15 recommendations addressing antibiotic duration in COVID-19, most focused on modifying duration on the basis of clinical and laboratory findings (e.g., discontinuation if bacterial infection is unlikely, n=9). Other recommendations included fixed duration of therapy if antibiotic therapy is prescribed (e.g., five to seven days, n=3) or duration of therapy as per local/institutional protocols (n=2).

3.4 Antimicrobial Stewardship and Resistance Incorporation into Guidelines

Concepts related to antimicrobial stewardship were often incorporated more broadly into the guideline rather than in specific recommendations, as such we assessed these aspects at the guideline level. Of the 28 guidelines, ten (36%) contained explicit statements regarding judicious antibiotic prescribing (i.e., regarding the need for appropriate and careful antibiotic use). Twelve (43%) incorporated explicit statements on antimicrobial resistance as a potential outcome (e.g., indiscriminate of antibiotics drive selective pressure for antimicrobial resistance). Thirteen (53%) mention other harms of antibiotics as part of the guideline (e.g., adverse effects, *C. difficile* infection). Twenty (71%) guidelines incorporated at least one of the above concepts relating to antibiotic stewardship. Four guidelines incorporated all three concepts, explicitly mentioning judicious prescribing, antimicrobial resistance, and other antimicrobial-associated harms. Examples of statements addressing these concepts are provided in Table 2.

Table 2. Example Guideline Statements Addressing Antibiotic Stewardship and Harms of Antibiotic Use in the Setting of COVID-19

Dimension Addressed	Example Statement
Judicious Prescribing	"…Based on the currently available evidence and antibiotic stewardship principles, the committee recommends restrictive use of antibacterial drugs in patients with community-acquired respiratory infection and proven or high likelihood of COVID-19." Guideline 15
Antimicrobial Resistance	"…indiscriminate and perilous use of antibiotics in many patients with COVID-19 without bacterial infections… increasing the selective pressure for antimicrobial resistance both in patients and in the environment." Guideline 1

Other Antimicrobial Harms	"Adverse events and secondary infections were slightly increased in groups treated with azithromycin compared to placebo..." Guideline 19 "…this recommendation is intended to mitigate the unintended consequences of side effects and resistance." Guideline 7

3.5 AGREE II

Guidelines exhibited a wide range in quality as shown by their AGREE II scores. Median score for Domain 1 (Scope and Purpose) was 81% (range 58 to 97, IQR 69 to 89%), Domain 2. (Stakeholder Involvement) was 53% (range 8 to 94, IQR 41 to 70%), Domain 3 (Rigour of Development) was 51% (2 to 88%, IQR 21 to 69%), Domain 4 (Clarity of Presentation) was 76% (range 39 to 100%, IQR 63 to 92%), Domain 5 (Applicability) was 10% (range 0 to 83.3%, IQR 6 to 29%) and Domain 6 (Editorial Independence) was 67% (range 0 to 100%, IQR 45 to 80%).

According to the scoring criteria listed above, most guidelines were categorized as low quality (n=14, 50%), followed by high quality (n=12, 43%), and moderate quality (n=2, 7%). Supplementary Table 2.

3.6 AGREE-REX

Across the three raters, according to Krippendorff's alpha, agreement was moderate at the individual item level at 0.55 (95%CI: 0.50 to 0.60), good for agreement at the domain level 0.84 (95%CI: 0.81 to 0.87), and good for agreement of the overall AGREE-REX score at 0.80 (95%CI: 0.72 to 0.87). There was substantial variation in agreement across individual AGREE-REX items. The item with the highest inter-rater agreement was Item 1. Evidence (alpha 0.70, 95%CI: 0.58 to 0.81) and the items with the lowest agreement included Item 8. Purpose (alpha 0.27, 95%CI: 0.09 to 0.44). (Table 3)

Similar to the AGREE II score, there was a wide range in the AGREE-REX score between guidelines across items, domains, and overall. Median score for Domain 1 (Clinical Applicability) was 70% (range 13 to 96%, IQR 50 to 83%), Domain 2 (Values and Preferences) was 54% (range 25 to 81%, IQR 47 to 65%), and Domain 3 (Implementability) was 61% (range 31 to 86%, IQR 53 to 64%).

The item with the highest AGREE-REX score was 2, Applicability to Target Users at 78% (range 22 to 94%, IQR 64 to 89%), whereas the item with the lowest score was 6, Values and Preferences of Policy Makers at 50% (range 6 to 78%, IQR 32 to 61%). The median overall AGREE-REX score was 64% (range 23 to 85%, IQR 52 to 73%). Based on the overall AGREE-REX score, most guideline recommendations were deemed moderate quality (n=19, 68%), followed by high quality (n=8, 29%), whereas only one guideline met the criteria for classification as low quality recommendations (n=1, 4%). Supplementary Table 2.

Table 3. AGREE-REX Inter-Rater Agreement

Domain/Item	Median % Score (range)	Krippendorff's alpha	95% Confidence Interval
A. Clinical Applicability	70 (13 to 96)	0.69	0.58 to 0.78
1. Evidence	72 (0 to 100)	0.70	0.58 to 0.81
2. Applicability to target users	78 (22 to 94)	0.34	0.14 to 0.50
3. Applicability to patients/populations	67 (17 to 94)	0.50	0.36 to 0.63
B. Values and Preferences	54 (25 to 81)	0.72	0.64 to 0.80
4. Values and preferences of users	58 (50 to 83)	0.43	0.23 to 0.61
5. Values and preferences of patients	53 (50 to 89)	0.71	0.55 to 0.84
6. Values and preferences of policy makers	50 (6 to 78)	0.49	0.32 to 0.64
7. Values and preferences of guideline developers	67 (0 to 89)	0.52	0.38 to 0.63
C. Implementability	61 (31 to 86)	0.47	0.34 to 0.60
8. Purpose	67 (11 to 94)	0.27	0.09 to 0.44
9. Local adaptation and adoption	56 (44 to 89)	0.33	0.15 to 0.50
Overall Score	**64 (23 to 85)**	**0.80**	**0.72 to 0.87**
All domains (A-C)	**-**	**0.84**	**0.81 to 0.87**

All items (1-9)	**-**	**0.55**	**0.50 to 0.60**

3.7 Guideline Characteristics and Incorporation of Antimicrobial Stewardship Principles

When evaluating guideline characteristics associated with incorporation of antimicrobial stewardship considerations, we found several factors that predicted whether guidelines would address such concepts.

In terms of year of publication, the odds ratios for addressing antimicrobial stewardship were 1.50 (97.5%CI: 0.15 to 15.46) for 2021, and 3.75 (97.5%CI: 0.33 to 42.95) for 2022, when compared to 2020. Guidelines focusing on LMIC were associated with a lower odds of addressing antimicrobial stewardship (0.19, 97.5%CI: 0.02 to 1.92). Presence of ID expertise on the guideline panel was associated with an over 9-fold odds (OR 9.44, 97.5%CI: 1.09 to 81.59) of incorporating antimicrobial stewardship considerations in the guideline. Public health expertise on the guideline panel was associated with a higher odds (OR 4.67, 97.5%CI: 0.34 to 63.17) of incorporating antimicrobial stewardship considerations. All nine guidelines in which pharmacist expertise was included on the panel incorporated antimicrobial stewardship considerations, but only 11 of 19 guidelines in which pharmacists were not stated to be on the panel included these considerations (OR >1000, 97.5%CI: 0 to infinity). (Table 4).

Higher guideline quality overall was associated with a higher odds of incorporating antimicrobial considerations (OR 8.56, 97.5%CI: 0.64 to 115.11) but the confidence intervals did not exclude no association. Although higher AGREE II scores were associated with a numerically higher odds of incorporating antimicrobial stewardship considerations across all domains, specific domains of AGREE II score were associated with a statistically significantly higher odds of incorporating antimicrobial stewardship principles in the guidelines. Most notably, guidelines with higher AGREE II scores for domain 3 (Rigour of Development) (OR 1.67, 97.5%CI: 1.02 to 2.72) and domain 4 (Clarity of Presentation) were associated with a higher odds of addressing antimicrobial stewardship (OR 3.45 per 10% increase in score, 97.5%CI 1.15 to 10.39) (Table 4, Figure 3).

At the guideline recommendation level, recommendation quality was associated with a numerically higher odds of incorporating antimicrobial stewardship considerations across a number all AGREE-REX domains. Most notably, recommendations scoring higher in the domain 1.Evidence, 2. Applicability to target users, 3. Applicability to patients and populations, 6. Values and preferences of policy makers, 7. Values and preferences of guideline developers, were all associated with a statistically significantly higher odds of addressing antimicrobial stewardship and resistance. Similarly, overall AGREE-REX score was associated with a higher odds of addressing antimicrobial stewardship and resistance (OR 3.26, 97.5%CI: 1.14 to 9.31, per 10% increase in score) (Table 4, Figure 4).

Table 4. Association between Guideline Characteristics and Incorporation of Antimicrobial Stewardship Considerations (Univariable Model)

Characteristic	**Addresses Antimicrobial Stewardship (n=20)**	**Does Not Address Antimicrobial Stewardship (n=8)**	**Odds Ratio for Addressing Antimicrobial Stewardship**	**97.5% confidence interval**
Guideline-level Characteristics				
Year of publication				
2020	4	3	Reference	-
2021	6	3	1.50	0.15 to 15.46
2022	10	2	3.75	0.33 to 42.95
Country Income				
HIC	18	5	Reference	-
LMIC	2	3	0.19	0.02 to 1.92
ID expert on panel				
No	3	5	Reference	-
Yes	17	3	9.44	1.09 to 81.59
Public health expert on panel				
No	12	7	Reference	
Yes	8	1	4.67	0.34 to 63.17
Pharmacy expert on panel				
No	11	8	Reference	-
Yes	9	0	>1000	0 to infinity
Any expert on panel				
No	3	5	Reference	
Yes	17	3	9.44	1.09 to 81.59
AGREE II Score (Guideline Level)				
1. Scope and purpose	Per 10% increase		1.76	0.73 to 4.29
2. Stakeholder involvement			1.53	0.91 to 2.57
3. Rigor of development			1.67	1.02 to 2.72
4. Clarity of presentation			3.45	1.15 to 10.39
5. Applicability			2.14	0.73 to 6.33
6. Editorial independence			1.01	0.71 to 1.44
AGREE II quality				

Low or moderate	9	7	Reference	-
High	11	1	8.56	0.64 to 115.11
AGREE REX Score (Recommendation Level)				
1. Evidence	Per 10% increase		1.51	1.01 to 2.25
2. Applicability to target users			2.25	1.08 to 4.69
3. Applicability to patients/populations			2.16	1.01 to 4.65
4. Values of users			10.82	0.96 to 122.52
5. Values of patients			>1000	0 to infinity
6. Values of policy makers			4.08	1.25 to 13.28
7. Values of guideline developers			1.90	1.01 to 3.57
8. Purpose			1.82	0.93 to 3.59
9. Local adaptation and adoption			6.37	0.75 to 54.00
Overall Score			3.26	1.14 to 9.31
AGREE REX quality				
Low or moderate	12	8	Reference	-
High	8	0	>1000	0 to infinity

Figure 3. AGREE II Score Box Plots for Guidelines and Incorporation of Antimicrobial Stewardship Considerations

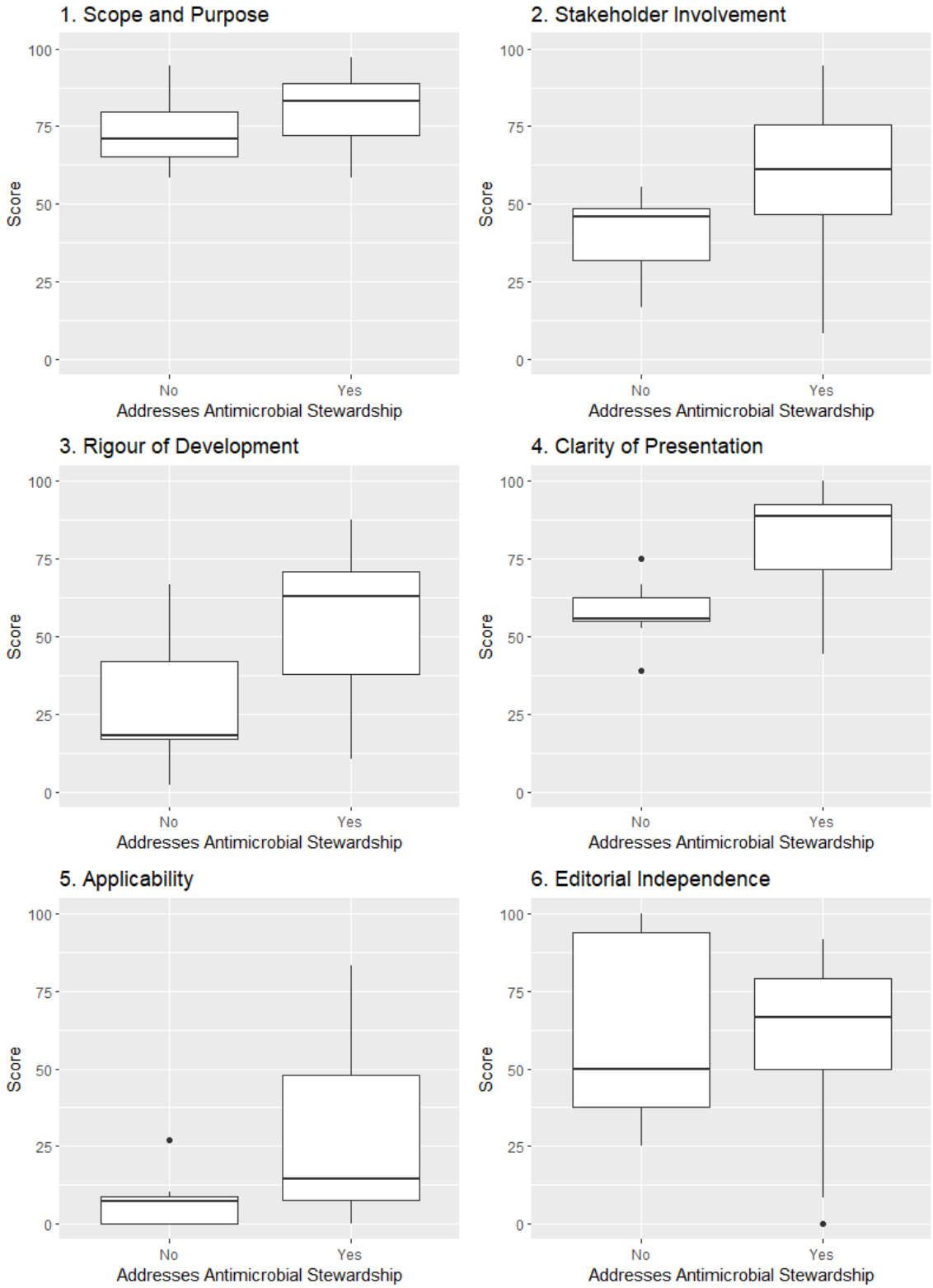
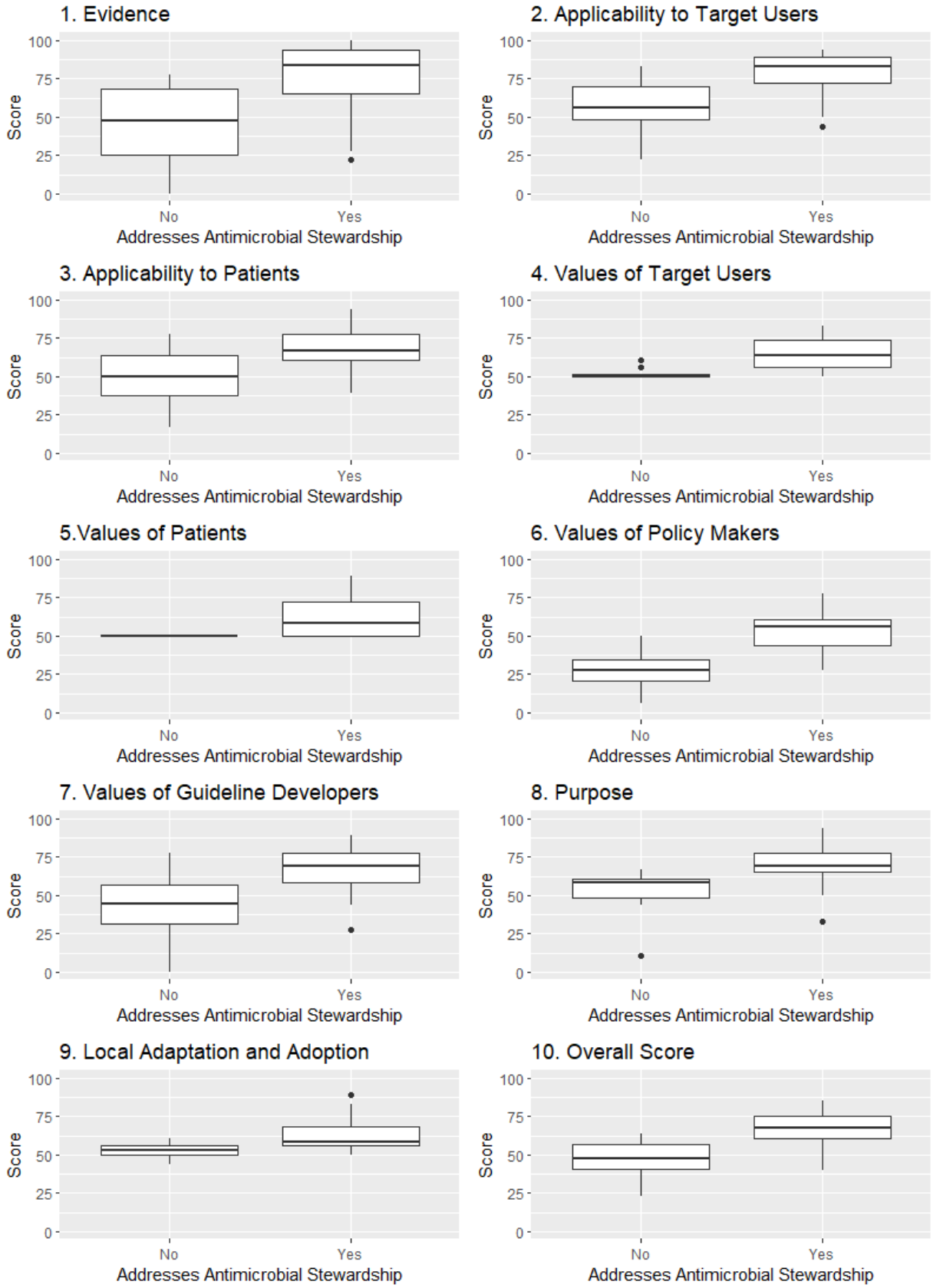


Figure 4. AGREE-REX Score Box Plots for Guidelines with and without Incorporation of Antimicrobial Stewardship Considerations



CHAPTER 4. DISCUSSION

4.1 Summary of Key Findings

Our systematic survey of antibiotic prescribing recommendations in COVID-19 identified a wide range in guideline and recommendation quality as demonstrated by AGREE II and AGREE-REX scores, respectively. There was inconsistency in the extent to which guidelines incorporated antimicrobial stewardship principles, with 71% of guidelines addressing at least one of these concepts and only 14% addressing all antimicrobial stewardship concepts, including encouraging judicious prescribing, antimicrobial resistance, and the risk of adverse effects associated with antibiotic use. We found that higher guideline and recommendation quality score was associated with greater odds of incorporating antimicrobial stewardship considerations for a number of guideline (rigour of development, clarity of presentation) and recommendation (evidence, applicability, values of users and policy makers, and purpose) quality domains. Further, including an infectious diseases expert and pharmacist on the guideline panel were also associated with a greater odds of incorporating considerations related to antimicrobial stewardship which suggests the importance of panel composition in developing guidelines and recommendations that aim to mitigate antimicrobial resistance.

Our survey found consistency in recommendations to avoid empiric antibiotic prescribing in most outpatient and non-critically ill inpatient COVID-19 populations who do not exhibit signs or symptoms of bacterial infection. However, some guidelines suggested empiric antibiotic use in critically ill patients given their severity of illness and the urgency for immediate therapy prior to identifying proven infectious etiology. Despite the general consistency related to antibiotic initiation of therapy, guideline recommendations varied in their strength of recommendation and certainty of evidence, which may reflect the lack of high quality data to support these recommendations, indirectness of the evidence, inconsistent interpretation of the evidence, and changes in the quality of evidence over time.

Given that COVID-19 is caused by a virus, SARS-CoV-2, trials to assess the efficacy of antibiotics for this condition, are not supported by a biological rationale. Hence, high

quality RCT data are largely lacking. But, in clinical practice when patients present with respiratory symptoms consistent with COVID-19, the clinician's uncertainty regarding microbiological etiology prior to SARS-CoV-2 identification, and the concern for bacterial co-infection after SARS-CoV-2 identification drive antibiotic prescribing. These clinical decisions are generally made on a case-by-case basis and as such rely on indirect evidence (such as a low, but non-negligible risk of bacterial co-infection reported across observational studies[13]) to support decision-making. This observation is supported by the high number of "Good Practice Statements" in which recommendations are not formal and are supported by indirect evidence. However, there remain opportunities to provide more direct evidence to support widespread practice improvements in antimicrobial stewardship, such as the use of rapid and accurate diagnostic approaches to help differentiate bacterial from viral etiology.[65]

On the other hand, the use of specific antibiotics with purported immunomodulatory activity, like azithromycin, have been assessed more formally for treatment of COVID-19. Randomized controlled trials have generally provided high quality evidence with high certainty of the lack of benefit of azithromycin as treatment for COVID-19.[15] This greater confidence was reflected in our systematic survey where azithromycin-focused recommendations generally exhibit a higher certainty of evidence and a strong recommendations to avoid use compared to general recommendations about antibiotic prescribing.

Our findings echo those of a previous systematic survey evaluating the extent to which non-COVID infectious disease guidelines, specifically tuberculosis, gonorrhea, and respiratory tract infections, consider antimicrobial resistance. The authors identified that only 35% of guideline recommendations considered AMR as an untoward outcome of antimicrobial therapy.[22] While our systematic survey focused on guidelines as a whole, rather than individual recommendations, we found a similar, albeit slightly higher, prevalence of 43% of guidelines addressing AMR as an outcome. Different quality definitions were used, but both systematic surveys also found a wide range in AGREE II score with a substantial proportion of low quality guidelines, suggesting there is an opportunity to improve the rigor and robustness of antimicrobial prescribing recommendations.

4.2 Strengths and Limitations

4.2.1 Strengths

Strengths of this systematic survey include our use of COVID-19 RecMap as a pre-existing tool to streamline the guideline and recommendation identification process. RecMap facilitated identification of 63 antimicrobial-related recommendations from 28 guidelines from across the globe including pre-extracted guideline data and AGREE II scores. This study is the first to evaluate the incorporation of a range of antimicrobial stewardship and resistance related considerations. Given the growing impact of AMR globally, addressing such considerations more comprehensively and systematically as part may be of increasing interest for guideline developers.

4.2.2 Limitations

On the other hand, some key limitations exist. COVID-19 RecMap facilitates streamlined access to a vast array of recommendations, however it may miss some guidelines that a targeted literature search could better identify. A direct search of published and unpublished literature, while more time consuming, may increase the yield and decrease the lag between publication and inclusion.

While important in principle, it is not yet clear if addressing antimicrobial stewardship and antimicrobial resistance as part of a guideline recommendation influences prescribing practice. While clinical practice guidelines are perceived as a foundational aspect of antimicrobial stewardship efforts,[66] and their implementation is associated with more appropriate prescribing,[67] there is a lack of data of how and whether the structure and language of such recommendations can influence practice. Similarly, the link between guideline quality and impact on clinical practice is not clear.

Due to the cross-sectional nature of such data, a causal association cannot be established between guideline elements and their incorporation of antimicrobial stewardship principles. Also, the small sample of eligible guidelines compromises statistical power. As a result, we reported odds ratios alongside 97.5% confidence intervals to gauge the magnitude and uncertainty of such associations.

Guideline formatting and brevity may adversely impact incorporation of antimicrobial and antimicrobial stewardship principles. While we didn’t explicitly measure guideline length, very brief guideline documents may be less likely to address antimicrobial stewardship and antimicrobial resistance given their succinctness. This finding is

supported by the fact that AGREE II score domain 4 (Clarity of Presentation) was associated with a higher odds of guidelines incorporating antimicrobial stewardship and AMR considerations. Similarly, ease of data extraction and identification of guideline characteristics varied depending on guideline clarity. For example, many guidelines did not clearly indicate the panel members or roles of the members, and as such we could not identify whether they included public health, infectious diseases, or pharmacy experts. These factors may favour longer, more detailed, and more transparent guidelines to "check off" more criteria but in practice may not necessarily have a more positive impact on antimicrobial prescribing.

Another key limitation is that this systematic survey did not assess relevant guidelines that decidedly do not make recommendations on antibiotic prescribing in COVID-19. For example, the Surviving Sepsis Campaign Guidelines on the Management of COVID-19 do not currently make recommendations for antibiotic prescribing.[68] Given the lack of direct evidence for or against empiric antimicrobial prescribing in critically ill patients with COVID-19 it could be considered justified to remain silent on this issue, but on the other hand a statement on antibiotic prescribing would be helpful to provide clinicians guidance, reassurance, and support antimicrobial stewardship in the face of such uncertainty for a common question in practice.

AGREE-REX is a relatively new tool to assess guideline recommendation quality across a number of key domains. This may be an important distinction to evaluating overall guideline quality assessed by the AGREE II instrument. However, AGREE-REX posed some challenges when applying the tool to antibiotic prescribing recommendations in COVID-19. This situation may be relatively unique compared to most recommendations assessed using this tool. Firstly, most COVID-19 guidelines do not focus exclusively on antibiotic prescribing but rather a broad array of treatment options, whereby antibiotic use represents only one of several treatment considerations. As such, information gathered from beyond the individual guideline provided a more thorough context to rate the recommendation quality when compared to evaluating the recommendation in isolation. Secondly, many antibiotic prescribing recommendations fall into the "good practice" category where experts agree antibiotics should not be prescribed for infections that are likely viral in nature. Thirdly, since the main decision node regarding antibiotic prescribing in this context is whether or not to

prescribe, and a general lack of equipoise for non-critically ill patients, values and preferences, acceptability, and local application play a less significant role. As a result, the three AGREE-REX appraisers agreed to rate several items at a minimum of neutral (values and preferences of target users, patients, and local application and adoption).

The AGREE-REX scoring tool provides clear criteria for rating but given the relatively unique topic of antibiotic prescribing in COVID-19, the reviewers agreed that there was a high degree of subjectivity to some of the items, particularly those related to applicability and values and preferences. Each AGREE REX item contains several criteria but the relative weight of such criteria is not clear. Additionally, some criteria may not be explicitly described in the guideline (e.g., item 4 "*The guideline differentiates between recommended actions for which clinical flexibility and individual patient tailoring is more appropriate in the decision-making process and those for which it is less appropriate*") or may be less applicable to the context (e.g., item 5 "*The guideline differentiates between recommended actions for which patient choice and/or values are likely to play a large part in the decision-making process and those for which they are likely to play a small role*"). This challenge of standardizing AGREE REX criteria interpretation is reflected by the relatively low inter-rater agreement for certain items such as purpose, applicability and adaptation, applicability to and values and preferences of target users. Incorporation of a 'not-applicable' or 'not clearly reported' category may be helpful to augment the tool to support usability in a wider variety of contexts. On the other hand, more objective items such as the assessment of evidence used in constructing recommendations had high inter-rater agreement. Despite the low agreement for some items, overall AGREE-REX inter-rater agreement was high, suggesting overall AGREE-REX score may be a more appropriate estimate of recommendation quality than the score for individual items or domains.

4.3 Implications to Public Health

This systematic survey identifies important considerations that apply to infectious diseases guidelines more generally beyond COVID-19. There is an opportunity for guidelines to further emphasize the potential risks of antibiotic harms to provide more balanced recommendations. Many prospective studies involving antibiotics are underpowered to detect secondary harms data, particularly antimicrobial resistance.[69]

So it may appear that there is no detectable difference in risk of AMR between individuals, when in fact this risk is more significant at a population level.[70–72] As such, a responsible and balanced approach to communicating the importance of antimicrobial stewardship and the of potential harms of antibiotic overuse may be warranted. Incorporation of infectious diseases experts (e.g., infectious diseases physicians, antimicrobial stewardship pharmacists) on guideline panels may help to encourage such statements. From an implementation science perspective, however, the existence of high quality guidelines incorporating antimicrobial stewardship principles alone does not necessarily lead to improved antimicrobial prescribing. Efforts must be made to ensure recommendations are appropriately disseminated, incorporated into the antimicrobial prescribing workflow, and assessed for opportunities to improve.

As a potential tool to support the findings of this study, we developed a brief checklist of 15 considerations to support high quality antimicrobial prescribing recommendations adapted from previous work to provide a comprehensive checklist of 146 items to facilitate high quality guideline development and implementation.[73]

CHAPTER 5. CONCLUSION

Across 28 guidelines and 63 recommendations pertaining to antibiotic prescribing in patients with COVID-19, there was generally consistency to avoid empiric antibiotic therapy in non-critically ill patients with COVID-19 and no evidence of bacterial infection. However, guideline and recommendation quality varied importantly. A third of guidelines did not incorporate any antimicrobial stewardship principles to encourage judicious prescribing and mitigate antimicrobial resistance. Including infectious diseases expertise on the guideline panel and higher recommendation quality may be associated with a higher odds of incorporation of antimicrobial stewardship considerations. These findings provide considerations for the development of future antibiotic prescribing recommendations, including the importance of guideline quality, panel composition, and the need to incorporate antimicrobial stewardship considerations.

REFERENCES

1. Nieuwlaat R, Mbuagbaw L, Mertz D, Burrows LL, Bowdish DME, Moja L, et al. Coronavirus Disease 2019 and Antimicrobial Resistance: Parallel and Interacting Health Emergencies. Clinical Infectious Diseases. 2021;72:1657–9.

2. Murray CJ, Ikuta KS, Sharara F, Swetschinski L, Robles Aguilar G, Gray A, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. The Lancet. 2022;S0140673621027240.

3. Our World In Data. Cumulative confirmed COVID-19 cases and deaths, world [Internet]. [cited 2022 May 12]. Available from: https://ourworldindata.org/grapher/cumulative-deaths-and-cases-covid-19

4. Holmes AH, Moore LSP, Sundsfjord A, Steinbakk M, Regmi S, Karkey A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. The Lancet. 2016;387:176–87.

5. Langford BJ, Daneman N, Leung V, Wu JHC, Brown K, Schwartz KL, et al. The second-hand effects of antibiotics: communicating the public health risks of drug resistance. JAC-Antimicrobial Resistance. 2019;1:dlz059.

6. Fleming-Dutra KE, Hersh AL, Shapiro DJ, Bartoces M, Enns EA, File TM, et al. Prevalence of Inappropriate Antibiotic Prescriptions Among US Ambulatory Care Visits, 2010-2011. JAMA. 2016;315:1864.

7. Magill SS, O'Leary E, Ray SM, Kainer MA, Evans C, Bamberg WM, et al. Assessment of the Appropriateness of Antimicrobial Use in US Hospitals. JAMA Netw Open. 2021;4:e212007.

8. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clinical Infectious Diseases. 2016;62:e51–77.

9. Collignon P, Beggs J. CON: COVID-19 will not result in increased antimicrobial resistance prevalence. JAC-Antimicrobial Resistance [Internet]. 2020 [cited 2020 Jul 20];2. Available from: http://fdslive.oup.com/www.oup.com/pdf/production_in_progress.pdf

10. Clancy CJ, Buehrle DJ, Nguyen MH. PRO: The COVID-19 pandemic will result in increased antimicrobial resistance rates. JAC-Antimicrobial Resistance [Internet]. 2020 [cited 2020 Jul 20];2. Available from: http://fdslive.oup.com/www.oup.com/pdf/production_in_progress.pdf

11. Witt LS, Howard-Anderson JR, Jacob JT, Gottlieb LB. The impact of COVID-19 on multidrug-resistant organisms causing healthcare-associated infections: a narrative review. JAC-Antimicrobial Resistance. 2022;5:dlac130.

12. Langford BJ, So M, Leung V, Raybardhan S, Westwood D, Lo J, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a rapid living review: 2021 update with meta-regression [Internet]. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021241098

13. Langford BJ, So M, Leung V, Raybardhan S, Lo J, Kan T, et al. Predictors and microbiology of respiratory and bloodstream bacterial infection in patients with COVID-19: living rapid review update and meta-regression. Clinical Microbiology and Infection. 2021;S1198743X21006364.

14. Langford BJ, So M, Raybardhan S, Leung V, Soucy JPR, Westwood D, et al. Antibiotic prescribing in patients with COVID-19: rapid review and meta-analysis. Clinical Microbiology and Infection. 2021;27:520–31.

15. Popp M, Stegemann M, Riemer M, Metzendorf MI, Romero CS, Mikolajewska A, et al. Antibiotics for the treatment of COVID-19. Cochrane Haematology Group, editor. Cochrane Database of Systematic Reviews [Internet]. 2021 [cited 2023 Mar 3];2022. Available from: http://doi.wiley.com/10.1002/14651858.CD015025

16. Huttner BD, Catho G, Pano-Pardo JR, Pulcini C, Schouten J. COVID-19: don't neglect antimicrobial stewardship principles! Clinical Microbiology and Infection. 2020;26:808–10.

17. Elligsen M, Wan M, Lam PW, Lo J, Taggart LR, Chan AJ, et al. Trends in hospital antibiotic utilization during the coronavirus disease 2019 (COVID-19) pandemic: A multicenter interrupted time-series analysis. ASHE. 2022;2:e128.

18. Langford BJ, Soucy JPR, Leung V, So M, Kwan ATH, Portnoff JS, et al. Antibiotic resistance associated with the COVID-19 pandemic: a systematic review and meta-analysis. Clinical Microbiology and Infection. 2022;S1198743X22006103.

19. Langford BJ, So M, Simeonova M, Leung V, Lo J, Kan T, et al. Antimicrobial resistance in patients with COVID-19: a systematic review and meta-analysis. The Lancet Microbe. 2023;4:e179–91.

20. Langford BJ, So M, Simeonova M, Leung V, Lo J, Kan T, et al. Antimicrobial Resistance in Patients with COVID-19: A Systematic Review and Meta-Analysis. SSRN Journal [Internet]. 2022 [cited 2022 May 12]; Available from: https://www.ssrn.com/abstract=4099404

21. MacFadden DR, Maxwell C, Bowdish D, Bronskill S, Brooks J, Brown K, et al. COVID-19 Vaccination is Associated with Reduced Outpatient Antibiotic Prescribing In Older Adults with Confirmed SARS-CoV-2: A Population Wide Cohort Study. Clinical Infectious Diseases. 2023;ciad190.

22. Stalteri Mastrangelo R, Santesso N, Bognanni A, Darzi A, Karam S, Piggott T, et al. Consideration of antimicrobial resistance and contextual factors in infectious disease guidelines: a systematic survey. BMJ Open. 2021;11:e046097.

23. Nasir ZH, Mertz D, Nieuwlaat R, Santesso N, Lotfi T, Motilall A, et al. An evaluation of the COVID-19 recommendation map identified diverging clinical and public health guidance. Journal of Clinical Epidemiology. 2022;147:83–94.

24. World Health Organization. WHO COVID-19 Clinical management: living guidance [Internet]. Geneva, Switzerland; 2021 [cited 2022 May 12]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-2

25. National Institute for Health and Care Excellence: Guidelines. COVID-19 rapid guideline: antibiotics for pneumonia in adults in hospital [Internet]. London: National Institute for Health and Care Excellence (NICE); 2020 [cited 2022 May 12]. (National Institute for Health and Care Excellence: Guidelines). Available from: http://www.ncbi.nlm.nih.gov/books/NBK566162/

26. Johnston A, Kelly SE, Hsieh SC, Skidmore B, Wells GA. Systematic reviews of clinical practice guidelines: a methodological guide. Journal of Clinical Epidemiology. 2019;108:64–76.

27. COVID19 Recommendations and Gateway to Contextualization [Internet]. 2022 [cited 2022 May 12]. Available from: https://covid19.recmap.org/

28. Lotfi T, Stevens A, Akl EA, Falavigna M, Kredo T, Mathew JL, et al. Getting trustworthy guidelines into the hands of decision-makers and supporting their consideration of contextual factors for implementation globally: recommendation mapping of COVID-19 guidelines. Journal of Clinical Epidemiology. 2021;135:182–6.

29. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. Journal of Clinical Epidemiology. 2011;64:383–94.

30. Dewidar O, Lotfi T, Langendam M, Parmelli E, Saz Parkinson Z, Solo K, et al. Which actionable statements qualify as good practice statements In Covid-19 guidelines? A systematic appraisal. BMJ EBM. 2022;27:361–9.

31. The AGREE Enterprise. AGREE: Advancing the science of practice guidelines [Internet]. 2022 [cited 2022 May 12]. Available from: https://www.agreetrust.org/

32. Brouwers MC, Spithoff K, Kerkvliet K, Alonso-Coello P, Burgers J, Cluzeau F, et al. Development and Validation of a Tool to Assess the Quality of Clinical Practice Guideline Recommendations. JAMA Netw Open. 2020;3:e205535.

33. Appraisal of Guidelines Research and Evaluation (AGREE). AGREE-REX: Recommendation EXcellence Reporting Checklist [Internet]. 2019. Available from: www.agreetrust.org

34. Bargeri S, Iannicelli V, Castellini G, Cinquini M, Gianola S. AGREE II appraisals of clinical practice guidelines in rehabilitation showed poor reporting and moderate variability in quality ratings when users apply different cuff-offs: a methodological study. Journal of Clinical Epidemiology. 2021;139:222–31.

35. Hallgren KA. Computing Inter-Rater Reliability for Observational Data: An Overview and Tutorial. TQMP. 2012;8:23–34.

36. Hayes AF, Krippendorff K. Answering the Call for a Standard Reliability Measure for Coding Data. Communication Methods and Measures. 2007;1:77–89.

37. Bassetti M, Giacobbe DR, Bruzzi P, Barisione E, Centanni S, Castaldo N, et al. Clinical Management of Adult Patients with COVID-19 Outside Intensive Care Units: Guidelines from the Italian Society of Anti-Infective Therapy (SITA) and the Italian Society of Pulmonology (SIP). Infect Dis Ther. 2021;10:1837–85.

38. Pan American Health Organization. Guidelines for Care of Critically Ill Adult Patients with COVID-19 in the Americas. Summary, version 3 [Internet]. 2021. Available from: https://iris.paho.org/handle/10665.2/53895

39. Peyronnet V, Sibiude J, Huissoud C, Lescure FX, Lucet JC, Mandelbrot L, et al. [Infection with SARS-CoV-2 in pregnancy. Update of Information and proposed care. CNGOF]. Gynecol Obstet Fertil Senol. 2020;48:858–70.

40. Liu E, Smyth RL, Luo Z, Qaseem A, Mathew JL, Lu Q, et al. Rapid advice guidelines for management of children with COVID-19. Ann Transl Med. 2020;8:617–617.

41. Vidal-Cortés P, Díaz Santos E, Aguilar Alonso E, Amezaga Menéndez R, Ballesteros MÁ, Bodí MA, et al. Recommendations for the management of critically ill patients with COVID-19 in Intensive Care Units. Medicina Intensiva (English Edition). 2022;46:81–9.

42. De Simone B, Chouillard E, Sartelli M, Biffl WL, Di Saverio S, Moore EE, et al. The management of surgical patients in the emergency setting during COVID-19 pandemic: the WSES position paper. World J Emerg Surg. 2021;16:14.

43. National Institutes of Health. COVID-19 Treatment Guidelines [Internet]. 2022. Available from: https://www.covid19treatmentguidelines.nih.gov/about-the-guidelines/whats-new/

44. Waghmare A, Abidi MZ, Boeckh M, Chemaly RF, Dadwal S, El Boghdadly Z, et al. Guidelines for COVID-19 Management in Hematopoietic Cell Transplantation and Cellular Therapy Recipients. Biology of Blood and Marrow Transplantation. 2020;26:1983–94.

45. Mendes JJ, Paiva JA, Gonzalez F, Mergulhão P, Froes F, Roncon R, et al. Update of the recommendations of the Sociedade Portuguesa de Cuidados Intensivos and the Infection and Sepsis Group for the approach to COVID-19 in Intensive Care Medicine. Rev Bras Ter Intensiva. 2022;33:487–536.

46. Nadeem S, Aamdani SS, Ayub B, Rizvi NA, Arslan FS, Martins RS, et al. Development of Evidence-Based COVID-19 Management Guidelines for Local Context: The Methodological Challenges. Bayramlar OF, editor. Global Health. 2022;2022:1–30.

47. García-Álvarez JL, García-Vigil JL. Guidelines for clinical management of SARS-CoV-2 infection. GMM. 2021;156:6012.

48. National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing COVID-19 [Internet]. 2022. Available from: https://www.nice.org.uk/guidance/ng191/resources/covid19-rapid-guideline-managing-covid19-pdf-51035553326

49. Shetty VU, Brotherton BJ, Achilleos A, Akrami KM, Barros LM, Checkley W, et al. Pragmatic Recommendations for Therapeutics of Hospitalized COVID-19 Patients in Low- and Middle-Income Countries. Am J Trop Med Hyg. 2020;104:48–59.

50. Halpin DMG, Criner GJ, Papi A, Singh D, Anzueto A, Martinez FJ, et al. Global Initiative for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease. The 2020 GOLD Science Committee Report on COVID-19 and Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2021;203:24–36.

51. Sieswerda E, de Boer MGJ, Bonten MMJ, Boersma WG, Jonkers RE, Aleva RM, et al. Recommendations for antibacterial therapy in adults with COVID-19 - an evidence based guideline. Clin Microbiol Infect. 2021;27:61–6.

52. Falavigna M, Colpani V, Stein C, Azevedo LCP, Bagattini AM, Brito GV de, et al. Guidelines for the pharmacological treatment of COVID-19. The task force/consensus guideline of the Brazilian Association of Intensive Care Medicine, the Brazilian Society of Infectious Diseases and the Brazilian Society of Pulmonology and Tisiology. Revista Brasileira de Terapia Intensiva [Internet]. 2020 [cited 2023 Mar 15];32. Available from: http://rbti.org.br/artigo/detalhes/0103507X-32-2-1

53. Ontario COVID-19 Science Advisory Table. Clinical Practice Guideline Summary: Recommended Drugs and Biologics in Adult Patients with COVID-19 [Internet]. 2022. Available from: https://covid19-sciencetable.ca/sciencebrief/clinical-practice-guideline-summary-recommended-drugs-and-biologics-in-adult-patients-with-covid-19-version-11-0/

54. Brazilian Association of Emergency Medicine (ABRAMEDE), Brazilian Medical Association (AMB), Brazilian Society of Angiology and Vascular Surgery (SBACV), Brazilian Society of Geriatrics and Gerontology (SBGG), Brazilian Society of Infectious Diseases (SBI), Brazilian Society of Family and Community Medicine (SBFMC), and Brazilian Thoracic Society (SBPT). Brazilian guidelines for the treatment of outpatients with suspected or confirmed COVID-19. A joint guideline of the Brazilian Association of Emergency Medicine (ABRAMEDE), Brazilian Medical Association (AMB), Brazilian Society of Angiology and Vascular Surgery (SBACV), Brazilian Society of Geriatrics and Gerontology (SBGG), Brazilian Society of Infectious Diseases (SBI), Brazilian Society of Family and Community Medicine (SBFMC), and Brazilian Thoracic Society (SBPT) [Internet]. 2022. Available from: https://www.bjid.org.br/en-brazilian-guidelines-for-treatment-outpatients-articulo-S1413867022000356

55. Malin JJ, Spinner CD, Janssens U, Welte T, Weber-Carstens S, Schälte G, et al. Key summary of German national treatment guidance for hospitalized COVID-19 patients : Key pharmacologic recommendations from a national German living guideline using an Evidence to Decision Framework (last updated 17.05.2021). Infection. 2022;50:93–106.

56. Bartoletti M, Azap O, Barac A, Bussini L, Ergonul O, Krause R, et al. ESCMID COVID-19 living guidelines: drug treatment and clinical management. Clinical Microbiology and Infection. 2022;28:222–38.

57. Chalmers JD, Crichton ML, Goeminne PC, Cao B, Humbert M, Shteinberg M, et al. Management of hospitalised adults with coronavirus disease 2019 (COVID-19): a European Respiratory Society living guideline. Eur Respir J. 2021;57:2100048.

58. Australian COVID-19 Clinical Evidence Taskforce. Australian guidelines for the clinical care of people with COVID-19 [Internet]. 2022. Available from: https://snlg.iss.it/wp-content/uploads/2020/11/LG-australian-Full-guidelines-COVID.pdf

59. Pan American Health Organization. Guidelines for Prophylaxis and Management of Patients with Mild and Moderate COVID-19 in Latin America and the Caribbean [Internet]. 2021. Available from: https://iris.paho.org/handle/10665.2/55068

60. Alunno A, Najm A, Machado PM, Bertheussen H, Burmester GRR, Carubbi F, et al. 2021 update of the EULAR points to consider on the use of immunomodulatory therapies in COVID-19. Ann Rheum Dis. 2022;81:34–40.

61. Infectious Diseases Society of America. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19 [Internet]. 2022. Available from: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

62. Ko HK, Yu WK, Pan SW, Chen WC, Yang KY, Lin YT, et al. Consensus statement and recommendations on the treatment of COVID-19: 2021 update. Journal of the Chinese Medical Association [Internet]. 2021 [cited 2023 Mar 15];Publish Ahead of Print. Available from: https://journals.lww.com/10.1097/JCMA.0000000000000617

63. Czech Health Research Council (AZV ČR). Prevention and treatment of COVID-19 [Prevence a léčba COVID-19] [Internet]. 2022. Available from: https://kdp.uzis.cz/index.php?pg=kdp&id=52

64. Clinical management of COVID-19: Living guideline [Internet]. Geneva: World Health Organization; 2022 [cited 2023 Aug 3]. (WHO Guidelines Approved by the Guidelines Review Committee). Available from: http://www.ncbi.nlm.nih.gov/books/NBK582435/

65. Broom JK, Broom AF, Kirby ER, Gibson AF, Post JJ. Clinical and social barriers to antimicrobial stewardship in pulmonary medicine: A qualitative study. American Journal of Infection Control. 2017;45:911–6.

66. Kruger SZ, Bronskill SE, Jeffs L, Steinberg M, Morris AM, Bell CM. Evaluating and prioritizing antimicrobial stewardship programs for nursing homes: A modified Delphi panel. Infect Control Hosp Epidemiol. 2020;41:1028–34.

67. Mol PGM, Wieringa JE, NannanPanday PV, Gans ROB, Degener JE, Laseur M, et al. Improving compliance with hospital antibiotic guidelines: a time-series intervention analysis. Journal of Antimicrobial Chemotherapy. 2005;55:550–7.

68. Alhazzani W, Evans L, Alshamsi F, Møller MH, Ostermann M, Prescott HC, et al. Surviving Sepsis Campaign Guidelines on the Management of Adults With Coronavirus Disease 2019 (COVID-19) in the ICU: First Update. Critical Care Medicine. 2021;49:e219–34.

69. Curran J, Lo J, Leung V, Brown K, Schwartz KL, Daneman N, et al. Estimating daily antibiotic harms: an umbrella review with individual study meta-analysis. Clinical Microbiology and Infection. 2022;28:479–90.

70. Daneman N, Bronskill SE, Gruneir A, Newman AM, Fischer HD, Rochon PA, et al. Variability in Antibiotic Use Across Nursing Homes and the Risk of Antibiotic-Related Adverse Outcomes for Individual Residents. JAMA InternMed. 2015;175:1331–9.

71. Brown K, Valenta K, Fisman D, Simor A, Daneman N. Hospital ward antibiotic prescribing and the risks of Clostridium difficile infection. JAMA InternMed. 2015;175:626–33.

72. Low M, Neuberger A, Hooton TM, Green MS, Raz R, Balicer RD, et al. Association between urinary community-acquired fluoroquinolone-resistant Escherichia coli and neighbourhood antibiotic consumption: a population-based case-control study. Lancet InfectDis. 2019;19:419–28.

73. Schünemann HJ, Wiercioch W, Etxeandia I, Falavigna M, Santesso N, Mustafa R, et al. Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise. CMAJ. 2014;186:E123–42.

74. Siemieniuk R, Guyatt G. BMJ Best Practice: Evidence-based medicine (EBM) toolkit [Internet]. BMJ Best Practice; Available from: https://bestpractice.bmj.com/info/toolkit/learn-ebm/what-is-grade/

75. Alonso-Coello P, Schünemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. BMJ. 2016;i2016.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Summary of Antibiotic Prescribing in COVID-19 Guideline Recommendations

Guideline #	Recommendation	Title	Author	Year	Country	Infectious Disease Expert	Public Health Expert	Pharmacist Expert	Setting	Recommendation Text (direct statements from guideline)	Antibiotic Category	Antibiotic Initiation	Antibiotic Selection	Antibiotic Duration	Microbiology related	Good practice statement	Additional Guidance	Certainty of evidence	Recommendation Strength	Addresses judicious use?	Addresses resistance?	Addresses other harms?	Statement on stewardship?
1	1.1	Clinical Management of Adult Patients with COVID-19 Outside Intensive Care Units: Guidelines from the Italian Society of Anti-Infective Therapy (SITA) and the Italian Society of Pulmonology (SIP)[37]	Italian Society of Anti-Infective Therapy (SITA) and the Italian Society of Pulmonology (SIP)	2021	Italy	Yes	No	Yes	Outpatient	In the absence of proven bacterial infections, the administration of antibiotics in outpatients with COVID19 should be considered only as empirical treatment of highly suspected bacterial co-infection or superinfections	Azithromycin	Y	N	N	N	N	N	very low	N/A	Y	Y	N	Y
1	1.2	Clinical Management of Adult Patients with COVID-19 Outside Intensive Care Units: Guidelines from the Italian Society of Anti-Infective Therapy (SITA) and the Italian Society of Pulmonology (SIP)[37]	Italian Society of Anti-Infective Therapy (SITA) and the Italian Society of Pulmonology (SIP)	2021	Italy	Yes	No	Yes	Outpatient	In the absence of proven bacterial infections, the administration of antibiotics in outpatients with COVID19 should be considered only as empirical treatment of highly suspected bacterial co-infection or superinfections.	All antibiotics	Y	N	N	N	Y	N	N/A	N/A	Y	Y	N	Y
1	1.3	Clinical Management of Adult Patients with COVID-19 Outside Intensive Care Units: Guidelines from the Italian Society of Anti-Infective Therapy (SITA) and the Italian Society of Pulmonology (SIP)[37]	Italian Society of Anti-Infective Therapy (SITA) and the Italian Society of Pulmonology (SIP)	2021	Italy	Yes	No	Yes	Inpatient non-ICU	We recommend against the routine use of antibiotics in hospitalized patients with COVID-19 without proven bacterial infection.	Azithromycin	Y	N	N	N	N	N	moderate	strong	Y	Y	N	Y
1	1.4	Clinical Management of Adult Patients with COVID-19 Outside Intensive Care Units: Guidelines from the Italian Society of Anti-Infective Therapy (SITA) and the Italian Society of Pulmonology (SIP)[37]	Italian Society of Anti-Infective Therapy (SITA) and the Italian Society of Pulmonology (SIP)	2021	Italy	Yes	No	Yes	Inpatient non-ICU	We recommend against the routine use of antibiotics in hospitalized patients with COVID-19 without proven bacterial infection.	All antibiotics	Y	N	N	N	N	N	very low	conditional	Y	Y	N	Y

Guideline #	Recommendation	Title	Author	Year	Country	Infectious Disease Expert	Public Health Expert	Pharmacist Expert	Setting	Recommendation Text (direct statements from guideline)	Antibiotic Category	Antibiotic Initiation	Antibiotic Selection	Antibiotic Duration	Microbiology related	Good practice statement	Additional Guidance	Certainty of evidence	Recommendation Strength	Addresses judicious use?	Addresses resistance?	Addresses other harms?	Statement on stewardship?
1	1.5	Clinical Management of Adult Patients with COVID-19 Outside Intensive Care Units: Guidelines from the Italian Society of Anti-Infective Therapy (SITA) and the Italian Society of Pulmonology (SIP)[37]	Italian Society of Anti-Infective Therapy (SITA) and the Italian Society of Pulmonology (SIP)	2021	Italy	Yes	No	Yes	Inpatient non-ICU	Empirical antibiotic treatment of suspected bacterial pneumonia alongside proper diagnostic procedures, should be considered in patients with COVID-19 with evidence of consolidative radiological lesions.	All antibiotics	Y	Y	N	N	Y	N	N/A	N/A	Y	Y	N	Y
2	2.1	Guidelines for Care of Critically Ill Adult Patients with COVID-19 in the Americas. Summary, version 3[38]	Pan American Health Organization	2021	Americas	Yes	Yes	No	Inpatient ICU	In mechanically ventilated patients with COVID-19 and respiratory failure, we suggested the administration of empiric antimicrobials/antibacterial agents for 5 to 7 days, following institutional protocols and considering the clinical diagnosis (for example, community- acquired pneumonia, sepsis, or suspected associated bacterial infection) and local data on bacterial resistance.	All antibiotics	Y	Y	Y	N	N	N	low	conditional	N	N	N	N
2	2.2	Guidelines for Care of Critically Ill Adult Patients with COVID-19 in the Americas. Summary, version 3[38]	Pan American Health Organization	2021	Americas	Yes	Yes	No	Inpatient ICU	The administration of antibiotics should be initiated within an hour of assessing the patient. Antibiotic therapy should be deescalated on the basis of microbiological results and clinical judgment.	All antibiotics	Y	Y	Y	Y	Y	N	N/A	N/A	N	N	N	N
2	2.3	Guidelines for Care of Critically Ill Adult Patients with COVID-19 in the Americas. Summary, version 3[38]	Pan American Health Organization	2021	Americas	Yes	Yes	No	Inpatient ICU	Coinfections should be treated based on diagnostic confirmation and clinical judgment following institutional protocols.	All antibiotics	Y	Y	Y	N	Y	N	N/A	N/A	N	N	N	N
2	2.4	Guidelines for Care of Critically Ill Adult Patients with COVID-19 in the Americas. Summary, version 3[38]	Pan American Health Organization	2021	Americas	Yes	Yes	No	Inpatient ICU	Remdesivir, lopinavir/ritonavir, chloroquine or hydroxychloroquine, with or without azithromycin, colchicine, and convalescent plasma, are not recommended for the management of the patients with COVID-19, nor for the conduct of clinical trials.	Azithromycin	Y	N	N	N	N	N	moderate	strong	N	N	N	N

Guideline #	Recommendation	Title	Author	Year	Country	Infectious Disease Expert	Public Health Expert	Pharmacist Expert	Setting	Recommendation Text (direct statements from guideline)	Antibiotic Category	Antibiotic Initiation	Antibiotic Selection	Antibiotic Duration	Microbiology related	Good practice statement	Additional Guidance	Certainty of evidence	Recommendation Strength	Addresses judicious use?	Addresses resistance?	Addresses other harms?	Statement on stewardship?
3	3.1	Infection par le SARS-CoV-2 chez les femmes enceintes. Actualisation de l'état des connaissances et de la proposition de prise en charge. CNGOF[39]	Collège national des gynécologues obstétriciens français (CNGOF)/French National College of French Obstetrician Gynaecologists	2020	France	No or Unclear	No or Unclear	No or Unclear	All	No antibiotic therapy is prescribed in principle in a patient with symptoms related to confirmed Covid-19 (apart from another source of infection) due to the exceptional nature of the bacterial co-infection. in case of doubt with a bacterial infection of the upper respiratory tract, the treatment recommendations [treatment recommendations provided]	All antibiotics	Y	Y	N	N	N	Y	N/A	N/A	Y	N	N	Y
4	4.1	Rapid advice guidelines for management of children with COVID-19[40]	unamed group	2020	Global	Yes	Yes	Yes	All	Antibiotics should not be used for children with COVID-19 if there is no evidence of bacterial coinfection	All antibiotics	Y	N	N	N	N	N	moderate	strong	Y	N	Y	Y
5	5.1	Recommendations for the management of critically ill patients with COVID-19 in Intensive Care Units[41]	Spanish Society of Intensive and Critical Care Medicine and Coronary Units [Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias	2022	Spain	No or Unclear	No or Unclear	No or Unclear	Inpatient ICU	We recommend early empirical treatment of possible bacterial pulmonary coinfection (strong clinical suspicion, purulent secretions, biomarker elevation, positive antigens, etc.) upon admission to the ICU of patients with COVID-19, since such coinfection is associated to increased mortality.	All antibiotics	Y	N	N	N	N	N	very low	strong	N	N	N	N
5	5.2	Recommendations for the management of critically ill patients with COVID-19 in Intensive Care Units[41]	Spanish Society of Intensive and Critical Care Medicine and Coronary Units [Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias	2022	Spain	No or Unclear	No or Unclear	No or Unclear	Inpatient ICU	We recommend daily evaluation of antibiotic treatment adjustment or suspension.	All antibiotics	N	Y	Y	N	N	N	low	strong	N	N	N	N

Guideline #	Recommendation	Title	Author	Year	Country	Infectious Disease Expert	Public Health Expert	Pharmacist Expert	Setting	Recommendation Text (direct statements from guideline)	Antibiotic Category	Antibiotic Initiation	Antibiotic Selection	Antibiotic Duration	Microbiology related	Good practice statement	Additional Guidance	Certainty of evidence	Recommendation Strength	Addresses judicious use?	Addresses resistance?	Addresses other harms?	Statement on stewardship?
5	5.3	Recommendations for the management of critically ill patients with COVID-19 in Intensive Care Units[41]	Spanish Society of Intensive and Critical Care Medicine and Coronary Units [Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias	2022	Spain	No or Unclear	No or Unclear	No or Unclear	Inpatient ICU	We recommend the early suspension of antimicrobial treatment once co-infection is ruled out	All antibiotics	N	N	Y	N	N	N	very low	strong	N	N	N	N
5	5.4	Recommendations for the management of critically ill patients with COVID-19 in Intensive Care Units[41]	Spanish Society of Intensive and Critical Care Medicine and Coronary Units [Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias	2022	Spain	No or Unclear	No or Unclear	No or Unclear	Inpatient ICU	We suggest an early diagnostic strategy and empirical treatment, in view of the high risk of bacterial and fungal superinfection in patients with COVID-19 subjected to mechanical ventilation.	All antibiotics	Y	N	N	N	N	N	very low	strong	N	N	N	N
5	5.5	Recommendations for the management of critically ill patients with COVID-19 in Intensive Care Units[41]	Spanish Society of Intensive and Critical Care Medicine and Coronary Units [Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias	2022	Spain	No or Unclear	No or Unclear	No or Unclear	Inpatient ICU	We suggest active microbiological assessment in all patients with prolonged ICU stays (over 7 days) in the event of suspected superinfection.	All antibiotics	N	N	N	Y	N	N	very low	strong	N	N	N	N

Guideline #	Recommendation	Title	Author	Year	Country	Infectious Disease Expert	Public Health Expert	Pharmacist Expert	Setting	Recommendation Text (direct statements from guideline)	Antibiotic Category	Antibiotic Initiation	Antibiotic Selection	Antibiotic Duration	Microbiology related	Good practice statement	Additional Guidance	Certainty of evidence	Recommendation Strength	Addresses judicious use?	Addresses resistance?	Addresses other harms?	Statement on stewardship?
5	5.6	Recommendations for the management of critically ill patients with COVID-19 in Intensive Care Units[41]	Spanish Society of Intensive and Critical Care Medicine and Coronary Units [Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias	2022	Spain	No or Unclear	No or Unclear	No or Unclear	Inpatient ICU	We suggest lower respiratory tract sampling in patients with COVID-19 suspected to have superinfection in relation to ventilator-associated pneumonia (VAP) or ventilator-associated tracheobronchitis, before starting antibiotic treatment. We suggest the quantitative analysis of distal samples obtained through bronchoalveolar lavage (BAL), mini-BAL or bronchial aspirate - provided these procedures can be carried out safely for both the operator and the patient. If not possible, the alternative would be a lower respiratory tract sample in the form of a quantitative or semi-quantitative tracheal aspirate.	All antibiotics	Y	N	N	Y	N	N	low	strong	N	N	N	N
6	6.1	The management of surgical patients in the emergency setting during COVID-19 pandemic: the WSES position paper | World Journal of Emergency Surgery[42]	World Society of Emergency Surgery	2021	Global	Yes	No	No	All	The World Society of Emergency Surgery educational board (WSES) recommends carefully administering antibiotics in COVID-19 surgical patients for the high risk of selecting resistant bacteria, especially in patients admitted in ICU for mechanical ventilation. Early empirical antibiotic treatment should be targeted to results from cultures, with de-escalation of treatment as soon as possible.	All antibiotics	Y	Y	Y	Y	N	N	moderate	strong	Y	Y	N	Y
7	7.1	COVID-19 Treatment Guidelines[43]	National Institutes of Health	2022	United States	Yes	Yes	Yes	Hospitalized	In the absence of a proven or suspected bacterial infection, the Panel recommends against the use of empiric broad spectrum antibiotics in adult patients with severe or critical COVID-19	All antibiotics	Y	N	N	N	N	Y	N/A	N/A	Y	Y	Y	Y
7	7.2	COVID-19 Treatment Guidelines[43]	National Institutes of Health	2022	United States	Yes	Yes	Yes	Hospitalized	As with any hospitalized patient, adult patients with COVID-19 who receive antibiotics should be reassessed daily to minimize the adverse consequences of unnecessary antimicrobial therapy	All antibiotics	N	Y	Y	N	N	Y	N/A	N/A	Y	Y	Y	Y
7	7.3	COVID-19 Treatment Guidelines[43]	National Institutes of Health	2022	United States	Yes	Yes	Yes	Outpatient	The Panel recommends against the use of antibacterial therapy (e.g., azithromycin, doxycycline) for the outpatient treatment of COVID-19 in the absence of another indication	All antibiotics	Y	N	N	N	N	Y	N/A	N/A	Y	Y	Y	Y

Guideline #	Recommendation	Title	Author	Year	Country	Infectious Disease Expert	Public Health Expert	Pharmacist Expert	Setting	Recommendation Text (direct statements from guideline)	Antibiotic Category	Antibiotic Initiation	Antibiotic Selection	Antibiotic Duration	Microbiology related	Good practice statement	Additional Guidance	Certainty of evidence	Recommendation Strength	Addresses judicious use?	Addresses resistance?	Addresses other harms?	Statement on stewardship?
8	8.1	Guidelines for COVID-19 Management in Hematopoietic Cell Transplantation and Cellular Therapy Recipients[44]	American Society for Transplantation and Cellular Therapy (ASTCT) Infectious Diseases Special Interest Group.	2020	United States	Yes	No	No	All	We do not recommend routine antibiotic use in patients with SARS-CoV-2 limited to the upper respiratory tract, unless indicated for other reasons according to local protocols (ie, management of febrile neutropenia)	All antibiotics	Y	N	N	N	N	Y	N/A	N/A	N	N	N	N
9	9.1	Update of the recommendations of the Sociedade Portuguesa de Cuidados Intensivos and the Infection and Sepsis Group for the approach to COVID-19 in Intensive Care Medicine[45]	Sociedade Portuguesa de Cuidados Intensivos	2021	Portugal	No or Unclear	No or Unclear	No or Unclear	Inpatient ICU	In critically ill patients with COVID-19, in the presence of septic shock, it is recommended to administer antibiotic therapy until obtaining cultural results that allow the affirmation or exclusion of the coexistence of bacterial infection. Related: For critically ill patients with COVID-19, it is recommended to maintain a high index of suspicion for nosocomial infection (namely, ventilator-associated pneumonia).	All antibiotics	Y	N	N	Y	Y	N	N/A	N/A	N	N	N	N
9	9.2	Update of the recommendations of the Sociedade Portuguesa de Cuidados Intensivos and the Infection and Sepsis Group for the approach to COVID-19 in Intensive Care Medicine[45]	Sociedade Portuguesa de Cuidados Intensivos	2021	Portugal	No or Unclear	No or Unclear	No or Unclear	Inpatient ICU	It is recommended to reassess decisions regarding antibiotic therapy initiated at admission up to 72 hours, depending on the microbiological results available, the clinical evolution and inflammatory biomarkers (namely, procalcitonin).	All antibiotics	N	Y	Y	Y	Y	N	N/A	N/A	N	N	N	N
10	10.1	Development of Evidence-Based COVID-19 Management Guidelines for Local Context: The Methodological Challenges[46]	Pakistan's National Command Operation Center (NCOC),	2022	Pakistan	No or Unclear	No or Unclear	No or Unclear	All	As per our systematic review, we recommend against the use of antibiotics, including hydroxychloroquine alone or in combination with other antibiotics in hospitalized COVID-19 patients.	All antibiotics	Y	N	N	N	N	N	moderate	conditional	N	N	N	N
11	11.1	Guidelines for clinical management of SARS-CoV-2 infection[47]	unnamed group	2020	Mexico	No or Unclear	No or Unclear	No or Unclear	All	Antibiotics are not initially recommended, although they could be indicated based on clinical findings, blood test results or microbiological results	All antibiotics	Y	N	N	Y	Y	N	N/A	N/A	N	N	N	N

Guideline #	Recommendation	Title	Author	Year	Country	Infectious Disease Expert	Public Health Expert	Pharmacist Expert	Setting	Recommendation Text (direct statements from guideline)	Antibiotic Category	Antibiotic Initiation	Antibiotic Selection	Antibiotic Duration	Microbiology related	Good practice statement	Additional Guidance	Certainty of evidence	Recommendation Strength	Addresses judicious use?	Addresses resistance?	Addresses other harms?	Statement on stewardship?
11	11.2	Guidelines for clinical management of SARS-CoV-2 infection[47]	unnamed group	2020	Mexico	No or Unclear	No or Unclear	No or Unclear	All	Guidelines recommend "Usual antimicrobial treatment" for pneumonia with and without CXR abnormalities	All antibiotics	Y	N	N	N	N	Y	N/A	N/A	N	N	N	N
12	12.1	COVID-19 rapid guideline: managing COVID-19[48]	National Institute for Health and Care Excellence	2022	United Kingdom	Yes	Yes	Yes	All	Antibiotics should not be used for preventing or treating COVID-19 unless there is clinical suspicion of additional bacterial co-infection.	All antibiotics	Y	N	N	N	Y	N	N/A	N/A	Y	Y	Y	Y
12	12.2	COVID-19 rapid guideline: managing COVID-19[48]	National Institute for Health and Care Excellence	2022	United Kingdom	Yes	Yes	Yes	Outpatient	In community settings, do not offer an antibiotic for preventing secondary bacterial pneumonia in people with COVID-19. If a person has suspected or confirmed secondary bacterial pneumonia, start antibiotic treatment as soon as possible.	All antibiotics	Y	N	N	N	Y	N	N/A	N/A	Y	Y	Y	Y
12	12.3	COVID-19 rapid guideline: managing COVID-19[48]	National Institute for Health and Care Excellence	2022	United Kingdom	Yes	Yes	Yes	All	Do not offer an antibiotic for preventing or treating pneumonia if SARS-CoV-2, another virus, or a fungal infection is likely to be the cause.	All antibiotics	Y	N	N	N	Y	N	N/A	N/A	Y	Y	Y	Y
12	12.4	COVID-19 rapid guideline: managing COVID-19[48]	National Institute for Health and Care Excellence	2022	United Kingdom	Yes	Yes	Yes	Hospitalized	Start empirical antibiotics if there is clinical suspicion of a secondary bacterial infection in people with COVID-19. When a decision to start antibiotics has been made: start empirical antibiotic treatment as soon as possible after establishing a diagnosis of secondary bacterial pneumonia, and certainly within 4 hours; start treatment within 1 hour if the person has suspected sepsis and meets any of the high-risk criteria for this outlined in the NICE guideline on sepsis.	All antibiotics	Y	N	N	N	Y	N	N/A	N/A	Y	Y	Y	Y

Guideline #	Recommendation	Title	Author	Year	Country	Infectious Disease Expert	Public Health Expert	Pharmacist Expert	Setting	Recommendation Text (direct statements from guideline)	Antibiotic Category	Antibiotic Initiation	Antibiotic Selection	Antibiotic Duration	Microbiology related	Good practice statement	Additional Guidance	Certainty of evidence	Recommendation Strength	Addresses judicious use?	Addresses resistance?	Addresses other harms?	Statement on stewardship?
12	12.5	COVID-19 rapid guideline: managing COVID-19[48]	National Institute for Health and Care Excellence	2022	United Kingdom	Yes	Yes	Yes	Hospitalized	In hospitals or other acute delivery settings (for example, virtual wards), to help identify non-SARS-CoV-2 viral, fungal or bacterial pneumonia, and to inform decision making about using antibiotics, consider the following tests: a full blood count; chest imaging (X-ray, CT or ultrasound); respiratory and blood samples (for example, sputum or a tracheal aspirate sample, blood culture; see Public Health England's COVID-19: guidance for sampling and for diagnostic laboratories); urine samples for legionella and pneumococcal antigen testing; throat samples for respiratory viral (and atypical pathogen) polymerase chain reaction testing. Do not use C-reactive protein to assess whether a person has a secondary bacterial infection if they have been having immunosuppressant treatment.	All antibiotics	N	N	N	Y	Y	N	N/A	N/A	Y	Y	Y	Y
13	13.1	Pragmatic Recommendations for Therapeutics of Hospitalized COVID-19 Patients in Low- and Middle-Income Countries[49]	COVID-LMIC Task Force and the Mahidol-Oxford Research Unit (MORU)	2021	Global	Yes	No	No	Hospitalized	We suggest close monitoring without additional empiric antimicrobials if there are no clinical or laboratory signs of other infections.	All antibiotics	Y	N	N	N	N	N	very low	conditional	Y	Y	N	Y
13	13.2	Pragmatic Recommendations for Therapeutics of Hospitalized COVID-19 Patients in Low- and Middle-Income Countries[49]	COVID-LMIC Task Force and the Mahidol-Oxford Research Unit (MORU)	2021	Global	Yes	No	No	Hospitalized	We suggest empiric antimicrobial treatment for likely coinfecting pathogens if an alternative infectious cause is likely	All antibiotics	Y	Y	N	N	N	N	very low	conditional	Y	Y	N	Y
14	14.1	Global Initiative for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: The 2020 GOLD Science Committee Report on COVID-19 & COPD[50]	Global Initiative for Chronic Obstructive Lung Disease (GOLD)	2020	Global	No or Unclear	No or Unclear	No	All	Use antibiotics and oral steroids in line with recommendations for exacerbations	All antibiotics	Y	N	N	N	Y	N	N/A	N/A	N	N	N	N

Guideline #	Recommendation	Title	Author	Year	Country	Infectious Disease Expert	Public Health Expert	Pharmacist Expert	Setting	Recommendation Text (direct statements from guideline)	Antibiotic Category	Antibiotic Initiation	Antibiotic Selection	Antibiotic Duration	Microbiology related	Good practice statement	Additional Guidance	Certainty of evidence	Recommendation Strength	Addresses judicious use?	Addresses resistance?	Addresses other harms?	Statement on stewardship?
15	15.1	Recommendations for antibacterial therapy in adults with COVID-19 - An evidence based guideline[51]	Dutch Working Party on Antibiotic Policy	2020	The Netherlands	Yes	No or Unclear	Yes	Hospitalized	We generally suggest restrictive use of antibacterial drugs in patients with proven or a high likelihood of COVID-19. This especially applies for patients upon admission who are mild to moderately ill	All antibiotics	Y	N	N	N	N	N	very low	conditional	Y	Y	Y	Y
15	15.2	Recommendations for antibacterial therapy in adults with COVID-19 - An evidence based guideline[51]	Dutch Working Party on Antibiotic Policy	2020	The Netherlands	Yes	No or Unclear	Yes	Hospitalized	We suggest that exceptions for the restrictive use of antibacterial drugs can be made for patients with proven or a high likelihood of COVID-19 who present with radiological findings and/or inflammatory markers compatible with bacterial co-infection. Other exceptions are patients who are severely ill or immunocompromised	All antibiotics	Y	N	N	N	Y	N	N/A	conditional	Y	Y	Y	Y
15	15.3	Recommendations for antibacterial therapy in adults with COVID-19 - An evidence based guideline[51]	Dutch Working Party on Antibiotic Policy	2020	The Netherlands	Yes	No or Unclear	Yes	Hospitalized	We recommend maximum efforts to obtain sputum and blood for culture as well as pneumococcal urinary antigen testing before start of empirical antibiotic therapy in patients with proven or high likelihood of COVID-19 upon admission	All antibiotics	Y	N	N	Y	Y	N	N/A	strong	Y	Y	Y	Y
15	15.4	Recommendations for antibacterial therapy in adults with COVID-19 - An evidence based guideline[51]	Dutch Working Party on Antibiotic Policy	2020	The Netherlands	Yes	No or Unclear	Yes	Hospitalized	In case of suspected bacterial co-infection, we suggest against empirical antibiotic treatment covering atypical pathogens in patients with proven or high likelihood of COVID-19 hospitalized at the general ward. Legionella urinary antigen testing should be performed according to local and/or national guidelines for CAP	All antibiotics	N	Y	N	N	N	N	very low	conditional	Y	Y	Y	Y
15	15.5	Recommendations for antibacterial therapy in adults with COVID-19 - An evidence based guideline[51]	Dutch Working Party on Antibiotic Policy	2020	The Netherlands	Yes	No or Unclear	Yes	Hospitalized	We recommend that the empirical antibiotic regimens in case of suspected bacterial co-infection depends on the severity of disease and according to local and/or national guidelines. For those fulfilling criteria of mild and moderate-severe CAP, we recommend to follow local and/or national guideline recommendations on antibacterial treatment in CAP	All antibiotics	N	Y	N	N	N	N	very low	conditional	Y	Y	Y	Y
15	15.6	Recommendations for antibacterial therapy in adults with COVID-19 - An evidence based guideline[51]	Dutch Working Party on Antibiotic Policy	2020	The Netherlands	Yes	No or Unclear	Yes	Hospitalized	We recommend to follow local and/or national guideline recommendations on antibacterial treatment for patients with COVID-19 and suspected bacterial secondary infection	All antibiotics	N	Y	N	N	Y	N	N/A	strong	Y	Y	Y	Y

Guideline #	Recommendation	Title	Author	Year	Country	Infectious Disease Expert	Public Health Expert	Pharmacist Expert	Setting	Recommendation Text (direct statements from guideline)	Antibiotic Category	Antibiotic Initiation	Antibiotic Selection	Antibiotic Duration	Microbiology related	Good practice statement	Additional Guidance	Certainty of evidence	Recommendation Strength	Addresses judicious use?	Addresses resistance?	Addresses other harms?	Statement on stewardship?
15	15.7	Recommendations for antibacterial therapy in adults with COVID-19 - An evidence based guideline[51]	Dutch Working Party on Antibiotic Policy	2020	The Netherlands	Yes	No or Unclear	Yes	Hospitalized	We suggest to stop antibiotics when representative sputum and blood culture as well as urinary antigen tests taken before start of empirical antibiotic therapy in patients with proven or high likelihood of COVID-19 show no bacterial pathogens after 48 hours of incubation	All antibiotics	N	N	Y	Y	Y	N	N/A	conditional	Y	Y	Y	Y
15	15.8	Recommendations for antibacterial therapy in adults with COVID-19 - An evidence based guideline[51]	Dutch Working Party on Antibiotic Policy	2020	The Netherlands	Yes	No or Unclear	Yes	Hospitalized	We suggest an antibiotic treatment duration of five days in patients with COVID-19 and suspected bacterial infection upon improvement of signs, symptoms and inflammatory markers	All antibiotics	N	N	Y	N	Y	N	N/A	conditional	Y	Y	Y	Y
16	16.1	Guidelines for the pharmacological treatment of COVID-19. The task-force/consensus guideline of the Brazilian Association of Intensive Care Medicine, the Brazilian Society of Infectious Diseases and the Brazilian Society of Pulmonology and Tisiology[52]	Brazilian Association of Intensive Care Medicine, the Brazilian Society of Infectious Diseases and the Brazilian Society of Pulmonology and Tisiology	2020	Brazil	Yes	Yes	Yes	All	We suggest against the use prophylactic antibiotics in patients with a suspected or confirmed COVID-19 diagnosis (weak recommendation	All antibiotics	Y	N	N	N	N	N	very low	conditional	N	Y	Y	Y
16	16.2	Guidelines for the pharmacological treatment of COVID-19. The task-force/consensus guideline of the Brazilian Association of Intensive Care Medicine, the Brazilian Society of Infectious Diseases and the Brazilian Society of Pulmonology and Tisiology[52]	Brazilian Association of Intensive Care Medicine, the Brazilian Society of Infectious Diseases and the Brazilian Society of Pulmonology and Tisiology	2020	Brazil	Yes	Yes	Yes	All	We recommend the use of antibiotics in COVID-19 patients with suspected bacterial infection	All antibiotics	Y	N	N	N	N	Y	N/A	N/A	N	Y	Y	Y

Guideline #	Recommendation	Title	Author	Year	Country	Infectious Disease Expert	Public Health Expert	Pharmacist Expert	Setting	Recommendation Text (direct statements from guideline)	Antibiotic Category	Antibiotic Initiation	Antibiotic Selection	Antibiotic Duration	Microbiology related	Good practice statement	Additional Guidance	Certainty of evidence	Recommendation Strength	Addresses judicious use?	Addresses resistance?	Addresses other harms?	Statement on stewardship?
16	16.3	Guidelines for the pharmacological treatment of COVID-19. The task-force/consensus guideline of the Brazilian Association of Intensive Care Medicine, the Brazilian Society of Infectious Diseases and the Brazilian Society of Pulmonology and Tisiology[52]	Brazilian Association of Intensive Care Medicine, the Brazilian Society of Infectious Diseases and the Brazilian Society of Pulmonology and Tisiology	2020	Brazil	Yes	Yes	Yes	All	We suggest against the routine use the hydroxychloroquine or chloroquine plus azithromycin combination for treatment of COVID-19 patients	Azithromycin	Y	N	N	N	N	N	very low	conditional	N	Y	Y	Y
17	17.1	Clinical Practice Guideline Summary: Recommended Drugs and Biologics in Adult Patients with COVID-19[53]	Ontario COVID-19 Science Advisory Table	2022	Canada (Ontario)	Yes	Yes	Yes	Inpatient ICU	Bacterial co-infection is uncommon in COVID-19 pneumonia at presentation. Do not add empiric antibiotics for bacterial pneumonia unless bacterial infection is strongly suspected. Continue empiric antibiotics for no more than 5 days, and de-escalate on the basis of microbiology results and clinical judgment.	All antibiotics	Y	N	Y	Y	N	Y	N/A	N/A	N	N	N	N
17	17.2	Clinical Practice Guideline Summary: Recommended Drugs and Biologics in Adult Patients with COVID-19[53]	Ontario COVID-19 Science Advisory Table	2022	Canada (Ontario)	Yes	Yes	Yes	All	RECOMMENDED AGAINST* The following therapies are not recommended for treatment of COVID-19 due to lack of benefit, potential harm, and system implications of overuse: antibiotics.	All antibiotics	Y	N	N	N	N	Y	N/A	N/A	N	Y	Y	Y

Guideline #	Recommendation	Title	Author	Year	Country	Infectious Disease Expert	Public Health Expert	Pharmacist Expert	Setting	Recommendation Text (direct statements from guideline)	Antibiotic Category	Antibiotic Initiation	Antibiotic Selection	Antibiotic Duration	Microbiology related	Good practice statement	Additional Guidance	Certainty of evidence	Recommendation Strength	Addresses judicious use?	Addresses resistance?	Addresses other harms?	Statement on stewardship?
18	18.1	Brazilian guidelines for the treatment of outpatients with suspected or confirmed COVID-19. A joint guideline of the Brazilian Association of Emergency Medicine (ABRAMEDE), Brazilian Medical Association (AMB), Brazilian Society of Angiology and Vascular Surgery (SBACV), Brazilian Society of Geriatrics and Gerontology (SBGG), Brazilian Society of Infectious Diseases (SBI), Brazilian Society of Family and Community Medicine (SBFMC), and Brazilian Thoracic Society (SBPT)[54]	Brazilian Association of Emergency Medicine (ABRAMEDE), Brazilian Medical Association (AMB), Brazilian Society of Angiology and Vascular Surgery (SBACV), Brazilian Society of Geriatrics and Gerontology (SBGG), Brazilian Society of Infectious Diseases (SBI), Brazilian Society of Family and Community Medicine (SBFMC), and Brazilian Thoracic Society (SBPT)	2022	Brazil	Yes	No	No	Outpatient	Recommendation 2: We recommend against using azithromycin in outpatients with suspected or confirmed COVID-19	Azithromycin	Y	N	N	N	N	N	moderate	strong	N	N	Y	Y
19	19.1	Key summary of German national treatment guidance for hospitalized COVID-19 patients[55]	Association of the Scientifc Medical Societies in Germany (AWMF) in collaboration with the COVID-19 Evidence Ecosystem Project (CEOsys).	2022	Germany	Yes	No or Unclear	No or Unclear	Hospitalized	Azithromycin should not be administered to hospitalized COVID-19 patients as antiviral therapy	Azithromycin	Y	N	N	N	N	N	high	strong	N	Y	Y	Y

Guideline #	Recommendation	Title	Author	Year	Country	Infectious Disease Expert	Public Health Expert	Pharmacist Expert	Setting	Recommendation Text (direct statements from guideline)	Antibiotic Category	Antibiotic Initiation	Antibiotic Selection	Antibiotic Duration	Microbiology related	Good practice statement	Additional Guidance	Certainty of evidence	Recommendation Strength	Addresses judicious use?	Addresses resistance?	Addresses other harms?	Statement on stewardship?
20	20.1	ESCMID COVID-19 living guidelines: drug treatment and clinical management[56]	European Society of Clinical Microbiology and Infectious Diseases COVID-19 Task Force	2021	Europe	Yes	No or Unclear	No or Unclear	All	Strong recommendation against use of azithromycin for COVID19	Azithromycin	Y	N	N	N	N	N	high	strong	Y	N	Y	Y
20	20.2	ESCMID COVID-19 living guidelines: drug treatment and clinical management[56]	European Society of Clinical Microbiology and Infectious Diseases COVID-19 Task Force	2021	Europe	Yes	No or Unclear	No or Unclear	All	Insufficient evidence to make a proper recommendation. Antibiotics should not be routinely prescribed in patients with COVID19 unless bacterial coinfection or secondary infection is suspected or confirmed	All antibiotics	Y	N	N	N	N	Y	N/A	N/A	Y	N	Y	Y
21	21.1	Management of hospitalised adults with coronavirus disease 2019 (COVID-19): a European Respiratory Society living guideline[57]	European Respiratory Society	2022	Europe	Yes	No or Unclear	No or Unclear	Hospitalized	The panel suggests NOT to offer azithromycin to hospitalised patients with COVID-19 in the absence of bacterial infection	Azithromycin	Y	N	N	N	N	N	very low	conditional	N	Y	N	Y
21	21.2	Management of hospitalised adults with coronavirus disease 2019 (COVID-19): a European Respiratory Society living guideline[57]	European Respiratory Society	2022	Europe	Yes	No or Unclear	No or Unclear	Hospitalized	The panel suggests NOT to offer hydroxychloroquine and azithromycin in combination to patients with COVID-19	Azithromycin	Y	N	N	N	N	N	moderate	conditional	N	Y	N	Y
22	22.1	Australian guidelines for the clinical care of people with COVID-19[58]	Australian COVID-19 Clinical Evidence Taskforce	2022	Australia	Yes	No or Unclear	Yes	All	Do not use azithromycin [with or without hydroxychloroquine] for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.	Azithromycin	Y	N	N	N	N	N	low	strong	N	N	Y	Y
23	23.1	Guidelines for Prophylaxis and Management of Patients with Mild and Moderate COVID-19 in Latin America and the Caribbean[59]	Pan American Health Organization	2021	Americas	Yes	Yes	No or Unclear	Outpatient and Inpatient non-ICU	It is recommended not to administer antibiotics to patients with a suspected or confirmed diagnosis of mild or moderate COVID-19 without suspicion of superadded bacterial infection.	All antibiotics	Y	N	N	N	N	N	low	strong	N	N	Y	Y

Guideline #	Recommendation	Title	Author	Year	Country	Infectious Disease Expert	Public Health Expert	Pharmacist Expert	Setting	Recommendation Text (direct statements from guideline)	Antibiotic Category	Antibiotic Initiation	Antibiotic Selection	Antibiotic Duration	Microbiology related	Good practice statement	Additional Guidance	Certainty of evidence	Recommendation Strength	Addresses judicious use?	Addresses resistance?	Addresses other harms?	Statement on stewardship?
24	24.1	2021 update of the EULAR points to consider on the use of immunomodulatory therapies in COVID-19[60]	European Alliance of Associations for Rheumatology	2021	Europe	No or Unclear	No or Unclear	No or Unclear	All	Hydroxychloroquine (HCQ) should be avoided for treating any stage of SARS-CoV-2 infection since it does not provide any additional benefit to the SOC, and could worsen the prognosis in more severe patients particularly if coprescribed with azithromycin.	Azithromycin	Y	N	N	N	N	Y	N/A	N/A	N	Y	N	Y
25	25.1	Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19[61]	Infectious Diseases Society of America	2022	United States	Yes	Yes	Yes	Hospitalized	Among hospitalized patients with COVID-19, the IDSA guideline panel recommends against hydroxychloroquine plus azithromycin.	Azithromycin	Y	N	N	N	N	N	low	strong	N	Y	Y	Y
26	26.1	Consensus statement and recommendations on the treatment of COVID-19: 2021 update[62]	Research Center for Epidemic Prevention - National Yang Ming Chiao Tung University (RCEP-NYCU)	2021	China	Yes	No or unclear	No or unclear	All	The use of HCQ with azithromycin for COVID-19 treatment is not generally recommended.	Azithromycin	Y	N	N	N	N	N	high	strong	N	N	N	N
27	27.1	Prevention and treatment of COVID-19 [Prevence a léčba COVID-19][63]	Czech Health Research Council (AZV ČR)	2022	Czech Republic	No or unclear	No or unclear	No or unclear	Hospitalized	We recommend not administering the combination of hydroxychloroquine and azithromycin to hospitalized patients with COVID-19.	Azithromycin	Y	N	N	N	N	N	low	strong	N	N	Y	Y
28	28.1	Living guideline for the clinical management of COVID-19[64]	World Health Organization	2022	Global	Yes	Yes	No or unclear	All	We recommend that antibiotic therapy or prophylaxis should not be used in patients with mild COVID-19.	All antibiotics	Y	N	N	N	N	N	N/A	strong	Y	Y	Y	Y
28	28.2	Living guideline for the clinical management of COVID-19[64]	World Health Organization	2022	Global	Yes	Yes	No or unclear	All	For COVID-19 patients with severe or critical disease, also collect blood cultures, ideally prior to initiation of antimicrobial therapy.	All antibiotics	Y	N	N	Y	N	N	N/A	strong	Y	Y	Y	Y

Guideline #	Recommendation	Title	Author	Year	Country	Infectious Disease Expert	Public Health Expert	Pharmacist Expert	Setting	Recommendation Text (direct statements from guideline)	Antibiotic Category	Antibiotic Initiation	Antibiotic Selection	Antibiotic Duration	Microbiology related	Good practice statement	Additional Guidance	Certainty of evidence	Recommendation Strength	Addresses judicious use?	Addresses resistance?	Addresses other harms?	Statement on stewardship?
28	28.3	Living guideline for the clinical management of COVID-19[64]	World Health Organization	2022	Global	Yes	Yes	No or unclear	All	We recommend for patients with suspected or confirmed moderate COVID-19, that antibiotics should not be prescribed unless there is clinical suspicion of a bacterial infection	All antibiotics	Y	N	N	N	N	N	N/A	strong	Y	Y	Y	Y

Supplementary Table 2. AGREE II and AGREE-REX Scores Guidelines with Recommendations for Antibiotic Therapy in Patients with COVID-19

	Guideline	AGREE II Score (%)							AGREE-REX Score (%)									
		1 Scope and Purpose	2 Stakeholder Involvement	3 Rigour of Development	4 Clarity of Presentation	5 Applicability	6 Editorial Independence	Quality	1 Evidence	2 Applicability to Target Users	3 Applicability to Patients	4 Values of Target Users	5 Values of Patients	6 Values of Decision Makers	7 Values of Guideline Developers	8 Purpose	9 Local Application and Adoption	Quality
1	Clinical Management of Adult Patients with COVID-19 Outside Intensive Care Units: Guidelines from the Italian Society of Anti-Infective Therapy (SITA) and the Italian Society of Pulmonology (SIP)	89	56	37	86	10	75	low	89	72	61	56	50	44	50	67	61	moderate
2	Guidelines for Care of Critically Ill Adult Patients with COVID-19 in the Americas. Summary, version 3	94	56	67	75	8	92	high	39	44	33	50	50	39	39	61	56	moderate
3	Infection par le SARS-CoV-2 chez les femmes enceintes. Actualisation de l'état des connaissances et de la proposition de prise en charge. CNGOF	69	44	22	64	6	8	low	22	50	39	56	50	28	28	33	50	moderate
4	Rapid advice guidelines for management of children with COVID-19	81	78	55	89	23	67	moderate	89	83	72	67	72	56	67	78	72	high
5	Recommendations for the management of critically ill patients with COVID-19 in Intensive Care Units	94	53	18	56	0	100	low	67	78	72	56	50	28	50	61	56	moderate
6	The management of surgical patients in the emergency setting during COVID-19 pandemic: the WSES position paper | World Journal of Emergency Surgery | Full Text	72	72	31	89	4	75	low	39	72	61	67	56	28	44	50	56	moderate
7	COVID-19 Treatment Guidelines	69	47	56	89	13	50	low	67	78	67	61	50	56	72	72	56	moderate
8	Guidelines for COVID-19 Management in Hematopoietic Cell Transplantation and Cellular Therapy Recipients	69	44	18	61	27	25	low	17	50	39	50	50	28	33	56	50	moderate
9	Update of the recommendations of the Sociedade Portuguesa de Cuidados Intensivos and the Infection and Sepsis Group for the approach to COVID-19 in Intensive Care Medicine - PMC	67	47	19	56	6	25	low	56	67	61	61	50	33	78	61	56	moderate
10	Development of Evidence-Based COVID-19 Management Guidelines for Local Context: The Methodological Challenges.	72	33	47	67	8	46	moderate	78	83	78	50	50	50	61	67	61	moderate
11	Guidelines for clinical management of SARS-CoV-2 infection.	58	17	2	39	0	54	low	0	22	17	50	50	6	0	11	50	low
12	COVID-19 rapid guideline: managing COVID-19	89	75	88	92	83	88	high	100	94	89	83	89	67	83	83	78	high
13	Pragmatic Recommendations for Therapeutics of Hospitalized COVID-19 Patients in Low- and Middle-Income Countries.	72	22	14	44	4	38	low	67	83	61	67	56	44	67	78	61	moderate
14	Global Initiative for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: The 2020 GOLD Science Committee Report on COVID-19 & COPD.	75	47	41	53	10	42	low	28	56	44	50	50	17	28	50	50	moderate

15	Recommendations for antibacterial therapy in adults with COVID-19 - An evidence based guideline.	92	28	65	72	8	83	high	100	89	67	56	50	56	72	72	56	moderate
16	Guidelines for the pharmacological treatment of COVID-19. The task-force/consensus guideline of the Brazilian Association of Intensive Care Medicine, the Brazilian Society of Infectious Diseases and the Brazilian Society of Pulmonology and Tisiology.	89	69	68	100	48	79	high	61	78	67	61	61	61	72	78	67	moderate
17	Clinical Practice Guideline Summary: Recommended Drugs and Biologics in Adult Patients with COVID-19	58	8	10	69	10	0	low	44	72	67	50	56	44	50	67	56	moderate
18	Brazilian guidelines for the treatment of outpatients with suspected or confirmed COVID-19.	89	61	62	78	17	67	high	89	83	78	72	67	78	78	83	67	high
19	Key summary of German national treatment guidance for hospitalized COVID-19 patients	67	64	39	78	4	33	low	94	89	78	67	72	56	72	72	56	high
20	ESCMID COVID-19 living guidelines: drug treatment and clinical management	75	53	44	67	0	67	low	89	89	72	61	61	50	78	67	56	moderate
21	Management of hospitalised adults with coronavirus disease 2019 (COVID-19): a European Respiratory Society living guideline	89	92	66	97	48	58	high	94	89	78	78	72	72	67	67	61	high
22	Australian guidelines for the clinical care of people with COVID-19	83	94	74	92	56	71	high	100	94	94	78	78	61	78	89	83	high
23	Guidelines for Prophylaxis and Management of Patients with Mild and Moderate COVID-19 in Latin America and the Caribbean	97	61	70	100	35	83	high	72	72	61	56	56	61	61	61	89	moderate
24	2021 update of the EULAR points to consider on the use of immunomodulatory therapies in COVID-19	83	33	70	64	8	58	high	28	44	50	50	50	39	44	33	50	moderate
25	Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19	81	50	80	92	19	92	high	100	89	83	83	67	61	78	67	56	high
26	Consensus statement and recommendations on the treatment of COVID-19: 2021 update.	61	28	15	56	0	100	low	72	56	56	50	50	22	56	44	44	moderate
27	Prevention and treatment of COVID-19 [Prevence a léčba COVID-19]	83	83	78	100	52	79	high	78	72	61	50	50	50	67	56	50	moderate
28	Living guidance for the clinical management of COVID-19	92	83	77	94	60	50	high	72	89	72	83	72	61	89	94	72	high

Checklist for Guidelines Relating to Antimicrobial Prescribing and/or Antimicrobial Stewardship*

Topic		Description
□	1. Organization, plan and train participants	Set specific, actionable goals, timelines, and priorities for guideline
□	2. Identify guideline group membership	Define who is involved in guideline panel. **Ensure infectious diseases specialists/ antimicrobial stewardship experts including pharmacists are incorporated into panel.**
□	3. Identify target audience and topic selection	Identify users and specific topics to be covered in guideline (e.g., uncomplicated cystitis)
□	4. Involve stakeholders	Ensure end users including prescribers, pharmacists, nurses, and patients are engaged as applicable
□	5. Declare conflict of interests	Financial, professional, and/or intellectual conflicts of interest should be declared
□	6. Generate Questions	Define key questions for recommendation (e.g., what is the optimal antibiotic treatment regimen for uncomplicated cystitis?). **Incorporate antibiotic initiation, selection (choice, dosing, route) and duration where appropriate. Address the role of microbiological and other diagnostic testing to support antimicrobial stewardship where appropriate.**
□	7. Select outcomes of interest by considering stakeholders' values and preferences	Consider those affected by guideline recommendations and possible consequences. Consider values and preferences of patients and providers. **Patient-important outcomes should be prioritized (e.g., reduced symptomatic recurrence is more important than microbiologic eradication of bacteria in cystitis).**
□	8. Gather and summarize evidence	Perform a systematic review or provide rationale (e.g., existing SR used). Summarize evidence using evidence tables, focusing on outcomes of interest.
□	9. Assess quality of evidence	Select a framework, such as GRADE (Grading of Recommendations Assessment, Development and Evaluation) and document judgements made in appraising the quality of evidence.[74]
□	10. Developing recommendations and determining their strength	Select a framework, such as GRADE Evidence to Decision (EtD) framework to ensure decision is well-informed and transparent.[75] **Incorporate epidemiological and local antimicrobial resistance considerations into the recommendation formulation.**
□	11. Refine recommendation wording and framing	Ensure recommendation is framed in a balanced way and consider implementation, feasibility, and equity factors in guideline use. **In addition to an assessment of the benefits and risks of antibiotic use for the condition of interest, include a Good Practice Statement addressing the need for judicious prescribing given patient- and population-level risks and include details on the known harms of antibiotic overuse, such as the potential for drug resistance, side effects, and super-infections (e.g., *C. difficile*)**
□	12. Reporting and Peer review	Consider peer-reviewed publication and/or thorough stakeholder review before reporting guideline.
□	13. Dissemination and implementation	Ensure relevant groups are aware of recommendation and consider tools to integrate recommendations into workflow (e.g., default recommendations on computerized provider order entry, electronic decision support systems).
□	14. Guideline Evaluation	Provide criteria and tools to monitor the implementation of guideline (process measures) and prospectively **evaluate the guideline to determine the impact (outcome measures) such as appropriateness of antibiotic prescribing, clinical outcomes, side effects, *C. difficile* infection, and antimicrobial resistance.**
□	15. Updating the Guideline	Set a policy, procedure, accountability, and timeline for updating review of literature and guideline recommendation.

**adapted from: Schünemann HJ, Wiercioch W, Etxeandia I, Falavigna M, Santesso N, Mustafa R, Ventresca M, Brignardello-Petersen R, Laisaar KT, Kowalski S, Baldeh T. Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise. CMAJ. 2014;186(3):E123-42*