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Antimicrobial Guidance: the need to consider antimicrobial resistance and context

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Objectives: Guidelines that include antimicrobial recommendations should explicitly consider contextual factors that influence antimicrobial resistance and their downstream effects on resistance selection. The objectives were to analyze how, and to what extent, guidelines are considering antimicrobial resistance; are of acceptable quality; and if they can be easily contextualized to fit the needs of specific populations and health systems.

Methods: We conducted a systematic review and searched Ovid MEDLINE and Embase from 2007 to June 7 2019 for tuberculosis, gonorrhoea, and respiratory tract infection guidelines published in English. To complement, we searched guideline databases, key websites, and reference lists. We identified guidelines and recommendations that considered contextual factors including antimicrobial resistance, values, resource use, equity, acceptability, and feasibility. We assessed quality of the guidelines using the Appraisal of Guidelines for Research and Evaluation II tool focusing on the domains scope and purpose, rigour of development, and editorial independence. PROSPERO, registration CRD42020145235.

Results: We screened 10,365 records of which, 74 guidelines met inclusion criteria. Approximately two thirds of recommendations considered antimicrobial resistance at the population- and/or outcome-level. 39% (n = 29/74) acceptable quality scores. Five of the 29 guidelines reported all factors required for recommendation contextualization. Equity was the least considered across guidelines.

Discussion: Relatively few guidelines for highly prevalent infectious diseases are considering local aspects including resistance and many do not consider contextual factors necessary for

appropriate antimicrobial use. Improving the quality of guidelines targeting specific regional areas is required.

Strengths and limitations of this study

- To our knowledge, this is the first study to assess the extent to which guidelines are considering local dimensions such as antimicrobial resistance.
- We also employed systematic methods to conduct our review and validated tools to measure the quality of guidelines.
- We used established frameworks including AGREE II, and GRADE Evidence to Decision framework to assess guidelines.
- The use of the credibility cut-off score of 60% or greater for three of the six AGREE II domains is based on limited guidance on cut-off thresholds, but by focusing on three key AGREE II domains and a relatively low score we were more inclusive.
- We used criteria of the GRADE Evidence to Decision Frameworks that are fairly general as they apply to any interventions. These dimensions could be complemented with specific criteria related to the antimicrobial field. For example, providing guidance on the appropriate threshold for escalating empiric guidance from narrower spectrum agents to broader spectrum agents.

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Keywords: Antimicrobial resistance, tuberculosis, gonorrhoea, respiratory tract infections, guidelines, recommendations, contexts, GRADE.

Introduction

Antimicrobials are essential to protecting human health. Their effectiveness is under threat due to antimicrobial resistance (AMR), generated by well documented excessive misuse of antimicrobials over several decades. At the 2015 United Nations General Assembly, member states committed to address AMR by adopting national plans centered on five strategic objectives outlined in the World Health Organization (WHO)'s Global Action Plan (1, 2). The fourth objective of the Global Action Plan is to implement national and hospital treatment guidelines for the optimization of antimicrobial medicines use (2). Guidelines are within a package of AMR stewardship interventions intended to modify clinician behavior by providing guidance on when, and how, to prescribe antimicrobials,-integrating information on antimicrobial consumption, resistance surveillance, research and development, and burden of resistance (3-5).

Preservation of antimicrobials requires the consideration of how, and under what conditions, is it appropriate to recommend antimicrobials. However, only a scant minority of recently published guidelines considered epidemiological and resistance pattern data (6). Concerns with guidelines in the context of AMR also involves the lack of considering important contextual factors. These include considering evidence on values, resource use, equity, acceptability, and feasibility that go beyond resistance patterns and may influence secular trends in AMR (7, 8). For example, guideline recommendations that account for antimicrobial resistance burden, public health infrastructure and medicine policies, and equitability of antimicrobial regimens are likely to better support effective use of antimicrobials in specific contexts (9). Such factors are also relevant for those implementing or adapting guidelines. These omissions likely result from the lack of formal guidance for developing recommendations that consider AMR and other local factors.

Incomplete reporting of evidence supporting recommendations, and the 'develop from scratch' mentality results in additional challenges. Scientific societies and other organizations duplicate the same work to develop recommendations. In turn, having multiple guidelines on the same topic may lead to confusion and loss of confidence by clinicians, and resource waste (8, 10). Through transparent reporting, and proper inclusion of AMR as more research becomes available, information can be effectively used in recommendations by others. Formal processes for adaptation permit societies and organizations to capitalize on existing evidence evaluation and interpretation by considering important contextual factors, among which AMR is the most noticeable. This would reduce cost and redundancy (7).

The objectives were to analyze how, and to what extent, guidelines are considering antimicrobial resistance; are of acceptable methodological quality; and if they can be easily contextualized to fit the needs of specific populations.

Methods

SELECTION CRITERIA AND SEARCH STRATEGY

We selected three types of infection: tuberculosis (TB), gonorrhoea, and respiratory tract infections, specifically otitis media, pharyngitis, sinusitis, and community-acquired pneumonia. These infections are a public health priority because they are becoming increasingly harder to treat due to AMR and/or are treated inappropriately, leading to higher risk of toxicity or resistance development. Harder to treat drug-resistant TB strains are increasing and projected to account for a quarter of all TB deaths by 2050 (11). Neisseria gonorrhoea is an urgent public health threat (12). The international spread of resistance to the last effective therapy, ceftriaxone and azithromycin, threatens sustained treatment of gonorrhoea (13, 14). Otitis media,

pharyngitis, sinusitis, and community-acquired pneumonia are prevalent and *Streptococcus pneumoniae* (the main causal microorganism*)*, was classified as a serious public health threat due to resistance observed by inappropriate use of antibiotics (12, 15, 16). All these syndromes have been prioritized by WHO as part of Access, Watch, and Reserve (AWaRe) — a new classification system that support a more nuanced approach to target inappropriate use of broad spectrum "Watch" antibiotics (17).

We included English language guidelines published between 2007 and 2019 on the above selected infections. We marked the 2007 WHO decision to update its guideline development and using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach as a major change in methodology, representing a division of two eras (18). We limited the focus of our analyses to the era following this change.

We included guidelines with clearly articulated recommendations as defined by the Institute of Medicine (IOM) Standards for Developing Trustworthy Clinical Practice Guidelines (14). After contacting guideline developers, we excluded guidelines with unobtainable supplementary materials required for analysis.

We searched Ovid MEDLINE and Embase from inception to June 7, 2019 (detailed search strategies in supplement). We conducted a second search in four guideline databases: TRIP (https://www.tripdatabase.com), G-I-N (https://www.g-i-n.net/home), BIGG (http://sites.bvsalud.org/bigg/en/biblio/), and the Canadian Medical Association clinical practice guideline (CPG) Infobase (https://joulecma.ca/cpg/homepage). We finally searched key international websites (table 6, supplement) and reviewed references of included guidelines.

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

DATA EXTRACTION AND QUALITY ASSESSMENT

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

Reviewers screened through recommendations classifying them as either considering AMR or not according to AMR dimensions. Although guidelines may have adopted different approaches to considering resistance with varying level of technicalities and detail, our operational definitions for considering a guideline "compliant" were inclusive. We assumed that for each recommendation, there would be an opportunity to consider information pertaining to AMR at the population- and outcome-level, given that formulation of specific recommendations is guided by population, intervention, comparison, and outcome (PICO) frameworks. Population-level considerations include recommendations for populations with some level of resistance, considerations of local resistance patterns, recommending the use of narrow-spectrum antimicrobials, and recommending the watchful-waiting approach to prescribing. Outcome-level dimensions included considering future prospects of AMR or the emergence of resistance as a consequence of antimicrobial use (examples provided in table 1)

Table 1: Satisfactory recommendations that consider antimicrobial resistance dimensions

AMR dimension(s)	Recommendation	Evidence illustration
AMR population-level dimensions considered	Amoxicillin-clavulanate rather than amoxicillin alone is recommended as empiric antimicrobial therapy for ABRS in adults (weak, low) (13).	Local national surveillance data in the United States of America for amoxicillin and beta-lactamase-producing *H. influenzae* was narratively described in the evidence summary was clearly linked to the recommendation.
AMR outcome-level dimensions considered	In neonates with gonococcal conjunctivitis, the WHO STI guideline suggests one of the following treatment options: • ceftriaxone 50 mg/kg (maximum 150 mg) IM as a single dose • kanamycin 25 mg/kg (maximum 75 mg) IM as a single dose • spectinomycin 25 mg/kg (maximum 75 mg) IM as a single dose (19).	The outcome of *'antimicrobial resistance'* was formally considered within a PICO framework within a supplementary appendix.
Population and outcome-level dimensions considered	Bedaquiline should be included in longer MDR-TB regimens for patients aged 18 years or more (strong recommendation, moderate certainty in the estimates of effect) (20).	The recommendation considers a multi-drug-resistant tuberculosis patients, and the outcome *'acquisition (amplification) of drug resistance'* (21) was formally considered within a PICO framework provided within a supplementary appendix.
	Alternative first choice of antibiotics for adults aged 18 years and over with pharyngitis and a penicillin allergy or intolerance: Clarithromycin 250 mg to 500 mg twice a day for 5 days (22).	Summary of committee discussions show that population-level resistance data was considered: "based on evidence, clinical experience and resistance data, the committee agreed to recommend the following alternative first-choice antibiotics for use in penicillin allergy or for phenoxymethylpenicillin intolerance: clarithromycin or erythromycin (which is preferred in pregnancy)" (22). Additional formal outcome considerations include *'antibiotic resistance'* in a supplementary appendix.

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

We assessed a guideline's quality using the Appraisal of Guidelines for Research and Evaluation (AGREE) II Instrument focusing on three relevant domains: a well-defined scope and purpose (domain one), rigorous development including a systematic search for evidence, transparent reporting of methods, links between evidence and recommendations, external review, and procedures for update (domain three), and editorial independence (domain six) (23). We defined acceptable quality as guidelines that scored 60% or greater in these three domains and allowed us to be inclusive (3).

We also abstracted information on values, resource use, equity, acceptability, and feasibility from guidelines that met our acceptability cut-off (i.e. 60%). Briefly, worldwide regions may differ in the accessibility of antimicrobials, the cultural view towards the use of antimicrobials, pharmaceutical costs, and health care structures. We selected these dimensions as the transparent reporting of these factors is essential: in appraising the evidence for antimicrobials, guideline developers should be aware of the breadth of implications of their recommendations when used by decision-makers (7, 10, 24, 25). Guidelines that ignore this wider agenda could provide narrow, misleading guidance.

DATA SYNTHESIS AND STATISTICAL ANALYSIS

We conducted descriptive statistics at the guideline and recommendation level, using counts and proportions (95%CI). We calculated the mean (SD) for AGREE II scores by region. We also

compared the quality of guidelines from the WHO versus regional guidelines using scaled domain scores, mean difference, and a two-sided t-test. We calculated the frequency of guideline reporting of: values, resource use, equity, acceptability, and feasibility. All analyses were conducted in Microsoft® Excel and R-studio (RStudio Team (2016). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA URL http://www.rstudio.com/.).

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

PATIENT AND PUBLIC INVOLVEMENT

One of the authors is a patient with a rare disease affected by repeated infections and treatment related issues of resistance to antimicrobials and was involved in aspects of the design and data abstraction. We specifically looked for information about patient values and preferences and included this in our review. However, we did not make any additional specific efforts to involve the patient and public in other aspects of this systematic review.

Results

Our initial search identified 10,365 records. After screening, we retrieved 79 guidelines that had at least one recommendation on antimicrobial selection: (n = 28 TB, n = 13 gonorrhea, n = 38 respiratory tract infections). Of these, 78 guidelines had sufficient information for assessment — one gonorrhoea guideline was excluded because we were unable to retrieve supplementary materials (figure 1) (26).

GUIDELINE RECOMMENDATIONS CONSIDERING AMR

After classifying recommendations, we found that 74 guidelines had at least one recommendation that considered AMR and four guidelines without such considerations (table 2) (27-30). These were excluded from further assessment. Of the 74 guidelines, the majority were developed in North America (n = 29), (13, 26, 31-58) and Europe (n = 26) (22, 48, 59-81). A smaller portion were from Asia (n = 7), (82-88) South America (n = 1), (89) Africa (n = 1), (90) and Oceania (n = 1) (91). Nine guidelines were internationally developed by the WHO (19-21, 92-97).

Table 2: Guidelines and recommendations with treatment recommendations with AMR considerations*

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

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

Within these 74 guidelines, we found that approximately two thirds of recommendations (n = 808/1198) considered AMR; that figure was 55·2% for TB recommendations (n = 272), 84·7% for gonorrhoea recommendations (n = 150), and 73·1% for respiratory tract infection recommendations (n = 386). The majority of recommendations were regionally developed (n = 736) (figure 2).

Most recommendations considered either population-level or outcome-level AMR dimensions, while fewer considered both simultaneously. Approximately 17·6% of recommendations (n = 142/808) considered AMR at the population-level only while 34·7% (n = 281/808) of recommendations considered resistance as an outcome only. Most notably, a majority of those considering AMR as an outcome were not explicitly stated in PICO format, but rather buried within evidence summaries. Clearly stated outcomes formally considered in PICO frameworks included: 'acquired drug-resistance', 'antimicrobial in vitro resistance', 'bacterial antibiotic resistance', and 'emergence of drug-resistance'. Among respiratory tract infection recommendations, 6·9% (n = 27/386) recommended no antimicrobial or back-up antimicrobial (i.e. the watchful waiting approach), which is a population-level dimension, e.g. recommendations for patients who likely have infections that are viral in nature or self-limiting.

Additionally, 47·6% (385/808) recommendations considered both population-level and outcome-level AMR dimensions simultaneously. For example, fully immunized infant or school-aged children with community-acquired pneumonia admitted to hospital are recommended to take ampicillin or penicillin G given that local epidemiologic data lacks a substantial high-level of penicillin-resistance for invasive *S. pneumoniae* (37). This recommendation is considering local resistance patterns (population-level dimension). It is also followed by an evidence summary the

explains that lower costs of ampicillin or penicillin G need to be balanced by the increased possibility of emergence of resistance (outcome-level dimension) that may occur from prescribing a broad-spectrum antimicrobial. About 22·5% (n = 182/808) of recommendations considered local resistance patterns in a similar manner.

CREDIBILITY OF INTERNATIONAL AND REGIONAL GUIDELINES WITH RECOMMENDATIONS THAT CONSIDER AMR

Overall, only 39·2% (n = 29/74) of all international and regional guidelines had scores of 60% or greater in scope and purpose, rigour of development, and editorial independence. Of the 29 guidelines that met our credibility cut-off, 10 were developed in North America (13, 38-43, 46, 57, 98), 9 in Europe (22, 48, 67, 70, 71, 75-78, 90), and 2 were developed in Asia (83, 85). When we compared international and regional guidelines, the majority of WHO guidelines performed significantly better than regional guidelines (table 3). Guidelines that did not meet our credibility cut-off score and excluded from further assessment included: nineteen from North America, seventeen from Europe, five from Asia, and three guidelines from South America, Africa, and Oceania.

Table 3: Performance of World Health Organization versus regional PGs with AMR considerations

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

Domain 6: Editorial independence				
Mean domain score (SD) as %	88(20)	56(30)	-32 (-0.48, -0.15)	0.001
Score range as %	38–100	0–100		
Scored 60% or greater as % (n)	89 (n = 8)	49 (n = 32)		

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

GUIDELINES CONSIDERING VALUES, RESOURCE USE, ACCEPTABILITY, FEASIBILITY, AND EQUITY

Only 5 (19, 20, 93, 94, 96) of the 29 guidelines reported all factors required for contextualization: values, resource use, equity, acceptability, and feasibility. The WHO was the only guideline developer to report on all five criteria in four TB guidelines and one gonorrhoea guideline.

Across all 29 guidelines, resource use was the most frequently considered (n = 23 guidelines), followed by values (n = 16 guidelines), acceptability (n = 12 guidelines), and feasibility (n = 12 guidelines). Equity was the least considered factor with only seven guidelines that made such considerations (figure 3): two were regionally and five were internationally developed. The WHO, the National Institute for Health and Care Excellence (NICE), and the United States Preventative Task Force (USPSTF) were the only organizations to consider equity.

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

Discussion

SUMMARY OF FINDINGS

Over a 13-year period, relatively few guidelines on antibiotics for highly prevalent infectious diseases included AMR considerations. Approximately 60% of regionally developed guidelines were of low quality, and tended to report less factors for contextualization of recommendations. International WHO guidelines had quality scores that were substantially better than regional guidelines. International guidelines also consistently considered important information required for developing recommendations that are appropriate for specific contexts compared to regional guidelines.

The compliance of recommendations to consider contextual factors is often unsatisfactory despite the emerging consensus that the reporting of Evidence to Decision dimensions is ethically and scientifically essential. Some of the proposed criteria seemed to be adopted by guideline developers (i.e. values and resource use), while others were less so: guideline quality was variable among guidelines and there were inconsistencies between regions and guidelines promoted/sponsored by different entities.

Frameworks including the GRADE Evidence to Decision and its use by the WHO and NICE, seem to positively influence the consideration of contextual factors in the guidelines we reviewed. A high proportion of WHO and NICE guidelines contained complete information necessary to provide optimal guidance on how to use antimicrobials in the considered syndromes addressing contextual factors.

STRENGTHS AND LIMITATIONS

Our work has strengths. To our knowledge, this is the first study to assess the extent to which guidelines are considering local dimensions such as AMR, and to use established frameworks: AGREE II, and GRADE Evidence to Decision. We also employed systematic methods to conduct our review and validated tools to measure the quality of guidelines (23, 99).

There are several limitations to our study. The use of the credibility cut-off score of 60% or greater for three of the six AGREE II domains is based on limited guidance on cut-off thresholds, but by focusing on three domains and a relatively low score we were more inclusive (3, 100). We used criteria of the GRADE Evidence to Decision Frameworks that are fairly general as they apply to any interventions. These dimensions could be complemented with specific criteria related to the antimicrobial field. For example, providing guidance on the appropriate threshold for escalating empiric guidance from narrower spectrum agents to broader spectrum agents. In other words, the real test for antimicrobial guidelines may be whether they facilitate making the potential implications of antimicrobial prescribing on resistance fully considered by prescribers and the public. This would lead to virtuous and parsimonious prescribing and consumption habits.

CONTEXT TO OTHER RESEARCH

We previously found that about two thirds of respiratory tract infection recommendations on empirical antimicrobial use did not consider country-specific resistance patterns. The use of a broader framework and additional focus areas may have resulted in the larger number of recommendations that considered AMR uncovered by this study. Both studies support that there are inconsistencies in considering AMR in recommendation development and potential duplication of work among infectious disease guidelines.

IMPLICATIONS FOR PRACTICE

There are several implications for guideline developers. Given the suboptimal quality of guidelines in our sample, guideline methodology should improve particularly when recommendations move from global to regional levels. This includes improving the processes used in evidence syntheses and recommendation formulation, transparency, and addressing potential unduly biases with competing interests. As far as regional guidelines need to incorporate contextual information when developing their recommendations, global guidelines need to provide information about how to contextualize recommendations for appropriate AMR considerations.

Guideline development can be done more efficiently and economically by using work done by other developers including the WHO. Rather developing guidelines from scratch, time and resources (101) may be shifted towards refining AMR surveillance systems that provide national resistance data to support recommendations and appropriate antimicrobial use. Further, country-level participation of the Global Antimicrobial Resistance Surveillance System (GLASS) supports global monitoring of resistance trends, emerging resistance, and the ability to evaluate the effectiveness of interventions (102). As of 2020, 94 countries are participating in GLASS (102). However, some countries lack public health infrastructure, national laboratory capacities, and data management which is essential for surveillance systems (6, 103). In 2018, there was at least one country within each WHO regions with the ability to collect national resistance data (103). Regions facing unique challenges to antimicrobial stewardship capacities, may look to recommendations developed by other regions with similar resistance experiences. Finally, as new antimicrobial therapies become available, and the scientific community cumulates more

evidence on resistance patterns and their implications for local prescribing, future infectious disease guidelines may require more frequent updating.

IMPLICATIONS FOR RESEARCH

Although we focused on recommendations on antimicrobial selection and prescribing, there are many other approaches that could be assessed in future research (e.g. rapid diagnostics to rule-out viral infections and resistant strains). In addition, research should also explore whether recommendations are appropriately guided by evidence, resistance data, and the WHO's Essential Medicines List and AWaRe Classification Database of Antimicrobials updates (104). With regards to contextualization of infectious disease recommendations, we have developed transparent recommendation maps that facilitate use of recommendations across jurisdictions for TB (https://tuberculosis.evidenceprime.com/) and COVID-19 (https://covid19.evidenceprime.com/) where we apply some of our findings.

Conclusion (word count: 69)

Our study offers information on how current infectious disease guidelines are considering contextual factors necessary to appropriately prescribe antimicrobials. We also present dimensions that can be considered by a formal AMR framework used in combination with GRADE Evidence to Decision Frameworks to facilitate amelioration of the cornerstones that are guiding current antimicrobial use. This may preserve the remaining and essential medicines we have left, and the future of new classes of antimicrobials (105).

Contributors

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

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Competing interests

We declare no competing interests. Drs. Loeb and Schünemann report personal fees or research support from the World Health Organization, outside of this research.

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References

1. United Nations meeting on antimicrobial resistance. Bull World Health Organ. 2016;94(9):638-9.
2. Organization WH. Global Action Plan on Antimicrobial Resistance. Geneva; 2015. Report No.: ISBN 978 92 4 150976 3.

3. Johnston A, Kelly SE, Hsieh S-C, Skidmore B, Wells GA. Systematic reviews of clinical practice guidelines: a methodological guide. Journal of Clinical Epidemiology. 2019;108:64-76.
4. Canada PHAo. Tackling Antimicrobial Resistance and Antimicrobial Use: A Pan-Canadian Framework for Action. Canada; 2017. Report No.: ISBN: 978-0-660-08168-7.
5. Anderson M, Schulze K, Cassini A, Plachouras D, Mossialos E. A governance framework for development and assessment of national action plans on antimicrobial resistance. Lancet Infect Dis. 2019;19(11):e371-e84. doi: 10.1016/S473-3099(19)30415-3. Epub 2019 Oct 3.
6. Elias C, Moja L, Mertz D, Loeb M, Forte G, Magrini N. Guideline recommendations and antimicrobial resistance: the need for a change. BMJ Open. 2017;7(7):e016264. doi: 10.1136/bmjopen-2017-.
7. Schünemann HJ, Wiercioch W, Brozek J, Etxeandia-Ikobaltzeta I, Mustafa RA, Manja V, et al. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. J Clin Epidemiol. 2017;81:101-110.(doi):10.1016/j.jclinepi.2016.09.009. Epub Oct 3.
8. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol. 2013;66(7):719-25. doi: 10.1016/j.jclinepi.2012.03.013. Epub 3 Jan 9.
9. Rzewuska M, Duncan EM, Francis JJ, Morris AM, Suh KN, Davey PG, et al. Barriers and Facilitators to Implementation of Antibiotic Stewardship Programmes in Hospitals in Developed Countries: Insights From Transnational Studies. Frontiers in Sociology. 2020;5(41).
10. Scott IA, Guyatt GH. Clinical practice guidelines: the need for greater transparency in formulating recommendations. Med J Aust. 2011;195(1):29-33.
11. O'Neill J. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. London; 2016.
12. CDC. Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA; 2019.
13. Chow AWB, M. S.; Brook, I.; Brozek, J. L.; Goldstein, E. J. C.; Hicks, L. A.; Pankey, G. A.; Seleznick, M.; Volturo, G.; Wald, E. R.; File, T. M. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clinical Infectious Diseases. 2012;54(8):e72-e112.
14. Guidelines IoMUCoSfDTCP. Clinical Practice Guidelines We Can Trust. Washington (DC): National Academies Press (US); 2011. Available from: https://www.ncbi.nlm.nih.gov/books/NBK209539/?report=classic.
15. Knowles R, Sharland M, Hsia Y, Magrini N, Moja L, Siyam A, et al. Measuring antibiotic availability and use in 20 low- and middle-income countries. Bull World Health Organ. 2020;98(3):177-87C.
16. Knowles R, Sharland M, Hsia Y, Magrini N, Moja L, Siyam A, et al. Measuring antibiotic availability and use in 20 low- and middle-income countries. Bull World Health Organ. 2020;98(3):177-87C.
17. Sharland M, Gandra S, Huttner B, Moja L, Pulcini C, Zeng M, et al. Encouraging AWaRe-ness and discouraging inappropriate antibiotic use-the new 2019 Essential Medicines List becomes a global antibiotic stewardship tool. Lancet Infect Dis. 2019;19(12):1278-80. doi: 10.016/S473-3099(19)30532-8.
18. Schünemann HJ, Hill SR, Kakad M, Vist GE, Bellamy R, Stockman L, et al. Transparent development of the WHO rapid advice guidelines. PLoS Med. 2007;4(5):e119-e.

19. WHO guidelines for the treatment of Neisseria gonorrhoeae. World Health Organisation Guidelines. 2016.
20. Anonymous. WHO consolidated guidelines on drug-resistant tuberculosis treatment World Health Organization. 2019.
21. Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary tuberculosis among adults and adolescents. Recommendations for HIV-prevalent and resource-constrained settings. World Health Organization. 2007.
22. AHRQ - Agency for Healthcare Research + Quality. Surgical management of otitis media with effusion in children. National Collaborating Centre for Women's and Children's Health. NGC:007182 [Guideline Clearing Report]. 2008 [Available from: http://guidelines.gov/summary/summary.aspx?doc_id=14314&nbr=7182.
23. Brouwers MC, Kerkvliet K, Spithoff K. The AGREE Reporting Checklist: a tool to improve reporting of clinical practice guidelines. BMJ. 2016;352:i1152.
24. Moberg J, Oxman AD, Rosenbaum S, Schünemann HJ, Guyatt G, Flottorp S, et al. The GRADE Evidence to Decision (EtD) framework for health system and public health decisions. Health Research Policy and Systems. 2018;16(1):45.
25. 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;353:i2016.
26. Ontario PH. Ontario Gonorrhea Testing and Treatment Guide, 2nd Edition. 2018.
27. Organization WH. THE USE OF ANTIRETROVIRAL DRUGS FOR TREATING AND PREVENTING HIV INFECTION. 2016.
28. Kawaguchi RM, K.; Akira, S.; Ishitani, K.; Iwasaku, K.; Ueda, Y.; Okagaki, R.; Okano, H.; Oki, T.; Koga, K.; Kido, M.; Kurabayashi, T.; Kuribayashi, Y.; Sato, Y.; Shiina, K.; Takai, Y.; Tanimura, S.; Chaki, O.; Terauchi, M.; Todo, Y.; Noguchi, Y.; Nose-Ogura, S.; Baba, T.; Hirasawa, A.; Fujii, T.; Maruyama, T.; Miyagi, E.; Yanagida, K.; Yoshino, O.; Iwashita, M.; Maeda, T.; Minegishi, T.; Kobayashi, H. Guidelines for office gynecology in Japan: Japan Society of Obstetrics and Gynecology (JSOG) and Japan Association of Obstetricians and Gynecologists (JAOG) 2017 edition. Journal of Obstetrics and Gynaecology Research. 2019;45(4):766-86.
29. Anonymous. Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. World Health Organization. 2012.
30. Di Comite AE, S.; Villani, A.; Stronati, M.; Italian Pediatric, T. B. Study Group. How to manage neonatal tuberculosis. J Perinatol. 2016;36(2):80-5.
31. Prevention CfDCa. Provisional CDC guidelines for the use and safety monitoring of bedaquiline fumarate (Sirturo) for the treatment of multidrug-resistant tuberculosis. Article. Atlanta; 2013 Oct 2013. Contract No.: 9.
32. Wald ERA, K. E.; Bordley, C.; Darrow, D. H.; Glode, M. P.; Marcy, S. M.; Nelson, C. E.; Rosenfeld, R. M.; Shaikh, N.; Smith, M. J.; Williams, P. V.; Weinberg, S. T. Clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years. Pediatrics. 2013;132(1):e262-e80.
33. Workowski KAB, G. A. Sexually transmitted diseases treatment guidelines, 2015. Article. Atlanta, Georgia; 2015 Jun 2015.
34. Desrosiers ME, G. A.; Keith, P. K.; Wright, E. D.; Kaplan, A.; Bouchard, J.; Ciavarella, A.; Doyle, P. W.; Javer, A. R.; Leith, E. S.; Mukherji, A.; Schellenberg, R. R.; Small, P.;

Witterick, I. J. Canadian clinical practice guidelines for acute and chronic rhinosinusitis. Allergy, Asthma and Clinical Immunology. 2011;7(1).
35. Mayor MTR, M. A.; Uduhiri, K. A. Diagnosis and management of gonococcal infections. Am Fam Physician. 2012;86(10):931-8.
36. Kaplan JEB, C.; Holmes, K. H.; Brooks, J. T.; Pau, A.; Masur, H. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR. 2009;Recommendations and reports:Morbidity and mortality weekly report. Recommendations and reports / Centers for Disease Control. 58 (RR-4) (pp 1-207; quiz CE1-2074).
37. The Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age. Infectious Diseases Society of America. 2011.
38. Diagnosis and Management of Acute Otitis Media. American Academy of Family Physicians. 2013.
39. Adult Sinusitis. American Academy of Otolaryngology - Head and Neck Surgery. 2015.
40. Otitis Media with Effusion (OME). American Academy of Otolaryngology - Head and Neck Surgery. 2016.
41. Treatment of Drug-Susceptible Tuberculosis: Official ATS/CDC/IDSA Clinical Practice Guidelines. American Thoracic Society. 2016.
42. Respiratory Illness in Children and Adults, Diagnosis and Treatment of. Institute for Clinical Systems Improvement. 2017.
43. IDSA - Infectious Diseases Society of America. Clinical Practice Guideline for the Diagnosis and Management of Group A Streptococcal Pharyngitis: 2012 Update by the Infectious Diseases Society of America [Guideline]. 2012 [Available from: http://cid.oxfordjournals.org/content/early/2012/09/06/cid.cis629.full.
44. Borisov ASBM, S.; Njie, G. J.; Winston, C. A.; Burton, D.; Goldberg, S.; Yelk Woodruff, R.; Allen, L.; LoBue, P.; Vernon, A. Update of Recommendations for Use of Once-Weekly Isoniazid-Rifapentine Regimen to Treat Latent Mycobacterium tuberculosis Infection. MMWR Morbidity and mortality weekly report. 2018;67(25):723-6.
45. Pogany LR, B.; Robinson, J.; Gale-Rowe, M.; Latham-Carmanico, C.; Weir, C.; Wong, T. Management of gonococcal infection among adults and youth: New key recommendations. Canadian Family Physician. 2015;61(10):869-73.
46. Richard M. Rosenfeld M, MPH1, Jay F. Piccirillo, MD2,, Sujana S. Chandrasekhar M, Itzhak Brook, MD, MSc4, Kaparaboyna Ashok Kumar, MD, FRCS5, Maggie Kramper, RN, FNP6, Richard R. Orlandi, MD7, James N. Palmer, MD8, Zara M. Patel, MD9, Anju Peters, MD10, Sandra A.Walsh11, and Maureen D. Corrigan. Clinical Practice Guideline (Update): Adult Sinusitis. 2015.
47. Report MaMW. Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children. 2009.
48. Canada PHAo. Canadian Tuberculosis Standards, 7th Edition. 2014.
49. Control BCfD. Sexually Transmitted Infections in Adolescents and Adults 2014.
50. Prevention CfDCa. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. 2019.
51. America IDSo. Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin- Resistant Staphylococcus aureus Infections in Adults and Children. 2011.

52. Infections CGoST. Gonococcal Infections Chapter. 2013.
53. Prevention CfDCa. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children. 2013.
54. Pharyngitis. University of Michigan Health System. 2013.
55. HIV/AIDS BCCfEi. Therapeutic guidelines for antiretroviral (ARV) treatment in adult HIV infection. 2015.
56. Mandell LAW, R. G.; Anzueto, A.; Bartlett, J. G.; Campbell, G. D.; Dean, N. C.; Dowell, S. F.; File Jr, T. M.; Musher, D. M.; Niederman, M. S.; Torres, A.; Whitney, C. G. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the management of community-acquired pneumonia in adults. Clinical Infectious Diseases. 2007;44(SUPPL. 2):S27-S72.
57. Ocular Prophylaxis for Gonococcal Ophthalmia Neonatorum: Preventive Medication. US Preventive Services Task Force. 2019.
58. Jereb JAG, S. V.; Powell, K.; Villarino, M. E.; Lobue, P. Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent mycobacterium tuberculosis infection. Morbidity and Mortality Weekly Report. 1650;60(48):1650-3.
59. Bignell CU, M. 2012 European guideline on the diagnosis and treatment of gonorrhoea in adults. International Journal of STD and AIDS. 2013;24(2):85-92.
60. Bignell CF, M. UK national guideline for the management of gonorrhoea in adults, 2011. International Journal of STD and AIDS. 2011;22(10):541-7.
61. Harris MC, J.; Coote, N.; Fletcher, P.; Harnden, A.; McKean, M.; Thomson, A. British Thoracic Society guidelines for the management of community acquired pneumonia in children: Update 2011. Thorax. 2011;66(SUPPL. 2).
62. Migliori GBZ, J. P.; Abubakar, I.; Ibraim, E.; Caminero, J. A.; De Vries, G.; D'Ambrosio, L.; Centis, R.; Sotgiu, G.; Menegale, O.; Kliiman, K.; Aksamit, T.; Cirillo, D. M.; Danilovits, M.; Dara, M.; Dheda, K.; Dinh-Xuan, A. T.; Kluge, H.; Lange, C.; Leimane, V.; Loddenkemper, R.; Nicod, L. P.; Raviglione, M. C.; Spanevello, A.; Thomsen, V. O.; Villar, M.; Wanlin, M.; Wedzicha, J. A.; Zumla, A.; Blasi, F.; Huitric, E.; Sandgren, A.; Manissero, D. European Union Standards for Tuberculosis Care. European Respiratory Journal. 2012;39(4):807-19.
63. Woodhead MB, F.; Ewig, S.; Garau, J.; Huchon, G.; Ieven, M.; Ortqvist, A.; Schaberg, T.; Torres, A.; Van Der Heijden, G.; Read, R.; Verheij, T. J. M. Guidelines for the management of adult lower respiratory tract infections - Full version. Clinical Microbiology and Infection. 2011;17(SUPPL. 6):E1-E59.
64. Spindler CS, K.; Eriksson, L.; Hjerdt-Goscinski, G.; Holmberg, H.; Lidman, C.; Nilsson, A.; Ortqvist, A.; Hedlund, J. Swedish guidelines on the management of community-acquired pneumonia in immunocompetent adults - Swedish Society of Infectious Diseases 2012. Scandinavian Journal of Infectious Diseases. 2012;44(12):885-902.
65. Thwaites GF, M.; Hemingway, C.; Scott, G.; Solomon, T.; Innes, J.; British Infection, Society. British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. J Infect. 2009;59(3):167-87.
66. Bignell CIW. 2009 European (IUSTI/WHO) guideline on the diagnosis and treatment of gonorrhoea in adults. Int J STD AIDS. 2009;20(7):453-7.
67. Internal Clinical Guidelines T. Tuberculosis Prevention, diagnosis, management and service organization. National Institute for Health and Care Excellence (UK). 2016;01:01.

68. Menendez RT, A.; Aspa, J.; Capelastegui, A.; Prat, C.; Rodriguez de Castro, F. Community acquired pneumonia. New guidelines of the Spanish society of chest diseases and thoracic surgery (SEPAR). Archivos de Bronconeumologia. 2010;46(10):543-58.
69. Respiratory tract infections (self-limiting): prescribing antibiotics. National Institute for Health and Clinical Excellence - Clinical Guidelines. 2008.
70. Guidelines for the management of community-acquired pneumonia in adults. British Infection Association. 2009.
71. CPG on the Diagnosis, Treatment and Prevention of Tuberculosis. GuiaSalud. 2010.
72. Sinusitis (acute): antimicrobial prescribing. National Institute for Health and Clinical Excellence - Clinical Guidelines. 2017.
73. British Association for Sexual Health and HIV national guideline for the management of infection with Neisseria gonorrhoeae. British Association for Sexual Health and HIV. 2019.
74. Stahl JPA, P.; Bruneel, F.; De Broucker, T.; Duval, X.; Fantin, B.; Girard, N.; Herrmann, J. L.; Honnorat, J.; Lecuit, M.; Mailles, A.; Martinez-Almoyna, L.; Morand, P.; Piroth, L.; Tattevin, P. Guidelines on the management of infectious encephalitis in adults. Medecine et Maladies Infectieuses. 2017;47(3):179-94.
75. Heidemann CL, J; Berg, J; Christensen, JJ; Håkonsen, SJ; Jakobsen, M; Johansen, CJ; Nielsen, LH; Hansen, MP; Poulsen, A; Schousboe, LP; Skrubbeltrang, C; Vind, AB; Homøe, P. Danish guidelines on management of otitis media in preschool children. 2016.
76. Management of sore throat and indications for tonsillectomy. SIGN. 2010.
77. Excellence ENIfHaC. Sore throat (acute): antimicrobial prescribing. 2018.
78. Excellence NIfHaC. Pneumonia (community-acquired): antimicrobial prescribing. 2019.
79. Wiersinga WJB, M. J.; Boersma, W. G.; Jonkers, R. E.; Aleva, R. M.; Kullberg, B. J.; Schouten, J. A.; Degener, J. E.; van de Garde, E. M. W.; Verheij, T. J.; Sachs, A. P. E.; Prins, J. M. Management of community-acquired pneumonia in adults: 2016 guideline update from the dutch working party on antibiotic policy (SWAB) and dutch association of chest physicians (NVALT). Netherlands Journal of Medicine. 2018;76(1):4-13.
80. Athlin SL, C.; Lundqvist, A.; Naucler, P.; Nilsson, A. C.; Spindler, C.; Stralin, K.; Hedlund, J. Management of community-acquired pneumonia in immunocompetent adults: updated Swedish guidelines 2017. Infectious Diseases. 2018;50(4):247-72.
81. Chiappini EM, R.; Bruzzese, E.; Capuano, A.; Colombo, M.; Cricelli, C.; Di Mauro, G.; Esposito, S.; Festini, F.; Guarino, A.; Miniello, V. L.; Principi, N.; Marchisio, P.; Rafaniello, C.; Rossi, F.; Sportiello, L.; Tancredi, F.; Venturini, E.; Galli, L.; de Martino, M. Rational use of antibiotics for the management of children's respiratory tract infections in the ambulatory setting: An evidence-based consensus by the Italian Society of Preventive and Social Pediatrics. Paediatric Respiratory Reviews. 2014;15(3):231-6.
82. Gupta DA, R.; Aggarwal, A.; Singh, N.; Mishra, N.; Khilnani, G.; Samaria, J.; Gaur, S.; Jindal, S. Guidelines for diagnosis and management of community-and hospital-acquired pneumonia in adults: Joint ICS/NCCP(I) recommendations. Lung India. 2012;29(SUPPL.2):S27-S62.
83. Abdul Rahaman JAK, H. B.; Yusof, M.; Hanafi, N. S.; Wong, J. L. Tuberculosis in adults. Malays Fam Physician. 2014;9(3):34-7.
84. Ministry of Public Health/Qatar. Community acquired pneumonia [Guideline]. 2016 [updated 19.03.2017. Available from: https://www.moph.gov.qa/health-strategies/Documents/Guidelines/MOPH%20Guideline%20-%20Community%20acquired%20pneumonia%20v2-1%20FINAL.pdf.

85. HTA DoH - HTA Unit, Ministry of Health,, Malaysia,. Management of Otitis Media with Effusion in Children [Guideline]. 2012 [Available from: http://www.moh.gov.my/attachments/7779.pdf.
86. Lee MSO, J. Y.; Kang, C. I.; Kim, E. S.; Park, S.; Rhee, C. K.; Jung, J. Y.; Jo, K. W.; Heo, E. Y.; Park, D. A.; Suh, G. Y.; Kiem, S. Guideline for antibiotic use in adults with community-acquired pneumonia. Infection and Chemotherapy. 2018;50(2):160-98.
87. Singapore MoH. Prevention, Diagnosis and Management of Tuberculosis. 2016.
88. WORKING ZAM-YMA-QAA-AMS-MSNATGC. Management and Prevention Strategies for Community-Acquired Pneumonia in the Gulf Corporation Council. Journal of Chemotherapy. 2007.
89. Ricardo de Amorim Corrêa FLCL, Jorge Luiz Pereira-Silva, Rodney Luiz Frare e Silva, Alexandre Pinto Cardoso, Antônio Carlos Moreira Lemos, Flávia Rossi, Gustavo Michel, Liany Ribeiro, Manuela Araújo de Nóbrega Cavalcanti, Mara Rúbia Fernandes de Figueiredo, Marcelo Alcântara Holanda, Maria Inês Bueno de André Valery, Miguel Abidon Aidê, Moema Nudilemon Chatkin, Octávio Messeder, Paulo José Zimermann Teixeira, Ricardo Luiz de Melo Martins e Rosali Teixeira da Rocha, em nome da Comissão de Infecções Respiratórias e Micoses –Sociedade Brasileira de Pneumologia e Tisiologia. Brazilian guidelines for community-acquired pneumonia in immunocompetent adults - 2009*. J Bras Pneumol. 2009.
90. Boyles THB, A.; Calligaro, G. L.; Cohen, C.; Dheda, K.; Maartens, G.; Richards, G. A.; Smit, R. Z.; Smith, C.; Wasserman, S.; Whitelaw, A. C.; Feldman, C. South African guideline for the management of communityacquired pneumonia in adults. Journal of Thoracic Disease. 1469;9(6):1469-502.
91. Chaves NJ PG, Biggs BA, Thambiran A, Smith M, Williams J, Gardiner J, Davis JS; on behalf of the Australasian Society for Infectious Diseases and Refugee Health Network of Australia Guidelines writing group. RECOMMENDATIONS FOR COMPREHENSIVE POST-ARRIVAL HEALTH ASSESSMENT FOR PEOPLE FROM REFUGEE-LIKE BACKGROUNDS AUSTRALASIAN SOCIETY FOR INFECTIOUS DISEASES AND REFUGEE HEALTH NETWORK OF AUSTRALIA 2ND EDITION. 2010.
92. Anonymous. Guidance for national tuberculosis programmes on the management of tuberculosis in children. World Health Organization 2nd WHO Guidelines Approved by the Guidelines Review Committee. 2014.
93. Guidelines on the management of latent tuberculosis infection. World Health Organisation Guidelines. 2015.
94. Recommendation on 36 months isoniazid preventive therapy to adults and adolescents living with HIV in resource-constrained and high TB and HIV-prevalence settings: 2015 update. World Health Organisation Guidelines. 2015.
95. Intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. World Health Organisation HIV Guidelines. 2011.
96. Organization WH. Latent tuberculosis infection Updated and consolidated guidelines for programmatic management. 2018.
97. Organization WH. Recommendations for management of common childhood conditions Newborn conditions, dysentery, pneumonia, oxygen use and delivery, common causes of fever, severe acute malnutrition and supportive care. 2012.
98. Prevention CfDCa. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis. 2013.

99. Johnston A, Kelly SE, Hsieh SC, Skidmore B, Wells GA. Systematic reviews of clinical practice guidelines: a methodological guide. J Clin Epidemiol. 2019;108:64-76.(doi):10.1016/j.jclinepi.2018.11.030. Epub Dec 5.
100. Tonelli M, Connor Gorber S, Moore A, Thombs BD, Canadian Task Force on Preventive Health C. Recommendations on routine screening pelvic examination: Canadian Task Force on Preventive Health Care adoption of the American College of Physicians guideline. Can Fam Physician. 2016;62(3):211-4.
101. Darzi A, Abou-Jaoude EA, Agarwal A, Lakis C, Wiercioch W, Santesso N, et al. A methodological survey identified eight proposed frameworks for the adaptation of health related guidelines. J Clin Epidemiol. 2017;86:3-10.(doi):10.1016/j.jclinepi.2017.01.016. Epub Apr 13.
102. Organization WH. Global antimicrobial resistance and use surveillance system (GLASS) report. 2020.
103. Organization WH. Worldwide country situation analysis: response to antimicrobial resistance2015. Available from: https://apps.who.int/iris/bitstream/handle/10665/163468/9789241564946_eng.pdf?sequence=1.
104. Organization WH. WHO Model Lists of Essential Medicines. 2019.
105. Foundation AtM. Antimicrobial Resistance Benchmark 2018. Available from: https://accesstomedicinefoundation.org/media/uploads/downloads/5bc5edd8367eb_Antimicrobial-Resistance-Benchmark-2018.pdf.

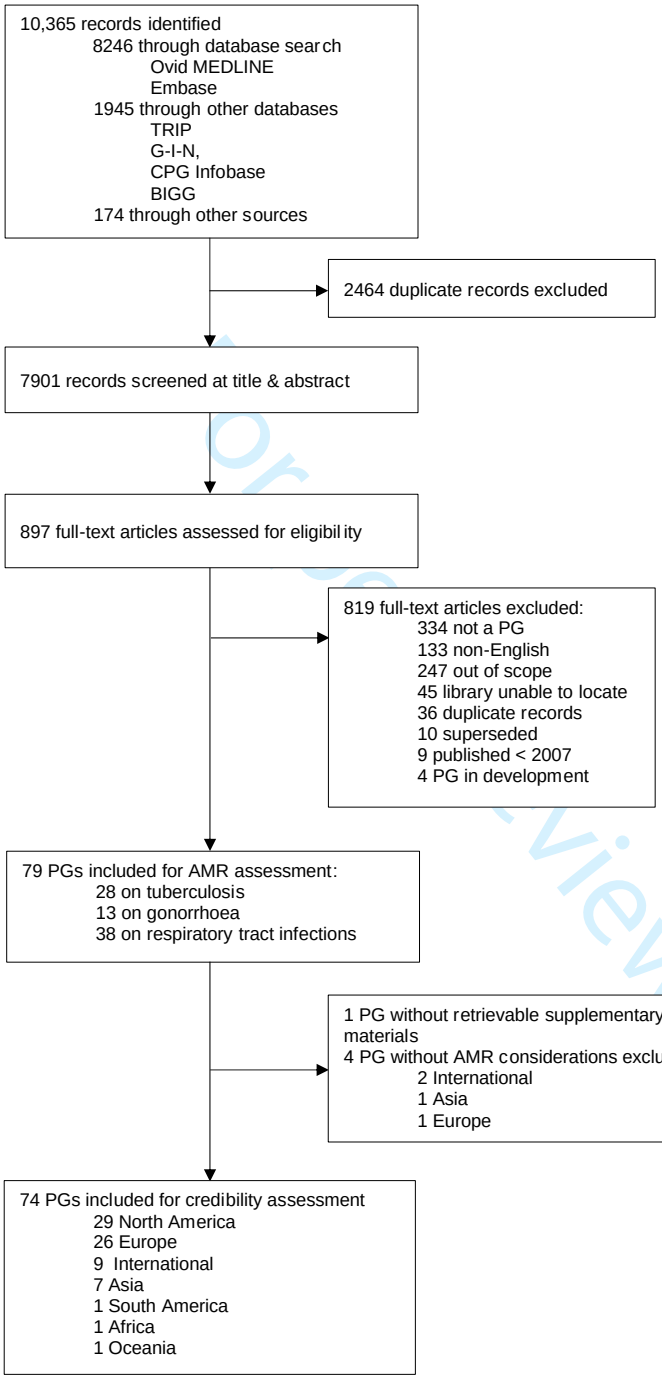

Figure 1: Flow diagram of the guideline selection process

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

Figure 1: Number of regional guideline recommendations that consider antimicrobial resistance

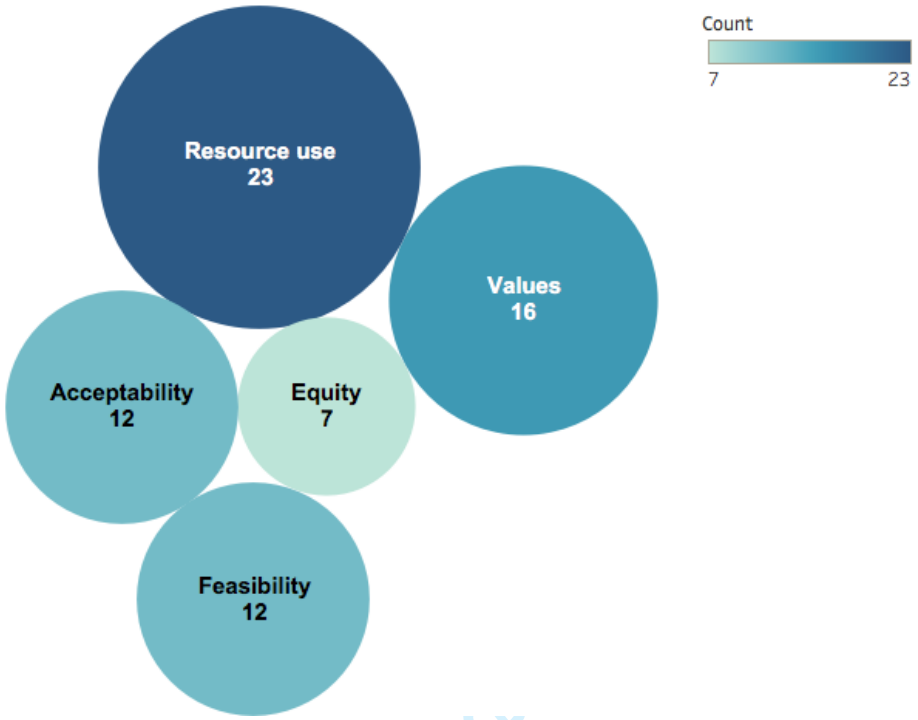

Figure 1: Contextualization of Grading of Recommendations Assessment, Development and Evaluation (GRADE) Evidence to Decision (EtD) frameworks in current guidelines

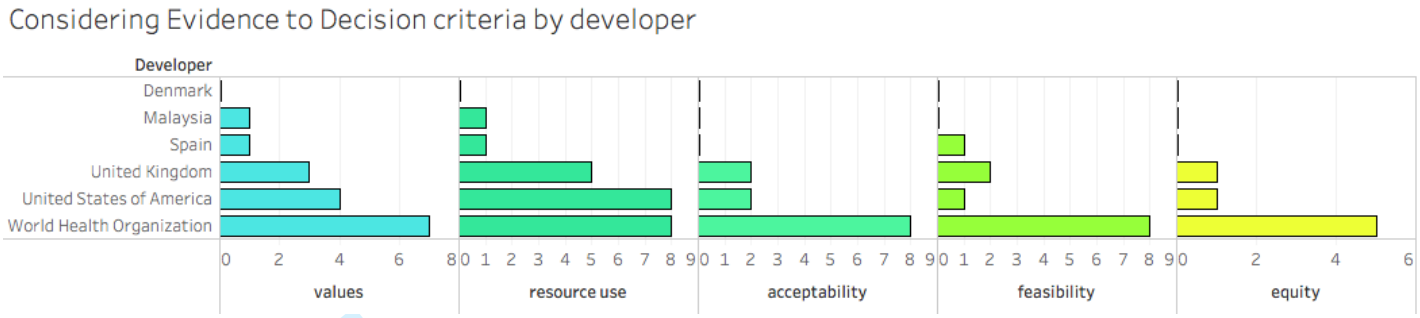

Figure 1: Number of internationally and regionally developed guidelines with considerations of Grading of Recommendations Assessment, Development and Evaluation (GRADE) Evidence to Decision (EtD) frameworks

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Appendix A

Extra figures & tables

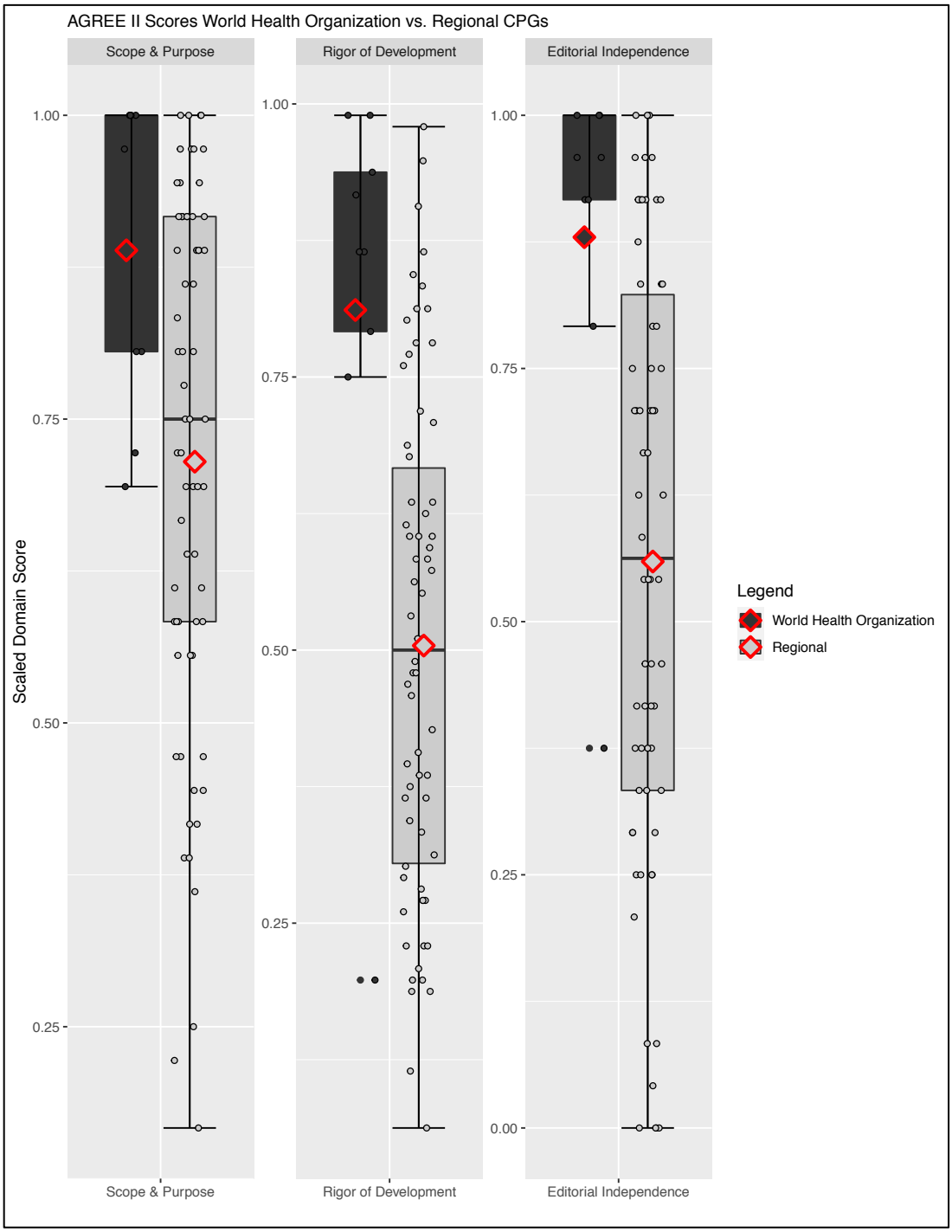

Figure 5: Boxplot of AGREE II scores comparing World Health Organization and regional PGs

AGREE II = Appraisal of Guidelines for Research & Evaluation II Instrument; Dark grey dots = World Health Organization clinical practice guidelines; light grey dots = Rest of the World clinical practice

guidelines. Scope and purpose = domain one; rigor of development = domain three; editorial independence = domain six.

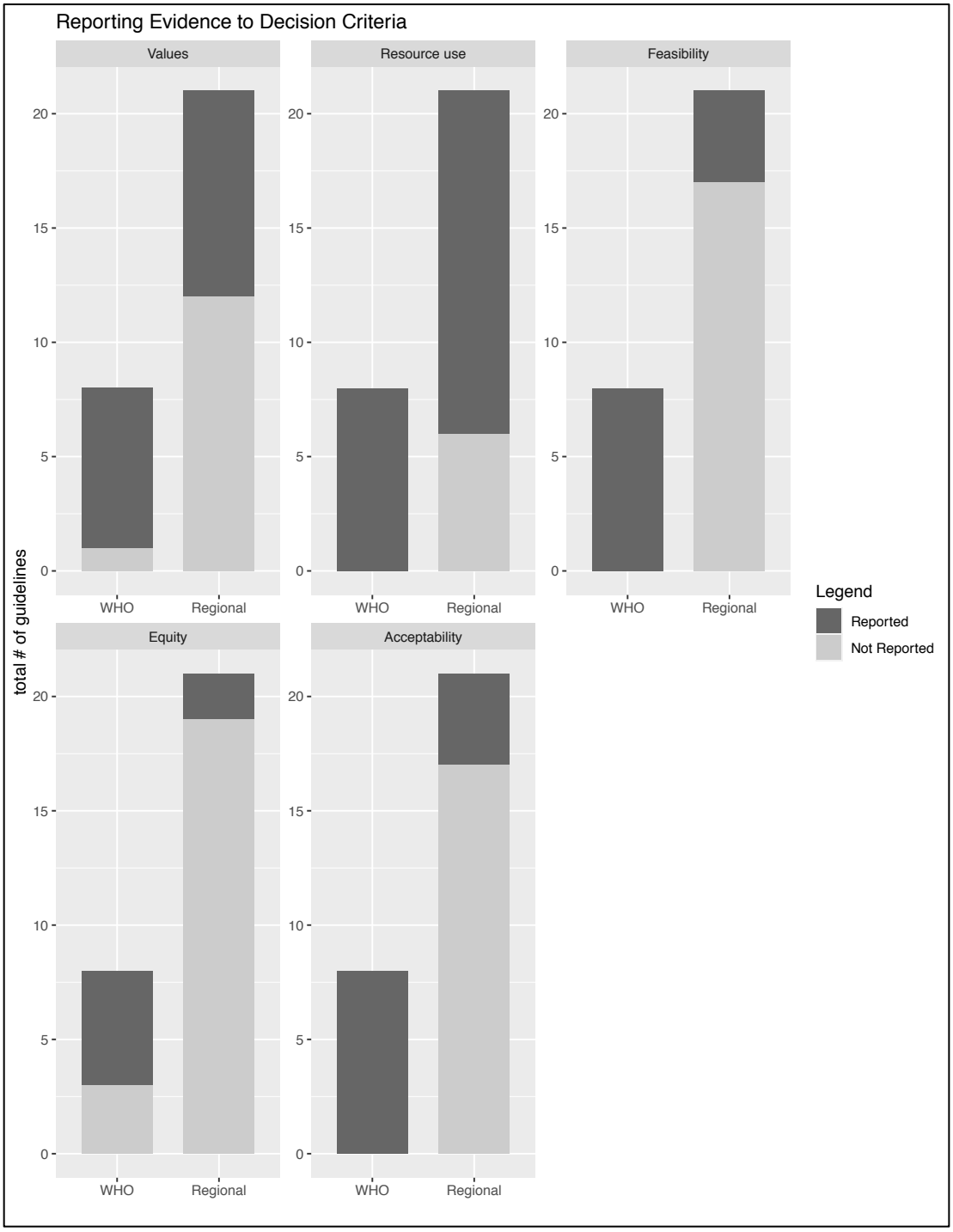

Figure 6: World Health Organization versus regional PGs meeting AGREE II scores >/= 60% reporting GRADE Evidence to Decision Frameworks

PGs = Practice guidelines; 29/75 clinical practice guidelines with AMR considerations had a scaled domain score of >/= 60%; EtD criteria = evidence to decision criteria: values, resource use, feasibility, acceptability, and equity

Table 1: Research question in PICAR format

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

Search strategy Ovid Medline and Embase

Database: Embase <1974 to 2019 June 07>, OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy:
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1 (tuberculosis or tuberculous or TB).mp. (510746)
2 (gonoc* or gonorr*).mp. (58460)
3 pneumonia*.mp. (557015)
4 strepto*.mp. (531324)
5 (pneumonia* adj2 strepto*).mp. (83649)
6 1 or 2 or 5 (648159)
7 exp clinical pathway/ (14358)
8 exp clinical protocol/ (252634)
9 exp consensus/ (72535)
10 exp consensus development conference/ (35258)
11 exp consensus development conferences as topic/ (26540)
12 critical pathways/ (14358)
13 exp guideline/ (32021)
14 guidelines as topic/ (375998)
15 exp practice guideline/ (526549)
16 practice guidelines as topic/ (381407)
17 health planning guidelines/ (93323)
18 (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt. (40981)
19 (position statement* or policy statement* or practice parameter* or best practice*).ti,ab,kf,kw. (71605)
20 (standards or guideline or guidelines).ti,kf,kw. (243012)
21 ((practice or treatment* or clinical) adj guideline*).ab. (90132)
22 (CPG or CPGs).ti. (12033)
23 consensus*.ti,kf,kw. (53111)
24 consensus*.ab. /freq=2 (52722)
25 ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf,kw. (47116)
26 recommendat*.ti,kf,kw. (85035)
27 (care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab,kf,kw. (142098)
28 (algorithm* adj2 (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti,ab,kf,kw. (16221)
29 (algorithm* adj2 (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti,ab,kf,kw. (22274)
30 or/7-29 (1489076)
31 6 and 30 (17406)
32 limit 31 to yr="2007 -Current" (11340)
33 (randomised or randomized or study or trial).ti. (3257255)
34 32 not 33 (10455)
35 limit 34 to (conference abstract or editorial or erratum or letter or tombstone or address or autobiography or biography or case reports or clinical trial, all or clinical trial protocol or clinical trial protocols as topic or clinical trial or comment or controlled clinical trial or interview or news or newspaper article or patient education handout or personal narrative or portrait or pragmatic clinical trial or randomized controlled trial) [Limit not valid in Embase,Ovid MEDLINE(R),Ovid

MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] (2878)
36 34 not 35 (7577)
37 limit 36 to yr="2014 -Current" (3831)
38 limit 36 to yr="2007 - 2014" (4415)
39 remove duplicates from 38 (3464)
40 remove duplicates from 37 (2937)
41 39 or 40 (5910)

Table 2: Definition of recommendations that consider antibiotic resistance

Recommendation	Definition	Example
Considers resistance if	1. The recommendation is for a ***population*** that is infected with a resistant organism (i.e. people with drug-resistant TB); **OR** 2. The recommendation is supported by ***country-specific resistance patterns;***[1] **OR** 3. The recommendation question (or PICO question) that has resistance as an ***outcome***. **OR** The ***outcome*** may be any of the following: 'resistance', 'resistant', 'drug-resistance', 'antibiotic resistance' 'antimicrobial resistance', 'antimicrobial in vitro resistance', 'acquired drug-resistance' 4. The recommendation is to prescribe narrow-spectrum antibiotics over broad-spectrum antibiotics. **OR** 5. A recommendation for no antibiotic prescription or back-up antibiotic prescription (i.e. watchful waiting approach)	***Example: A recommendation that considers country-specific resistance, and has a resistance-related outcome.*** "In adults and adolescents with gonococcal oropharyngeal infections, the WHO STI guideline suggests dual therapy over single therapy...and suggests single therapy (based on recent local resistance data confirming susceptibility to the antimicrobial)." The PICO table that was provided has 'antimicrobial in vitro resistance' as an outcome.[2]
DOES NOT consider resistance if	1. The recommendation is ***NOT*** for a population that is infected with a resistant organism. **AND** 2. The recommendation is ***NOT*** supported by country-specific resistant patterns. **AND** 3. The recommendation question (or PICO question) ***DOES NOT*** have any resistant outcomes. **AND** 4. Recommendation DOES NOT prescribe narrow-spectrum antibiotics. **AND** 5. There are no recommendations on no antibiotic nor back-up antibiotic or no watchful-waiting approach.	***Example: A recommendation that is not intended for a population that is infected with a resistant organism, nor is it supported by country specific resistant patterns, nor does it have outcomes pertaining to resistance.*** The BASHH 2013 guidelines recommended that "ceftriaxone 500mg intramuscularly single dose followed by oral Doxycycline 100mg bd plus oral Metronidazole 400mg bd both for 12 weeks was recommended for children over the age of 12."[3] For this recommendation, neither the guideline nor the supplementary materials mention that they considered England's resistance patterns when developing the recommendation, nor were there any outcomes pertaining to resistance.

[1] Informed by the Elias et al 2017.
[2] WHO guidelines for the Treatment of Neisseria gonorrhoeae. 2016.
[3] BASHH 2013 Management of gonorrhoea and pelvic inflammatory disease in children.

Table 3: List of websites of organizations and associations that provide clinical practice guidelines

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

Details to extract and record from the guidelines[4]:

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

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

20. EtD available.

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

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

Appendix B

Table 4: Number of GRADE Evidence to Decision Frameworks criteria reported in guidelines developed Internationally and regionally

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

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

World Health Organization	WHO	2015	Tuberculosis	5	Reported	Reported	Reported	Reported	Reported
Richard M. Rosenfeld et al.	American Academy of Otolaryngology—Head and Neck Surgery Foundation	2016	Otitis media	3	Reported	Reported	Reported	Not reported	Not reported
World Health Organization	WHO	2016	Gonorrhoea	5	Reported	Reported	Reported	Reported	Reported
P. Nahid et al.	IDSA	2016	Tuberculosis	0	Not reported	Not reported	Not reported	Not reported	Not reported
Institute for Clinical Systems Improvement	Institute for Clinical Systems Improvement	2017	Pharyngitis and sinusitis	1	Not reported	Reported	Not reported	Not reported	Not reported
Stanford T. Shulman et al.	IDSA	2012	Pharyngitis	1	Not reported	Reported	Not reported	Not reported	Not reported
Ministry of Health Malaysia	Ministry of Health Malaysia	2012	Otitis media	0	Not reported	Not reported	Not reported	Not reported	Not reported
Heidemann CL et al.	Danish Health and	2016	Otitis media	0	Not reported	Not reported	Not reported	Not reported	Not reported

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

The National Institute for Health and Care Excellence	NICE	2019	Community-acquired pneumonia	0	Not reported	Not reported	Not reported	Not reported	Not reported
National Institutes of Health, Centers for Disease Control and Prevention, et al.	NIH, CDC	2013	Tuberculosis	1	Not reported	Reported	Not reported	Not reported	Not reported
The National Institute for Health and Care Excellence; National Collaborating Centre for Women's and Children's Health (NCC-WCH)	NICE, NCC-WCH	2008	Otitis media	3	Not reported	Reported	Reported	Not reported	Reported
United States Preventative Task Force	USPTF	2019	Gonorrhoea	2	Not reported	Not reported	Not reported	Reported	Reported

Table 5: Characteristics of excluded studies

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	11
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7, and supplement pages 4-7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8-10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8-10, and supplement page 8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	10-11

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency ($e.g., I^2$) for each meta-analysis.	n/a

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11-12
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	14
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11-15
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	14
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20

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Consideration of antimicrobial resistance and contextual factors in infectious disease guidelines: a systematic survey

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Objectives: Guidelines that include antimicrobial recommendations should explicitly consider contextual factors that influence antimicrobial resistance and their downstream effects on resistance selection. The objectives were to analyze a) how, and to what extent, tuberculosis, gonorrhoea, and respiratory tract infection guidelines are considering antimicrobial resistance; b) are of acceptable quality; and c) if they can be easily contextualized to fit the needs of specific populations and health systems.

Methods: We conducted a systematic review and searched Ovid MEDLINE and Embase from January 1, 2007 to June 7, 2019 for tuberculosis, gonorrhoea, and respiratory tract infection guidelines published in English. We also searched guideline databases, key websites, and reference lists. We identified guidelines and recommendations that considered contextual factors including antimicrobial resistance, values, resource use, equity, acceptability, and feasibility. We assessed quality of the guidelines using the Appraisal of Guidelines for Research and Evaluation II tool focusing on the domains scope and purpose, rigour of development, and editorial independence. PROSPERO, registration CRD42020145235.

Results: We screened 10,365 records, of which 74 guidelines met inclusion criteria. Of these guidelines, 39% (n = 29/74) met acceptable quality scores. Approximately two thirds of recommendations considered antimicrobial resistance at the population- and/or outcome-level. Five of the 29 guidelines reported all factors required for recommendation contextualization. Equity was the least considered across guidelines.

Discussion: Relatively few guidelines for highly prevalent infectious diseases are considering resistance at a local level, and many do not consider contextual factors necessary for appropriate

antimicrobial use. Improving the quality of guidelines targeting specific regional areas is required.

Strengths and limitations of this study

- This is the first study to assess whether guidelines are considering local dimensions such as antimicrobial resistance.
- We employed systematic methods and used established frameworks to assess the credibility of guidelines.
- By focusing on three key AGREE II domains and a relatively low score we were is inclusive but we included only English language publications.
- The use of the credibility cut-off score of 60% or greater for three of the six AGREE II domains is based on limited guidance on cut-off thresholds.
- We used criteria of the GRADE Evidence to Decision Frameworks that are fairly general as they apply to any interventions and may need to be complemented with specific criteria related to the antimicrobial field.

Registration: International Prospective Register of Systematic Reviews (PROSPERO), CRD42020145235.

Funding: Michael G. DeGroote Cochrane Canada and McMaster GRADE centres (no specific award/grant number).

Keywords: Antimicrobial resistance, tuberculosis, gonorrhoea, respiratory tract infections, guidelines, recommendations, contexts, GRADE.

Introduction

Antimicrobials are essential to protecting human health. Their effectiveness is under threat due to antimicrobial resistance (AMR), resulting from misuse of antimicrobials over several decades. At the 2015 United Nations General Assembly, member states committed to address AMR by adopting national plans centered on five strategic objectives outlined in the World Health Organization's (WHO) Global Action Plan (1, 2). The fourth objective of this plan is to implement national and hospital treatment guidelines for the optimization of antimicrobial medicines use (2). Guidelines are among AMR stewardship interventions intended to modify clinician behavior by providing guidance on when, and how, to prescribe antimicrobials, integrating information on antimicrobial consumption, resistance surveillance, research and development, and burden of resistance (3-5).

Preservation of antimicrobials requires the consideration of how, and under what conditions, is it appropriate to recommend antimicrobials. However, only a small number of recently published guidelines considered epidemiological and resistance pattern data (6). There are also concerns that guidelines are not considering important contextual factors, including evidence on values, resource use, equity, acceptability, and feasibility that go beyond resistance patterns and that may influence secular trends in AMR (7, 8). For example, guideline recommendations are likely to better support effective use of antimicrobials in specific contexts when they account for how much people value the affected health outcomes ("values"), antimicrobial resistance burden, public health infrastructure, local medicine policies for consistent access to safe, effective, affordable medicines, and equitability of antimicrobial regimens (9). Considering these factors is also relevant for adapting and implementing. The failure to account for these factors likely

results from the lack of formal guidance for developing recommendations that consider AMR and other local factors.

Incomplete reporting of evidence supporting recommendations, and the existing belief that guideline developers must develop their recommendations 'from scratch', results in additional challenges. Scientific societies and other organizations duplicate the same work to develop recommendations resulting in multiple guidelines on the same topic, confusion and loss of confidence by clinicians, and resource waste (8, 10). However, guideline processes can become more effective, if they can be effectively adapted by others. This process requires transparent reporting of how the guideline development groups moved from evidence to recommendations, and properly include AMR. Formal processes for adaptation permit societies and organizations to capitalize on existing evidence evaluation and interpretation by considering important contextual factors, among which AMR is the most noticeable. This would reduce cost and redundancy (7).

Our objectives were to analyze how, and to what extent, tuberculosis, gonorrhoea, and respiratory tract infection guidelines are considering antimicrobial resistance; are of acceptable methodological quality; and if they can be easily contextualized to fit the needs of specific populations.

Methods

SELECTION CRITERIA AND SEARCH STRATEGY

We selected three types of infection: tuberculosis (TB), gonorrhoea, and respiratory tract infections, specifically otitis media, pharyngitis, sinusitis, and community-acquired pneumonia.

These infections are a public health priority because they are becoming increasingly harder to treat due to AMR and/or are treated inappropriately, leading to higher risk of toxicity or resistance development. Harder to treat drug-resistant TB strains are increasing and projected to account for a quarter of all TB deaths by 2050 (11). Neisseria gonorrhoea is an urgent public health threat (12). The international spread of resistance to the last effective therapy, ceftriaxone, and azithromycin, threatens sustained treatment of gonorrhoea (13, 14). Otitis media, pharyngitis, sinusitis, and community-acquired pneumonia are prevalent and *Streptococcus pneumoniae* (the main causal microorganism), was classified as a serious public health threat due to resistance observed by inappropriate use of antibiotics (12, 15, 16). All these syndromes have been prioritized by WHO as part of Access, Watch, and Reserve (AWaRe) — a new classification system that supports a more nuanced approach to target inappropriate use of broad spectrum "Watch" antibiotics (17).

We included English language guidelines published between 2007 and 2019 on the above selected infections. We restricted to English language guidelines because, from a practical standpoint, English language publications would be the simplest to contextualize for most international groups and the major international organizations like WHO publish their guidelines at least in English. We marked the 2007 WHO decision to update its guideline development and using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach as a major change in methodology, representing a division of two eras (18). We limited the focus of our analyses to the era following this change.

We included guidelines with clearly articulated recommendations as defined by the Institute of Medicine (IOM) Standards for Developing Trustworthy Clinical Practice Guidelines (14). After contacting guideline developers, we excluded guidelines with unobtainable supplementary

materials required for analysis (see supplement table 1S for our guideline and recommendation selection outlined in PICAR format).

We searched Ovid MEDLINE and Embase from inception to June 7, 2019 (detailed search strategies in supplement). We conducted a second search in four guideline databases: TRIP (https://www.tripdatabase.com), G-I-N (https://www.g-i-n.net/home), BIGG (http://sites.bvsalud.org/bigg/en/biblio/), and the Canadian Medical Association clinical practice guideline (CPG) Infobase (https://joulecma.ca/cpg/homepage). We finally searched key international websites (supplement, table 2S) and reviewed references of included guidelines.

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

DATA EXTRACTION AND QUALITY ASSESSMENT

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

Reviewers screened through recommendations classifying them as either considering AMR or not according to AMR dimensions (examples provided in table 1, and supplement table 3S). Although guidelines may have adopted different approaches to considering resistance with varying level of technicalities and detail, our operational definitions for considering a guideline "compliant" were inclusive. We assumed that for each recommendation, there would be an opportunity to consider information pertaining to AMR at the population- and outcome-level,

given that formulation of specific recommendations is guided by population, intervention, comparison, and outcome (PICO) frameworks. Population-level considerations include recommendations for populations with some level of resistance, considerations of local resistance patterns, recommending the use of narrow-spectrum antimicrobials, and recommending the watchful-waiting approach to prescribing. Outcome-level dimensions included considering prospects of AMR or the emergence of resistance as a consequence of antimicrobial use.

Table 1: Satisfactory recommendations that consider antimicrobial resistance dimensions

AMR dimension(s)	Recommendation	Evidence illustration
AMR population-level dimensions considered	Amoxicillin-clavulanate rather than amoxicillin alone is recommended as empiric antimicrobial therapy for ABRS in adults (weak, low) (13).	Local national surveillance data in the United States of America for amoxicillin and beta-lactamase-producing *H. influenzae* was narratively described in the evidence summary was clearly linked to the recommendation.
AMR outcome-level dimensions considered	In neonates with gonococcal conjunctivitis, the WHO STI guideline suggests one of the following treatment options: • ceftriaxone 50 mg/kg (maximum 150 mg) IM as a single dose • kanamycin 25 mg/kg (maximum 75 mg) IM as a single dose • spectinomycin 25 mg/kg (maximum 75 mg) IM as a single dose (19).	The outcome of *'antimicrobial resistance'* was formally considered within a PICO framework within the guideline's supplementary materials..
Population and outcome-level dimensions considered	Bedaquiline should be included in longer MDR-TB regimens for patients aged 18 years or more (strong recommendation, moderate certainty in the estimates of effect) (20).	The recommendation considers a multi-drug-resistant tuberculosis patients, and the outcome *'acquisition (amplification) of drug resistance'* (21) was formally considered within a PICO framework provided within the guideline's supplementary materials..
	Alternative first choice of antibiotics for adults aged 18 years and over with pharyngitis and a penicillin allergy or intolerance: Clarithromycin 250 mg to 500 mg twice a day for 5 days (22).	Summary of committee discussions show that population-level resistance data was considered: "based on evidence, clinical experience and resistance data, the committee agreed to recommend the following alternative first-choice antibiotics for use in penicillin allergy or for phenoxymethylpenicillin intolerance: clarithromycin or erythromycin (which is preferred in pregnancy)" (22). Additional formal outcome considerations include *'antibiotic resistance'* within the guideline's supplementary materials..

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

We assessed a guideline's quality using the Appraisal of Guidelines for Research and Evaluation (AGREE) II Instrument focusing on three relevant domains: a well-defined scope and purpose (domain one), rigorous development including a systematic search for evidence, transparent reporting of methods, links between evidence and recommendations, external review, and procedures for update (domain three), and editorial independence (domain six) (23). We defined acceptable quality as guidelines that scored 60% or greater in these three domains a priori based on limited guidance on cut-off thresholds (3, 24). Focusing on these three domains and selecting a relatively low score, allowed us to be inclusive.

We also abstracted information on values, resource use, equity, acceptability, and feasibility from guidelines that met our acceptability cut-off (i.e., 60%). Briefly, worldwide regions may differ in the accessibility of antimicrobials, the cultural view towards the use of antimicrobials, pharmaceutical costs, and health care structures. We selected these dimensions as the transparent reporting of these factors is essential: in appraising the evidence for antimicrobials, guideline developers should be aware of the breadth of implications of their recommendations when used by decision-makers (7, 10, 25, 26). Guidelines that ignore this wider agenda could provide narrow, misleading guidance.

DATA SYNTHESIS AND STATISTICAL ANALYSIS

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

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

PATIENT AND PUBLIC INVOLVEMENT

One of the authors is a patient with a rare disease affected by repeated infections and treatment related issues of resistance to antimicrobials and was involved in aspects of the design and data abstraction. We specifically looked for information about patient values and preferences and included this in our review. However, we did not make any additional specific efforts to involve the patient and public in other aspects of this systematic review.

Results

Our initial search identified 10,365 records. After screening, we retrieved 79 guidelines that had at least one recommendation on antimicrobial selection: (n = 28 TB, n = 13 gonorrhea, n = 38 respiratory tract infections). Of these, 78 guidelines had sufficient information for assessment — one gonorrhoea guideline was excluded because we were unable to retrieve supplementary materials (Figure 1,and supplement table 4S) (27).

GUIDELINE RECOMMENDATIONS CONSIDERING AMR

After classifying recommendations, we found that 74 guidelines had at least one recommendation that considered AMR and four guidelines without such considerations (table 2) (28-31). These were excluded from further assessment. Of the 74 guidelines, the majority were developed in North America (n = 29), (13, 27, 32-59) and Europe (n = 26) (22, 49, 60-82). A smaller portion were from Asia (n = 7), (83-89) South America (n = 1), (90) Africa (n = 1), (91) and Oceania (n = 1) (92). Nine guidelines were internationally developed by the WHO (19-21, 93-98).

Table 2: Guidelines and recommendations with treatment recommendations with AMR considerations*

Variable	Guidelines (N=78**)	Total number of recommendations (N=1198)	Number of recommendations with AMR consideration (N=808)	Proportion of recommendations with AMR consideration (95% CI)
Continent				
International***	11	93	72	0.77 (0.67, 0.85)
North America	29	503	321	0.64 (0.59, 0.68)
South America	1	26	7	0.27 (0.12, 0.48)
Europe	27	429	334	0.78 (0.74, 0.82)

Africa	1	24	8	0.33 (0.16, 0.55)
Asia	8	119	65	0.55 (0.45, 0.64)
Oceania	1	4	1	0.25 (0.01, 0.78)
Publication year				
2007	3	47	34	0.72 (0.57, 0.84)
2008	2	4	4	1.00 (0.40, 1.00)
2009	6	175	92	0.53 (0.45, 0.60)
2010	3	45	30	0.67 (0.51, 0.80)
2011	8	77	64	0.83 (0.72, 0.90)
2012	10	144	96	0.67 (0.58, 0.74)
2013	7	121	93	0.77 (0.68, 0.84)
2014	5	167	88	0.53 (0.45, 0.60)
2015	7	37	35	0.95 (0.80, 0.99)
2016	10	83	53	0.64 (0.53, 0.74)
2017	6	129	94	0.73 (0.64, 0.80)
2018	5	49	45	0.92 (0.80, 0.97)
2019	6	120	80	0.67 (0.57, 0.75)

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

Within these 74 guidelines, we found that approximately two thirds of recommendations (n = 808/1198) considered AMR; that figure was 55·2% for TB recommendations (n = 272), 84·7% for gonorrhoea recommendations (n = 150), and 73·1% for respiratory tract infection recommendations (n = 386). The majority of recommendations were regionally developed (n = 736) (Figure 2).

Most recommendations considered either population-level or outcome-level AMR dimensions, while fewer considered both simultaneously. Approximately 17·6% of recommendations (n = 142/808) considered AMR at the population-level only while 34·7% (n = 281/808) of recommendations considered resistance as an outcome only. Most notably, a majority of those considering AMR as an outcome were not explicitly stated in PICO format, but rather buried within evidence summaries. Clearly stated outcomes formally considered in PICO frameworks included: ‘acquired drug-resistance’, ‘antimicrobial in vitro resistance’, ‘bacterial antibiotic resistance’, and ‘emergence of drug-resistance’. Among respiratory tract infection

recommendations, 6·9% (n = 27/386) recommended no antimicrobial or back-up antimicrobial (i.e. the watchful waiting approach), which is a population-level dimension, e.g. recommendations for patients who likely have infections that are viral in nature or self-limiting.

Additionally, 47·6% (385/808) recommendations considered both population-level and outcome-level AMR dimensions simultaneously. For example, fully immunized infant or school-aged children with community-acquired pneumonia admitted to hospital are recommended to take ampicillin or penicillin G given that local epidemiologic data lacks a substantial high-level of penicillin-resistance for invasive *S. pneumoniae* (38). This recommendation is considering local resistance patterns (population-level dimension). It is also followed by an evidence summary the explains that lower costs of ampicillin or penicillin G need to be balanced by the increased possibility of emergence of resistance (outcome-level dimension) that may occur from prescribing broad-spectrum antimicrobials. About 22·5% (n = 182/808) of recommendations considered local resistance patterns in a similar manner.

CREDIBILITY OF INTERNATIONAL AND REGIONAL GUIDELINES WITH RECOMMENDATIONS THAT CONSIDER AMR

Overall, only 39·2% (n = 29/74) of all international and regional guidelines had scores of 60% or greater in scope and purpose, rigour of development, and editorial independence. Of the 29 guidelines that met our credibility cut-off, ten were developed in North America (13, 39-44, 47, 58, 99), nine in Europe (22, 49, 68, 71, 72, 76-79, 91), and two were developed in Asia (84, 86). When we compared international and regional guidelines, the majority of WHO guidelines performed significantly better than regional guidelines (table 3 and supplement, figure 1S). Guidelines that did not meet our credibility cut-off score and excluded from further assessment

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

Table 3: Performance of World Health Organization versus regional guidelines with AMR considerations

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

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

GUIDELINES CONSIDERING VALUES, RESOURCE USE, ACCEPTABILITY, FEASIBILITY, AND EQUITY

Only five (19, 20, 94, 95, 97) of the 29 guidelines reported all factors required for contextualization: values, resource use, equity, acceptability, and feasibility (supplement table 5S). The WHO was the only guideline developer to report on all five criteria in four TB guidelines and one gonorrhoea guideline.

Across all 29 guidelines, resource use was the most frequently considered (n = 23 guidelines), followed by values (n = 16 guidelines), acceptability (n = 12 guidelines), and feasibility (n = 12 guidelines). Equity was the least considered factor with only seven guidelines that made such considerations (Figure 3): two were regionally and five were internationally developed. The WHO, the National Institute for Health and Care Excellence (NICE), and the United States Preventative Task Force (USPSTF) were the only organizations to consider equity.

Regional guidelines tended to consider values, resource use, equity, acceptability, and feasibility less than internationally developed guidelines (supplement, figure 2S). Most regional guidelines considered one (n = 6/21) or two (n = 6/21) or three (n = 4/21) or none (n = 4/21) of the above contextual factors. Values and resource use were considered the most, while equity, acceptability, and feasibility were less considered in regionally developed guidelines (Figure 4).

Discussion

SUMMARY OF FINDINGS

Over a 13-year period, relatively few guidelines on antibiotics for highly prevalent infectious diseases included AMR considerations. Approximately 60% of regionally developed guidelines were of low quality and reported less factors required for tailoring recommendations to specific contexts. International WHO guidelines had substantially higher quality scores than regional guidelines. International guidelines also consistently considered important information required for developing recommendations that are appropriate for specific contexts compared to regional guidelines.

There is an emerging consensus that reporting of Evidence to Decision dimensions is ethically and scientifically essential. Unfortunately, reporting these dimensions is not always seen in practice. Our review highlighted that some of the proposed dimensions seemed to be adopted by guideline developers (i.e., values and resource use were most considered), while others were less so (i.e., acceptability, feasibility, and equity were the least considered). Further, the quality of these guidelines varied and there were inconsistencies between regions and guidelines promoted/sponsored by different entities.

The use of the GRADE Evidence to Decision framework by the WHO and NICE seems to positively influence the consideration of contextual factors in the guidelines we reviewed. A high proportion of WHO (n=5/7) and NICE (n=1/5) guidelines contained complete information necessary to provide optimal guidance on how to use antimicrobials in the considered syndromes. Other regional organizations provided limited information addressing contextual factors – most addressed one (n=6/21) or two (n=6/21) contextual factors and a good proportion did not address any (4/21).

STRENGTHS AND LIMITATIONS

Our work has strengths. To our knowledge, this is the first study to assess the extent to which guidelines are considering local dimensions such as AMR, and to use established frameworks: AGREE II, and GRADE Evidence to Decision. We also employed systematic methods to conduct our review and validated tools to measure the quality of guidelines (23, 100).

There are several limitations to our study. The use of a credibility score of 60% or greater for three of the six AGREE II domains is based on limited guidance on cut-off thresholds. However, by focusing on three domains and a low cut-off we were inclusive although we also focused on

English language publications only (3, 101). We used general criteria from the GRADE Evidence to Decision Frameworks that are applicable to various interventions, and not specific to antimicrobials. These general dimensions could be complemented with specific criteria related to the antimicrobial field such as providing guidance on the appropriate threshold for escalating empiric antimicrobials from narrower spectrum agents to broader spectrum agents. In other words, the real test for antimicrobial guidelines may be whether they enable prescribers and the public to fully consider the potential implications of antimicrobial prescribing on resistance. This would lead to virtuous and parsimonious prescribing and consumption habits.

CONTEXT TO OTHER RESEARCH

We previously found that about two thirds of respiratory tract infection recommendations on empirical antimicrobial use did not consider country-specific resistance patterns. The use of a broader framework and additional focus areas may have resulted in the larger number of recommendations that considered AMR uncovered by this study. Both studies support that there are inconsistencies in considering AMR in recommendation development and potential duplication of work among infectious disease guidelines.

IMPLICATIONS FOR PRACTICE

There are several implications for guideline developers. Given the suboptimal quality of guidelines in our sample, guideline methodology should improve particularly when recommendations move from global to regional levels. This includes improving the processes used in evidence syntheses and recommendation formulation, transparency, and addressing potential unduly biases with competing interests. As far as regional guidelines need to incorporate contextual information when developing their recommendations, global guidelines

need to provide information about how to contextualize recommendations for appropriate AMR considerations.

Guideline development can be done more efficiently and economically by using work done by other developers including the WHO. Rather developing guidelines from scratch, time and resources (102) may be shifted towards refining AMR surveillance systems that provide national resistance data to support recommendations and appropriate antimicrobial use. Further, country-level participation of the Global Antimicrobial Resistance Surveillance System (GLASS) supports global monitoring of resistance trends, emerging resistance, and the ability to evaluate the effectiveness of interventions (103). As of 2020, 94 countries are participating in GLASS (103). However, some countries lack public health infrastructure, national laboratory capacities, and data management which is essential for surveillance systems (6, 104). In 2018, there was at least one country within each WHO regions with the ability to collect national resistance data (104). Regions facing unique challenges to antimicrobial stewardship capacities, may look to recommendations developed by other regions with similar resistance experiences. Finally, as new antimicrobial therapies become available, and the scientific community cumulates more evidence on resistance patterns and their implications for local prescribing, future infectious disease guidelines may require more frequent updating.

IMPLICATIONS FOR RESEARCH

Although we focused on recommendations on antimicrobial selection and prescribing, there are many other approaches that could be assessed in future research (e.g. rapid diagnostics to rule-out viral infections and resistant strains). In addition, research should also explore whether recommendations are appropriately guided by evidence, resistance data, and the WHO's

Essential Medicines List and AWaRe Classification Database of Antimicrobials updates (105). With regards to contextualization of infectious disease recommendations, we have developed transparent recommendation maps that facilitate use of recommendations across jurisdictions for TB (https://who.tuberculosis.recmap.org) and COVID-19 (https://covid19.recmap.org) where we apply some of our findings.

Conclusion (word count: 69)

Our study offers information on how current infectious disease guidelines are considering contextual factors necessary to appropriately prescribe antimicrobials. We also present dimensions that can be considered by a formal AMR framework used in combination with GRADE Evidence to Decision Frameworks to facilitate amelioration of the cornerstones that are guiding current antimicrobial use. Improving the quality of guidelines targeting specific regional areas is required. This may help protect the remaining and essential medicines we have left, and the future of new classes of antimicrobials (106).

Contributors

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

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Competing interests

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Data sharing

No additional data available.

References

1. United Nations meeting on antimicrobial resistance. Bull World Health Organ. 2016;94(9):638-9.
2. Organization WH. Global Action Plan on Antimicrobial Resistance. Geneva; 2015. Report No.: ISBN 978 92 4 150976 3.
3. Johnston A, Kelly SE, Hsieh S-C, Skidmore B, Wells GA. Systematic reviews of clinical practice guidelines: a methodological guide. Journal of Clinical Epidemiology. 2019;108:64-76.
4. Canada PHAo. Tackling Antimicrobial Resistance and Antimicrobial Use: A Pan-Canadian Framework for Action. Canada; 2017. Report No.: ISBN: 978-0-660-08168-7.
5. Anderson M, Schulze K, Cassini A, Plachouras D, Mossialos E. A governance framework for development and assessment of national action plans on antimicrobial resistance.

Lancet Infect Dis. 2019;19(11):e371-e84. doi: 10.1016/S473-3099(19)30415-3. Epub 2019 Oct 3.
6. Elias C, Moja L, Mertz D, Loeb M, Forte G, Magrini N. Guideline recommendations and antimicrobial resistance: the need for a change. BMJ Open. 2017;7(7):e016264. doi: 10.1136/bmjopen-2017-.
7. Schünemann HJ, Wiercioch W, Brozek J, Etxeandia-Ikobaltzeta I, Mustafa RA, Manja V, et al. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. J Clin Epidemiol. 2017;81:101-110.(doi):10.1016/j.jclinepi.2016.09.009. Epub Oct 3.
8. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol. 2013;66(7):719-25. doi: 10.1016/j.jclinepi.2012.03.013. Epub 3 Jan 9.
9. Rzewuska M, Duncan EM, Francis JJ, Morris AM, Suh KN, Davey PG, et al. Barriers and Facilitators to Implementation of Antibiotic Stewardship Programmes in Hospitals in Developed Countries: Insights From Transnational Studies. Frontiers in Sociology. 2020;5(41).
10. Scott IA, Guyatt GH. Clinical practice guidelines: the need for greater transparency in formulating recommendations. Med J Aust. 2011;195(1):29-33.
11. O'Neill J. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. London; 2016.
12. CDC. Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA; 2019.
13. Chow AWB, M. S.; Brook, I.; Brozek, J. L.; Goldstein, E. J. C.; Hicks, L. A.; Pankey, G. A.; Seleznick, M.; Volturo, G.; Wald, E. R.; File, T. M. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clinical Infectious Diseases. 2012;54(8):e72-e112.
14. Guidelines IoMUCoSfDTCP. Clinical Practice Guidelines We Can Trust. Washington (DC): National Academies Press (US); 2011. Available from: https://www.ncbi.nlm.nih.gov/books/NBK209539/?report=classic.
15. Knowles R, Sharland M, Hsia Y, Magrini N, Moja L, Siyam A, et al. Measuring antibiotic availability and use in 20 low- and middle-income countries. Bull World Health Organ. 2020;98(3):177-87C.
16. Knowles R, Sharland M, Hsia Y, Magrini N, Moja L, Siyam A, et al. Measuring antibiotic availability and use in 20 low- and middle-income countries. Bull World Health Organ. 2020;98(3):177-87C.
17. Sharland M, Gandra S, Huttner B, Moja L, Pulcini C, Zeng M, et al. Encouraging AWaRe-ness and discouraging inappropriate antibiotic use-the new 2019 Essential Medicines List becomes a global antibiotic stewardship tool. Lancet Infect Dis. 2019;19(12):1278-80. doi: 10.016/S473-3099(19)30532-8.
18. Schünemann HJ, Hill SR, Kakad M, Vist GE, Bellamy R, Stockman L, et al. Transparent development of the WHO rapid advice guidelines. PLoS Med. 2007;4(5):e119-e.
19. WHO guidelines for the treatment of Neisseria gonorrhoeae. World Health Organisation Guidelines. 2016.
20. Anonymous. WHO consolidated guidelines on drug-resistant tuberculosis treatment World Health Organization. 2019.

21. Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary tuberculosis among adults and adolescents. Recommendations for HIV-prevalent and resource-constrained settings. World Health Organization. 2007.
22. AHRQ - Agency for Healthcare Research + Quality. Surgical management of otitis media with effusion in children. National Collaborating Centre for Women's and Children's Health. NGC:007182 [Guideline Clearing Report]. 2008 [Available from: http://guidelines.gov/summary/summary.aspx?doc_id=14314&nbr=7182.
23. Brouwers MC, Kerkvliet K, Spithoff K. The AGREE Reporting Checklist: a tool to improve reporting of clinical practice guidelines. BMJ. 2016;352:i1152.
24. Brouwers MC, Spithoff K, Lavis J, Kho ME, Makarski J, Florez ID. What to do with all the AGREEs? The AGREE portfolio of tools to support the guideline enterprise. Journal of Clinical Epidemiology. 2020;125:191-7.
25. Moberg J, Oxman AD, Rosenbaum S, Schünemann HJ, Guyatt G, Flottorp S, et al. The GRADE Evidence to Decision (EtD) framework for health system and public health decisions. Health Research Policy and Systems. 2018;16(1):45.
26. 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;353:i2016.
27. Ontario PH. Ontario Gonorrhea Testing and Treatment Guide, 2nd Edition. 2018.
28. Organization WH. THE USE OF ANTIRETROVIRAL DRUGS FOR TREATING AND PREVENTING HIV INFECTION. 2016.
29. Kawaguchi RM, K.; Akira, S.; Ishitani, K.; Iwasaku, K.; Ueda, Y.; Okagaki, R.; Okano, H.; Oki, T.; Koga, K.; Kido, M.; Kurabayashi, T.; Kuribayashi, Y.; Sato, Y.; Shiina, K.; Takai, Y.; Tanimura, S.; Chaki, O.; Terauchi, M.; Todo, Y.; Noguchi, Y.; Nose-Ogura, S.; Baba, T.; Hirasawa, A.; Fujii, T.; Maruyama, T.; Miyagi, E.; Yanagida, K.; Yoshino, O.; Iwashita, M.; Maeda, T.; Minegishi, T.; Kobayashi, H. Guidelines for office gynecology in Japan: Japan Society of Obstetrics and Gynecology (JSOG) and Japan Association of Obstetricians and Gynecologists (JAOG) 2017 edition. Journal of Obstetrics and Gynaecology Research. 2019;45(4):766-86.
30. Anonymous. Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. World Health Organization. 2012.
31. Di Comite AE, S.; Villani, A.; Stronati, M.; Italian Pediatric, T. B. Study Group. How to manage neonatal tuberculosis. J Perinatol. 2016;36(2):80-5.
32. Prevention CfDCa. Provisional CDC guidelines for the use and safety monitoring of bedaquiline fumarate (Sirturo) for the treatment of multidrug-resistant tuberculosis. Article. Atlanta; 2013 Oct 2013. Contract No.: 9.
33. Wald ERA, K. E.; Bordley, C.; Darrow, D. H.; Glode, M. P.; Marcy, S. M.; Nelson, C. E.; Rosenfeld, R. M.; Shaikh, N.; Smith, M. J.; Williams, P. V.; Weinberg, S. T. Clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years. Pediatrics. 2013;132(1):e262-e80.
34. Workowski KAB, G. A. Sexually transmitted diseases treatment guidelines, 2015. Article. Atlanta, Georgia; 2015 Jun 2015.
35. Desrosiers ME, G. A.; Keith, P. K.; Wright, E. D.; Kaplan, A.; Bouchard, J.; Ciavarella, A.; Doyle, P. W.; Javer, A. R.; Leith, E. S.; Mukherji, A.; Schellenberg, R. R.; Small, P.; Witterick, I. J. Canadian clinical practice guidelines for acute and chronic rhinosinusitis. Allergy, Asthma and Clinical Immunology. 2011;7(1).

36. Mayor MTR, M. A.; Uduhiri, K. A. Diagnosis and management of gonococcal infections. Am Fam Physician. 2012;86(10):931-8.
37. Kaplan JEB, C.; Holmes, K. H.; Brooks, J. T.; Pau, A.; Masur, H. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR. 2009;Recommendations and reports:Morbidity and mortality weekly report. Recommendations and reports / Centers for Disease Control. 58 (RR-4) (pp 1-207; quiz CE1-2074).
38. The Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age. Infectious Diseases Society of America. 2011.
39. Diagnosis and Management of Acute Otitis Media. American Academy of Family Physicians. 2013.
40. Adult Sinusitis. American Academy of Otolaryngology - Head and Neck Surgery. 2015.
41. Otitis Media with Effusion (OME). American Academy of Otolaryngology - Head and Neck Surgery. 2016.
42. Treatment of Drug-Susceptible Tuberculosis: Official ATS/CDC/IDSA Clinical Practice Guidelines. American Thoracic Society. 2016.
43. Respiratory Illness in Children and Adults, Diagnosis and Treatment of. Institute for Clinical Systems Improvement. 2017.
44. IDSA - Infectious Diseases Society of America. Clinical Practice Guideline for the Diagnosis and Management of Group A Streptococcal Pharyngitis: 2012 Update by the Infectious Diseases Society of America [Guideline]. 2012 [Available from: http://cid.oxfordjournals.org/content/early/2012/09/06/cid.cis629.full.
45. Borisov ASBM, S.; Njie, G. J.; Winston, C. A.; Burton, D.; Goldberg, S.; Yelk Woodruff, R.; Allen, L.; LoBue, P.; Vernon, A. Update of Recommendations for Use of Once-Weekly Isoniazid-Rifapentine Regimen to Treat Latent Mycobacterium tuberculosis Infection. MMWR Morbidity and mortality weekly report. 2018;67(25):723-6.
46. Pogany LR, B.; Robinson, J.; Gale-Rowe, M.; Latham-Carmanico, C.; Weir, C.; Wong, T. Management of gonococcal infection among adults and youth: New key recommendations. Canadian Family Physician. 2015;61(10):869-73.
47. Richard M. Rosenfeld M, MPH1, Jay F. Piccirillo, MD2,, Sujana S. Chandrasekhar M, Itzhak Brook, MD, MSc4, Kaparaboyna Ashok Kumar, MD, FRCS5, Maggie Kramper, RN, FNP6, Richard R. Orlandi, MD7, James N. Palmer, MD8, Zara M. Patel, MD9, Anju Peters, MD10, Sandra A.Walsh11, and Maureen D. Corrigan. Clinical Practice Guideline (Update): Adult Sinusitis. 2015.
48. Report MaMW. Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children. 2009.
49. Canada PHAo. Canadian Tuberculosis Standards, 7th Edition. 2014.
50. Control BCfD. Sexually Transmitted Infections in Adolescents and Adults 2014.
51. Prevention CfDCa. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. 2019.
52. America IDSo. Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin- Resistant Staphylococcus aureus Infections in Adults and Children. 2011.
53. Infections CGoST. Gonococcal Infections Chapter. 2013.

54. Prevention CfDCa. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children. 2013.
55. Pharyngitis. University of Michigan Health System. 2013.
56. HIV/AIDS BCCfEi. Therapeutic guidelines for antiretroviral (ARV) treatment in adult HIV infection. 2015.
57. Mandell LAW, R. G.; Anzueto, A.; Bartlett, J. G.; Campbell, G. D.; Dean, N. C.; Dowell, S. F.; File Jr, T. M.; Musher, D. M.; Niederman, M. S.; Torres, A.; Whitney, C. G. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the management of community-acquired pneumonia in adults. Clinical Infectious Diseases. 2007;44(SUPPL. 2):S27-S72.
58. Ocular Prophylaxis for Gonococcal Ophthalmia Neonatorum: Preventive Medication. US Preventive Services Task Force. 2019.
59. Jereb JAG, S. V.; Powell, K.; Villarino, M. E.; Lobue, P. Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent mycobacterium tuberculosis infection. Morbidity and Mortality Weekly Report. 1650;60(48):1650-3.
60. Bignell CU, M. 2012 European guideline on the diagnosis and treatment of gonorrhoea in adults. International Journal of STD and AIDS. 2013;24(2):85-92.
61. Bignell CF, M. UK national guideline for the management of gonorrhoea in adults, 2011. International Journal of STD and AIDS. 2011;22(10):541-7.
62. Harris MC, J.; Coote, N.; Fletcher, P.; Harnden, A.; McKean, M.; Thomson, A. British Thoracic Society guidelines for the management of community acquired pneumonia in children: Update 2011. Thorax. 2011;66(SUPPL. 2).
63. Migliori GBZ, J. P.; Abubakar, I.; Ibraim, E.; Caminero, J. A.; De Vries, G.; D'Ambrosio, L.; Centis, R.; Sotgiu, G.; Menegale, O.; Kliiman, K.; Aksamit, T.; Cirillo, D. M.; Danilovits, M.; Dara, M.; Dheda, K.; Dinh-Xuan, A. T.; Kluge, H.; Lange, C.; Leimane, V.; Loddenkemper, R.; Nicod, L. P.; Raviglione, M. C.; Spanevello, A.; Thomsen, V. O.; Villar, M.; Wanlin, M.; Wedzicha, J. A.; Zumla, A.; Blasi, F.; Huitric, E.; Sandgren, A.; Manissero, D. European Union Standards for Tuberculosis Care. European Respiratory Journal. 2012;39(4):807-19.
64. Woodhead MB, F.; Ewig, S.; Garau, J.; Huchon, G.; Ieven, M.; Ortqvist, A.; Schaberg, T.; Torres, A.; Van Der Heijden, G.; Read, R.; Verheij, T. J. M. Guidelines for the management of adult lower respiratory tract infections - Full version. Clinical Microbiology and Infection. 2011;17(SUPPL. 6):E1-E59.
65. Spindler CS, K.; Eriksson, L.; Hjerdt-Goscinski, G.; Holmberg, H.; Lidman, C.; Nilsson, A.; Ortqvist, A.; Hedlund, J. Swedish guidelines on the management of community-acquired pneumonia in immunocompetent adults - Swedish Society of Infectious Diseases 2012. Scandinavian Journal of Infectious Diseases. 2012;44(12):885-902.
66. Thwaites GF, M.; Hemingway, C.; Scott, G.; Solomon, T.; Innes, J.; British Infection, Society. British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. J Infect. 2009;59(3):167-87.
67. Bignell CIW. 2009 European (IUSTI/WHO) guideline on the diagnosis and treatment of gonorrhoea in adults. Int J STD AIDS. 2009;20(7):453-7.
68. Internal Clinical Guidelines T. Tuberculosis Prevention, diagnosis, management and service organization. National Institute for Health and Care Excellence (UK). 2016;01:01.
69. Menendez RT, A.; Aspa, J.; Capelastegui, A.; Prat, C.; Rodriguez de Castro, F. Community acquired pneumonia. New guidelines of the Spanish society of chest diseases and thoracic surgery (SEPAR). Archivos de Bronconeumologia. 2010;46(10):543-58.

70. Respiratory tract infections (self-limiting): prescribing antibiotics. National Institute for Health and Clinical Excellence - Clinical Guidelines. 2008.
71. Guidelines for the management of community-acquired pneumonia in adults. British Infection Association. 2009.
72. CPG on the Diagnosis, Treatment and Prevention of Tuberculosis. GuiaSalud. 2010.
73. Sinusitis (acute): antimicrobial prescribing. National Institute for Health and Clinical Excellence - Clinical Guidelines. 2017.
74. British Association for Sexual Health and HIV national guideline for the management of infection with Neisseria gonorrhoeae. British Association for Sexual Health and HIV. 2019.
75. Stahl JPA, P.; Bruneel, F.; De Broucker, T.; Duval, X.; Fantin, B.; Girard, N.; Herrmann, J. L.; Honnorat, J.; Lecuit, M.; Mailles, A.; Martinez-Almoyna, L.; Morand, P.; Piroth, L.; Tattevin, P. Guidelines on the management of infectious encephalitis in adults. Medecine et Maladies Infectieuses. 2017;47(3):179-94.
76. Heidemann CL, J; Berg, J; Christensen, JJ; Håkonsen, SJ; Jakobsen, M; Johansen, CJ; Nielsen, LH; Hansen, MP; Poulsen, A; Schousboe, LP; Skrubbeltrang, C; Vind, AB; Homøe, P. Danish guidelines on management of otitis media in preschool children. 2016.
77. Management of sore throat and indications for tonsillectomy. SIGN. 2010.
78. Excellence ENIfHaC. Sore throat (acute): antimicrobial prescribing. 2018.
79. Excellence NIfHaC. Pneumonia (community-acquired): antimicrobial prescribing. 2019.
80. Wiersinga WJB, M. J.; Boersma, W. G.; Jonkers, R. E.; Aleva, R. M.; Kullberg, B. J.; Schouten, J. A.; Degener, J. E.; van de Garde, E. M. W.; Verheij, T. J.; Sachs, A. P. E.; Prins, J. M. Management of community-acquired pneumonia in adults: 2016 guideline update from the dutch working party on antibiotic policy (SWAB) and dutch association of chest physicians (NVALT). Netherlands Journal of Medicine. 2018;76(1):4-13.
81. Athlin SL, C.; Lundqvist, A.; Naucler, P.; Nilsson, A. C.; Spindler, C.; Stralin, K.; Hedlund, J. Management of community-acquired pneumonia in immunocompetent adults: updated Swedish guidelines 2017. Infectious Diseases. 2018;50(4):247-72.
82. Chiappini EM, R.; Bruzzese, E.; Capuano, A.; Colombo, M.; Cricelli, C.; Di Mauro, G.; Esposito, S.; Festini, F.; Guarino, A.; Miniello, V. L.; Principi, N.; Marchisio, P.; Rafaniello, C.; Rossi, F.; Sportiello, L.; Tancredi, F.; Venturini, E.; Galli, L.; de Martino, M. Rational use of antibiotics for the management of children's respiratory tract infections in the ambulatory setting: An evidence-based consensus by the Italian Society of Preventive and Social Pediatrics. Paediatric Respiratory Reviews. 2014;15(3):231-6.
83. Gupta DA, R.; Aggarwal, A.; Singh, N.; Mishra, N.; Khilnani, G.; Samaria, J.; Gaur, S.; Jindal, S. Guidelines for diagnosis and management of community-and hospital-acquired pneumonia in adults: Joint ICS/NCCP(I) recommendations. Lung India. 2012;29(SUPPL.2):S27-S62.
84. Abdul Rahaman JAK, H. B.; Yusof, M.; Hanafi, N. S.; Wong, J. L. Tuberculosis in adults. Malays Fam Physician. 2014;9(3):34-7.
85. Ministry of Public Health/Qatar. Community acquired pneumonia [Guideline]. 2016 [updated 19.03.2017. Available from: https://www.moph.gov.qa/health-strategies/Documents/Guidelines/MOPH%20Guideline%20-%20Community%20acquired%20pneumonia%20v2-1%20FINAL.pdf.
86. HTA DoH - HTA Unit, Ministry of Health,, Malaysia,. Management of Otitis Media with Effusion in Children [Guideline]. 2012 [Available from: http://www.moh.gov.my/attachments/7779.pdf.

87. Lee MSO, J. Y.; Kang, C. I.; Kim, E. S.; Park, S.; Rhee, C. K.; Jung, J. Y.; Jo, K. W.; Heo, E. Y.; Park, D. A.; Suh, G. Y.; Kiem, S. Guideline for antibiotic use in adults with community-acquired pneumonia. Infection and Chemotherapy. 2018;50(2):160-98.
88. Singapore MoH. Prevention, Diagnosis and Management of Tuberculosis. 2016.
89. WORKING ZAM-YMA-QAA-AMS-MSNATGC. Management and Prevention Strategies for Community-Acquired Pneumonia in the Gulf Corporation Council. Journal of Chemotherapy. 2007.
90. Ricardo de Amorim Corrêa FLCL, Jorge Luiz Pereira-Silva, Rodney Luiz Frare e Silva, Alexandre Pinto Cardoso, Antônio Carlos Moreira Lemos, Flávia Rossi, Gustavo Michel, Liany Ribeiro, Manuela Araújo de Nóbrega Cavalcanti, Mara Rúbia Fernandes de Figueiredo, Marcelo Alcântara Holanda, Maria Inês Bueno de André Valery, Miguel Abidon Aidê, Moema Nudilemon Chatkin, Octávio Messeder, Paulo José Zimermann Teixeira, Ricardo Luiz de Melo Martins e Rosali Teixeira da Rocha, em nome da Comissão de Infecções Respiratórias e Micoses –Sociedade Brasileira de Pneumologia e Tisiologia. Brazilian guidelines for community-acquired pneumonia in immunocompetent adults - 2009*. J Bras Pneumol. 2009.
91. Boyles THB, A.; Calligaro, G. L.; Cohen, C.; Dheda, K.; Maartens, G.; Richards, G. A.; Smit, R. Z.; Smith, C.; Wasserman, S.; Whitelaw, A. C.; Feldman, C. South African guideline for the management of communityacquired pneumonia in adults. Journal of Thoracic Disease. 1469;9(6):1469-502.
92. Chaves NJ PG, Biggs BA, Thambiran A, Smith M, Williams J, Gardiner J, Davis JS; on behalf of the Australasian Society for Infectious Diseases and Refugee Health Network of Australia Guidelines writing group. Recommendations for comprehensive post-arrival health assessment for people from refugee-like backgrounds australasian society for infectious diseases And refugee health network of australia 2nd edition. 2010.
93. Anonymous. Guidance for national tuberculosis programmes on the management of tuberculosis in children. World Health Organization 2nd WHO Guidelines Approved by the Guidelines Review Committee. 2014.
94. Guidelines on the management of latent tuberculosis infection. World Health Organisation Guidelines. 2015.
95. Recommendation on 36 months isoniazid preventive therapy to adults and adolescents living with HIV in resource-constrained and high TB and HIV-prevalence settings: 2015 update. World Health Organisation Guidelines. 2015.
96. Intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. World Health Organisation HIV Guidelines. 2011.
97. Organization WH. Latent tuberculosis infection Updated and consolidated guidelines for programmatic management. 2018.
98. Organization WH. Recommendations for management of common childhood conditions Newborn conditions, dysentery, pneumonia, oxygen use and delivery, common causes of fever, severe acute malnutrition and supportive care. 2012.
99. Prevention CfDCa. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis. 2013.
100. Johnston A, Kelly SE, Hsieh SC, Skidmore B, Wells GA. Systematic reviews of clinical practice guidelines: a methodological guide. J Clin Epidemiol. 2019;108:64-76.(doi):10.1016/j.jclinepi.2018.11.030. Epub Dec 5.
101. Tonelli M, Connor Gorber S, Moore A, Thombs BD, Canadian Task Force on Preventive Health C. Recommendations on routine screening pelvic examination: Canadian Task Force on

Preventive Health Care adoption of the American College of Physicians guideline. Can Fam Physician. 2016;62(3):211-4.
102. Darzi A, Abou-Jaoude EA, Agarwal A, Lakis C, Wiercioch W, Santesso N, et al. A methodological survey identified eight proposed frameworks for the adaptation of health related guidelines. J Clin Epidemiol. 2017;86:3-10.(doi):10.1016/j.jclinepi.2017.01.016. Epub Apr 13.
103. Organization WH. Global antimicrobial resistance and use surveillance system (GLASS) report. 2020.
104. Organization WH. Worldwide country situation analysis: response to antimicrobial resistance2015. Available from: https://apps.who.int/iris/bitstream/handle/10665/163468/9789241564946_eng.pdf?sequence=1.
105. Organization WH. WHO Model Lists of Essential Medicines. 2019.
106. Foundation AtM. Antimicrobial Resistance Benchmark 2018. Available from: https://accesstomedicinefoundation.org/media/uploads/downloads/5bc5edd8367eb_Antimicrobial-Resistance-Benchmark-2018.pdf.

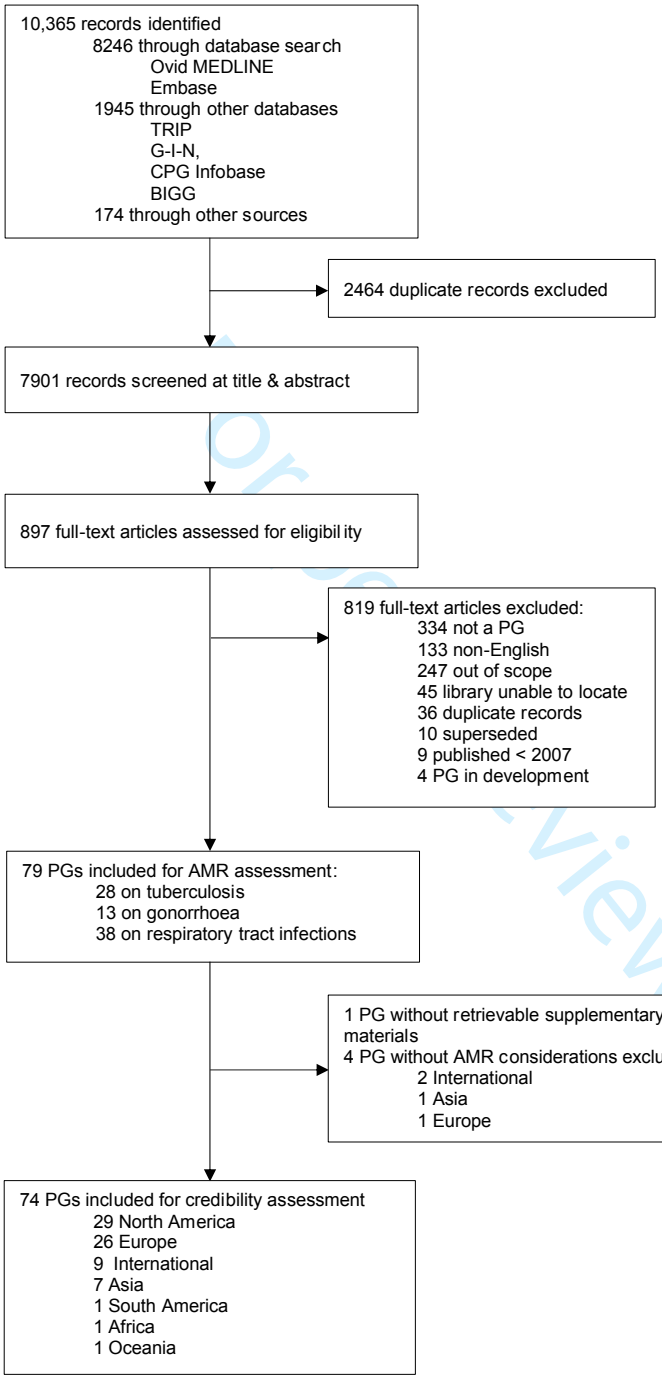
Figure legends

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

Figure 2: Number of regional guideline recommendations that consider antimicrobial resistance.

Figure 3: Contextualization of Grading of Recommendations Assessment, Development and Evaluation (GRADE) Evidence to Decision (EtD) frameworks in current guidelines.

Figure 4: Number of internationally and regionally developed guidelines with considerations of Grading of Recommendations Assessment, Development and Evaluation (GRADE) Evidence to Decision (EtD) frameworks.



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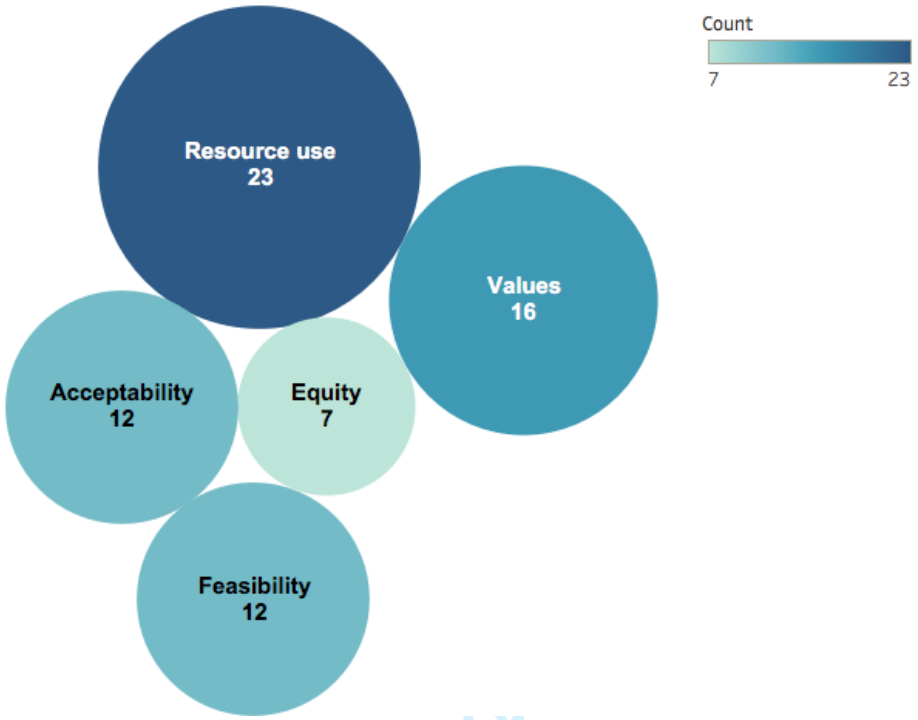

Figure 3: Contextualization of Grading of Recommendations Assessment, Development and Evaluation (GRADE) Evidence to Decision (EtD) frameworks in current guidelines

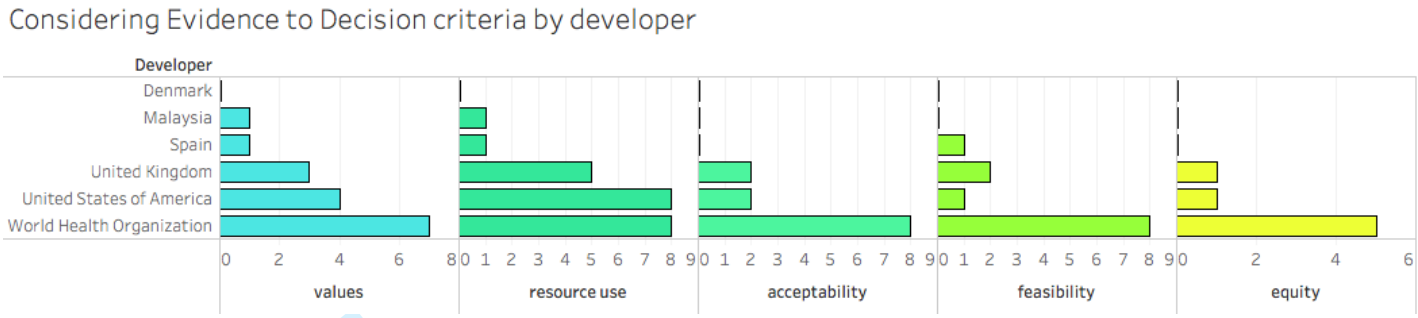

Figure 4: Number of internationally and regionally developed guidelines with considerations of Grading of Recommendations Assessment, Development and Evaluation (GRADE) Evidence to Decision (EtD) frameworks

Supplement

Extra figures & tables

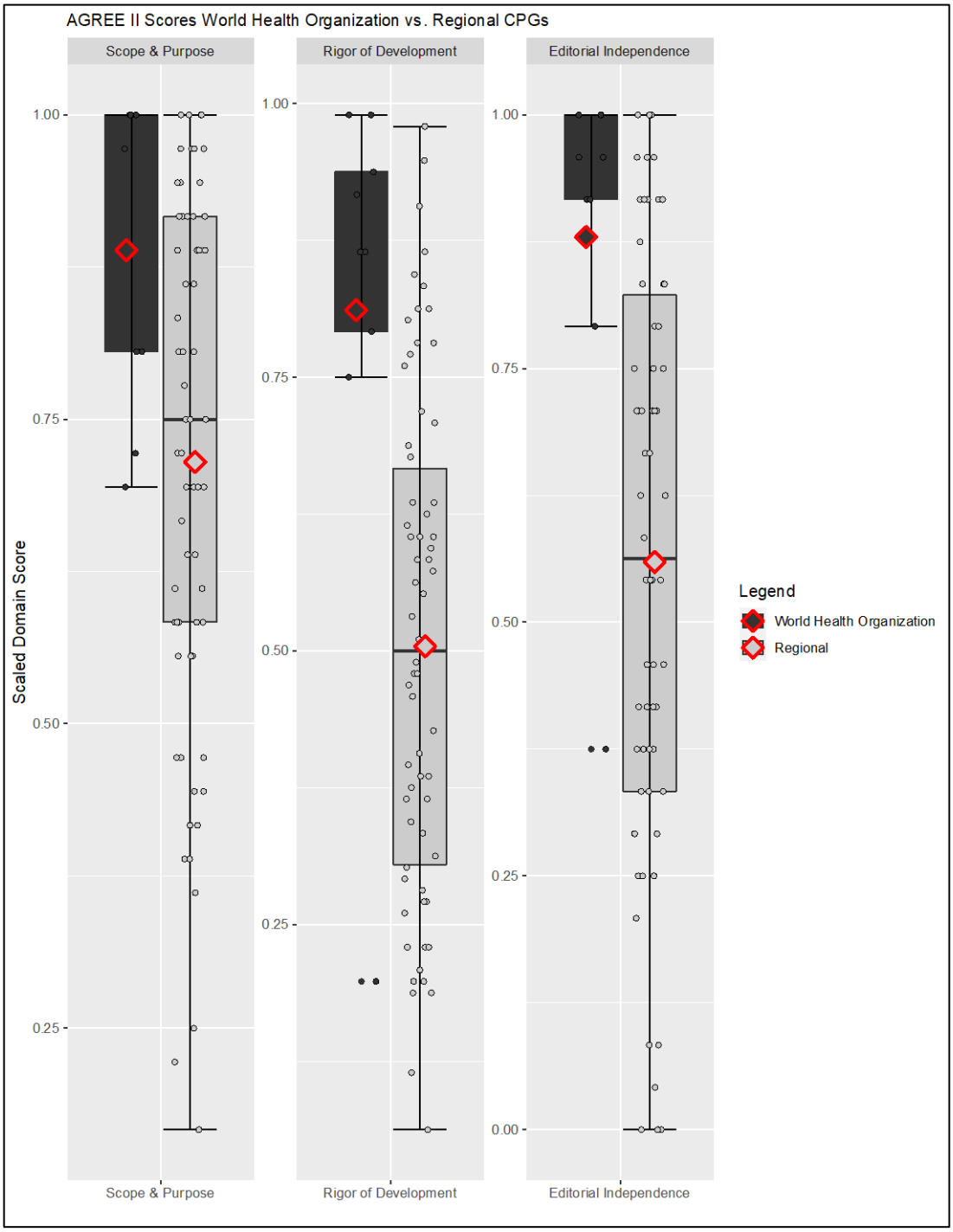

Figure 1S: Boxplot of AGREE II scores comparing World Health Organization and regional guidelines

AGREE II = Appraisal of Guidelines for Research & Evaluation II Instrument; Dark grey dots = World Health Organization guidelines; light grey dots = regional guidelines. Scope and purpose = domain one; rigor of development = domain three; editorial independence = domain six.

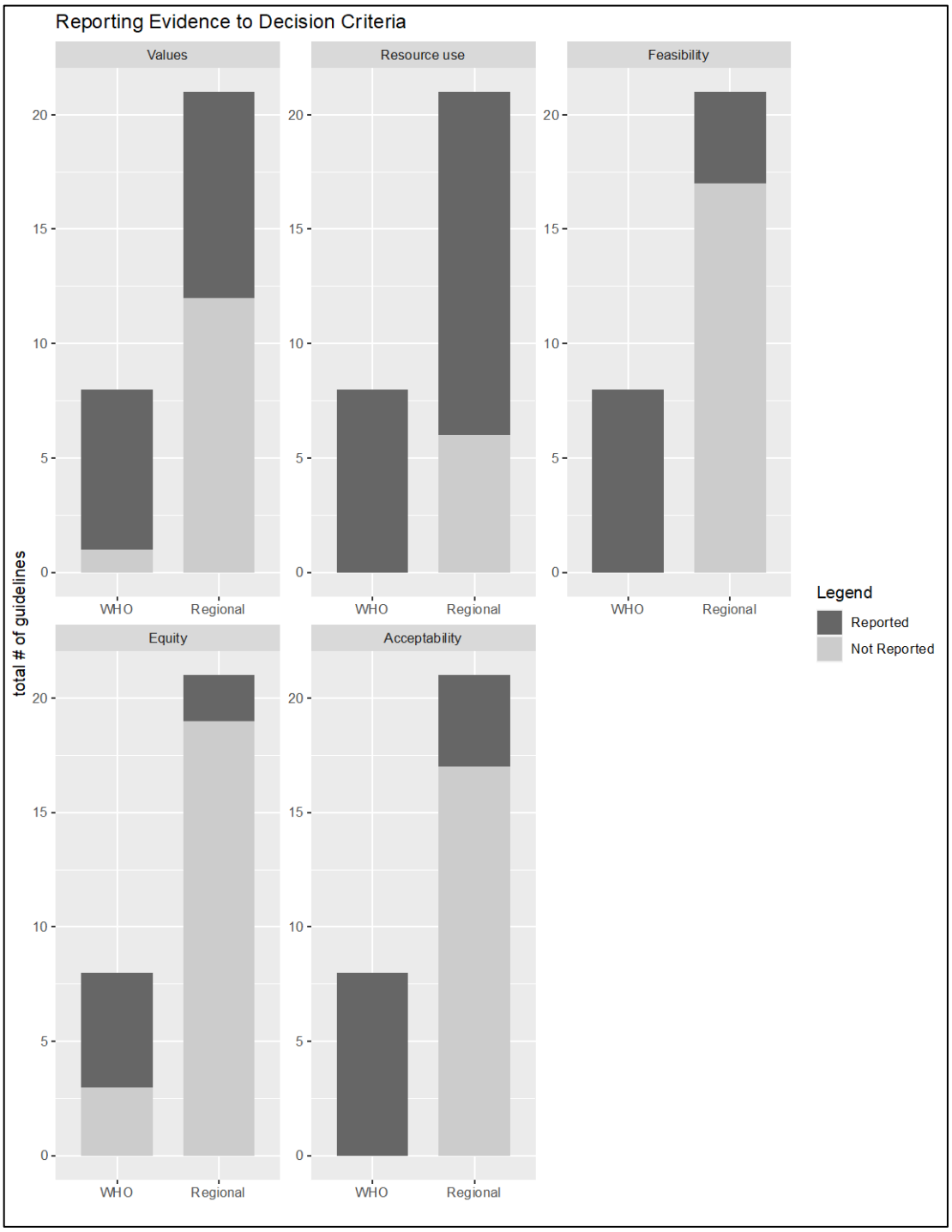

Figure 2S: World Health Organization versus regional guidelines meeting AGREE II scores >/= 60% reporting GRADE Evidence to Decision Frameworks

29/75 guidelines with AMR considerations had a scaled domain score of >/= 60%; EtD criteria = evidence to decision criteria: values, resource use, feasibility, acceptability, and equity

Supplemental Table 1S: Research question in PICAR format

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

Search strategy Ovid Medline and Embase

Database: Embase <1974 to 2019 June 07>, OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy:
---
1 (tuberculosis or tuberculous or TB).mp. (510746)
2 (gonoc* or gonorr*).mp. (58460)
3 pneumonia*.mp. (557015)
4 strepto*.mp. (531324)
5 (pneumonia* adj2 strepto*).mp. (83649)
6 1 or 2 or 5 (648159)
7 exp clinical pathway/ (14358)
8 exp clinical protocol/ (252634)
9 exp consensus/ (72535)
10 exp consensus development conference/ (35258)
11 exp consensus development conferences as topic/ (26540)
12 critical pathways/ (14358)
13 exp guideline/ (32021)
14 guidelines as topic/ (375998)
15 exp practice guideline/ (526549)
16 practice guidelines as topic/ (381407)
17 health planning guidelines/ (93323)
18 (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt. (40981)
19 (position statement* or policy statement* or practice parameter* or best practice*).ti,ab,kf,kw. (71605)
20 (standards or guideline or guidelines).ti,kf,kw. (243012)
21 ((practice or treatment* or clinical) adj guideline*).ab. (90132)
22 (CPG or CPGs).ti. (12033)
23 consensus*.ti,kf,kw. (53111)
24 consensus*.ab. /freq=2 (52722)
25 ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf,kw. (47116)
26 recommendat*.ti,kf,kw. (85035)
27 (care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab,kf,kw. (142098)
28 (algorithm* adj2 (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti,ab,kf,kw. (16221)
29 (algorithm* adj2 (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti,ab,kf,kw. (22274)
30 or/7-29 (1489076)
31 6 and 30 (17406)
32 limit 31 to yr="2007 -Current" (11340)
33 (randomised or randomized or study or trial).ti. (3257255)
34 32 not 33 (10455)
35 limit 34 to (conference abstract or editorial or erratum or letter or tombstone or address or autobiography or biography or case reports or clinical trial, all or clinical trial protocol or clinical trial protocols as topic or clinical trial or comment or controlled clinical trial or interview or news or newspaper article or patient education handout or personal narrative or portrait or pragmatic clinical trial

or randomized controlled trial) [Limit not valid in Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] (2878)
36 34 not 35 (7577)
37 limit 36 to yr="2014 -Current" (3831)
38 limit 36 to yr="2007 - 2014" (4415)
39 remove duplicates from 38 (3464)
40 remove duplicates from 37 (2937)
41 39 or 40 (5910)

Supplemental Table 2S: List of websites of organizations and associations that provide guidelines

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

Supplemental Table 3S: Definition of recommendations that consider antibiotic resistance

Recommendation	Definition	Example
Considers resistance if	1. The recommendation is for a ***population*** that is infected with a resistant organism (i.e. people with drug-resistant TB); **OR** 2. The recommendation is supported by ***country-specific resistance patterns;***[1] **OR** 3. The recommendation question (or PICO question) that has resistance as an ***outcome***. **OR** The ***outcome*** may be any of the following: 'resistance', 'resistant', 'drug-resistance', 'antibiotic resistance' 'antimicrobial resistance', 'antimicrobial in vitro resistance', 'acquired drug-resistance' 4. The recommendation is to prescribe narrow-spectrum antibiotics over broad-spectrum antibiotics. **OR** 5. A recommendation for no antibiotic prescription or back-up antibiotic prescription (i.e. watchful waiting approach)	***Example: A recommendation that considers country-specific resistance, and has a resistance-related outcome.*** "In adults and adolescents with gonococcal oropharyngeal infections, the WHO STI guideline suggests dual therapy over single therapy...and suggests single therapy (based on recent local resistance data confirming susceptibility to the antimicrobial)." The PICO table that was provided has 'antimicrobial in vitro resistance' as an outcome.[2]
DOES NOT consider resistance if	1. The recommendation is ***NOT*** for a population that is infected with a resistant organism. **AND** 2. The recommendation is ***NOT*** supported by country-specific resistant patterns. **AND** 3. The recommendation question (or PICO question) ***DOES NOT*** have any resistant outcomes. **AND** 4. Recommendation DOES NOT prescribe narrow-spectrum antibiotics. **AND**	***Example: A recommendation that is not intended for a population that is infected with a resistant organism, nor is it supported by country specific resistant patterns, nor does it have outcomes pertaining to resistance.*** The BASHH 2013 guidelines recommended that "ceftriaxone 500mg intramuscularly single dose followed by oral Doxycycline 100mg bd plus oral Metronidazole 400mg bd both for 12 weeks was recommended for children over the age of 12."[3]

[1] Informed by the Elias et al 2017.
[2] WHO guidelines for the Treatment of Neisseria gonorrhoeae. 2016.
[3] BASHH 2013 Management of gonorrhoea and pelvic inflammatory disease in children.

	5. There are no recommendations on no antibiotic nor back-up antibiotic or no watchful-waiting approach.	For this recommendation, neither the guideline nor the supplementary materials mention that they considered England's resistance patterns when developing the recommendation, nor were there any outcomes pertaining to resistance.

Details to extract and record from the guidelines[4]:

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

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

20. EtD available.

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

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

Supplemental Table 4S: Characteristics of excluded studies

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

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

Desrosiers, M et al.	2011	Canadian Society of Otolaryngology-Head and Neck Surgery	North America	Primary and secondary care	Sinusitis	Had a scaled domain score of < 60%
Mayor, M. T.; Roett, M. A.; Uduhiri, K. A.	2012	American Academy of Family Physicians	North America	Primary care	Gonorrhoea	Had a scaled domain score of < 60%
Thwaites, G.	2009	British Infection Society Guidelines	Europe	Secondary and tertiary	Tuberculosis	Had a scaled domain score of < 60%
Bignell, C.; Iusti/Who,	2009	IUSTI/WHO	Europe	Secondary and tertiary	Gonorrhoea	Had a scaled domain score of < 60%
Abdul Rahaman, J. A.; Ker, H. B.; Yusof, M.; Hanafi, N. S.; Wong, J. L.	2012	Malaysian Family Physician	Asia	Primary care but it should also be useful to those in the secondary/tertiary care.	Tuberculosis	Two EtD criteria reported: 1. Values 2. Resource use
World Health Organization (WHO)	2014	World Health Organization (WHO)	International	This document is targeted at national TB programmes, paediatricians and other health workers in low- and middle-income countries	Tuberculosis	Three EtD criteria reported: 1. Resource use 2. Acceptability 3. Feasibility
National Institute for Health and Care Excellence (NICE)	2016	The National Institute for Health and Care Excellence (NICE)	Europe	Primary, secondary and tertiary	Tuberculosis	Four EtD criteria reported: 1. Values 2. Resource use 3. Acceptability 4. Feasibility

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

and Thoracic Surgery, etc.						
Infectious Disease Society of America (IDSA)	2011	Infectious Disease Society of America (IDSA)	North America	Primary, secondary and tertiary care	Community-acquired pneumonia	Had a scaled domain score of < 60%
American Academy of Family Physicians	2013	American Academy of Pediatrics	North America	Primary care	Otitis media	Two EtD criteria reported: 1. Values 2. Resource use
National Institute for Health and Clinical Excellence (NICE)	2014	The National Institute for Health and Care Excellence (NICE)	Europe	Primary, secondary and tertiary	Community-acquired pneumonia	Two EtD criteria reported: 1. Values 2. Feasibility
American Academy of Otolaryngology	2015	American Academy of Otolaryngology—Head and Neck Surgery Foundation	North America	The guideline is intended for all clinicians who are likely to diagnose and manage adults with rhinosinusitis and applies to any setting in which an adult with rhinosinusitis would be identified, monitored, or managed.	Sinusitis	Three EtD criteria reported: 1. Values 2. Resource use 3. Acceptability
American Academy of Otolaryngology	2016	American Academy of Otolaryngology—Head and Neck	North America	Primary care	Otitis media	Three EtD criteria reported:

		Surgery Foundation, the American Academy of Pediatrics, and the American Academy of Family Physicians				1. Values 2. Resource use 3. Acceptability
Infectious Disease Society of America (IDSA)	2016	Infectious Disease Society of America (IDSA)	North America	well-resourced; low-incidence settings	Tuberculosis	No EtD reported
The National Institute for Health and Care Excellence (NICE)	2017	The National Institute for Health and Care Excellence (NICE)	Europe	Primary, secondary and tertiary care	Sinusitis	Had a scaled domain score of < 60%
Institute for Clinical Systems Improvement	2017	Institute for Clinical Systems Improvement	North America	ambulatory care	Pharyngitis and sinusitis	One EtD criteria reported: 1. Resource use
The National Institute for Health and Care Excellence (NICE)	2018	The National Institute for Health and Care Excellence (NICE)	Europe	Primary and secondary care (For the treatment of acute uncomplicated otitis media in primary, secondary or other care settings (for example walk-in-centres, urgent care, and minor ailment schemes) either by prescription or by any other legal means of supply of medicine (for example Patient Group Direction).	Otitis media	Had a scaled domain score of < 60%

British Association for Sexual Health and HIV	2019	British Association for Sexual Health and HIV (BASHH)	Europe	The guidelines are primarily aimed at level 3 sexual health services within the United Kingdom (UK) although the principles of the recommendations could be adopted at all levels.	Gonorrhoea	Had a scaled domain score of < 60%
Ministry of Public Health/Qatar	2016	Ministry of Public Health of Qatar (MOPH)	Asia	primary care and secondary care settings	Community-acquired pneumonia	Had a scaled domain score of < 60%
Infectious Disease Society of America (IDSA)	2012	Infectious Disease Society of America (IDSA)	North America	healthcare providers who care for adult and pediatric patients with group A streptococcal pharyngitis	Pharyngitis	One EtD criteria reported: 1. Resource use
Ministry of Health Malaysia Ministry of Higher Education and private sector	2012	Ministry of Health Malaysia Ministry of Higher Education and private sector	Asia	Outpatient, inpatient and community setting	Otitis media	No EtD criteria reported
Borisov, A. S et al.	2018	Centre for Disease Control and Prevention (CDC)	North America	n/a	Tuberculosis	Had a scaled domain score of < 60%
Lee, M. S. et al.	2018	the Korean Society for Chemotherapy, the Korean Society of Infectious Diseases the Korea Academy of	Asia	Primary care	Community-acquired pneumonia	Had a scaled domain score of < 60%

		Tuberculosis and Respiratory Diseases, the Korean Association of Family Medicine, the Korean Medical Practitioners Association, and the National Evidence-based Healthcare Collaborating Agency				
Pogany, L. et al.	2015	Canadian Family Physician	North America	Primary care	Gonorrhoea	Had a scaled domain score of < 60%
Stahl, J. P. et al.	2017	French Infectious Diseases Society (French acronym SPILF); National educational association for teaching therapeutics (French acronym APNET); French Society of Internal Medicine (French acronym SNFMI), etc.	Europe	n/a	Tuberculosis	Had a scaled domain score of < 60%
Heidemann, CH. et al.	2016	Danish Health and Medicines Authority and the Danish Society of Otorhinolaryngology, Head and Neck Surgery	Europe	primary health care	Otitis media	No EtD criteria reported

The Scottish Intercollegiate Guidelines Network (SIGN)	2010	The Scottish Intercollegiate Guidelines Network (SIGN)	Europe	Primary and secondary (general practitioners, nurses, paediatricians, pharmacists, otolaryngologists, anaesthetists, public health specialists)	Pharyngitis	Two EtD criteria reported: 1. Values 2. Resource use
World Health Organization (WHO)	2011	World Health Organization (WHO)	International	Resource constrained settings	Tuberculosis	Four EtD criteria reported: 1. Values 2. Resource use 3. Acceptability 4. Feasibility
American Academy of Otolaryngology	2015	American Academy of Otolaryngology	North America	(Primary, secondary and tertiary care) any setting in which an adult with rhinosinusitis would be identified	Sinusitis	Two EtD criteria reported: 1. Values 2. Resource use
Morbidity and Mortality Weekly Report	2009	CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics	North America	These guidelines are intended for use by clinicians and other health-care workers providing medical care for HIV-exposed and HIV-infected children in the United States.	Tuberculosis	Had a scaled domain score of < 60%

Public Health Agency of Canada	2014	Association of Medical Micro- biology and Infectious Disease Canada (AMMI Canada)	North America	Primary and secondary	Tuberculosis	Had a scaled domain score of < 60%
BC Centre for Disease Control	2014	British Columbia Centre for Disease Control (BCCDC)	North America	(Primary care) clinicians and public health professionals regarding care and treatment of STIs in British Columbia	Gonorrhoea	Had a scaled domain score of < 60%
Centres for Disease Control and Prevention	2019	Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America	North America	Primary, secondary and tertiary	Tuberculosis	Had a scaled domain score of < 60%
Infectious Disease Society of America (IDSA)	2011	Infectious Disease Society of America (IDSA)	North America	Secondary and tertiary	Community-acquired pneumonia	Had a scaled domain score of < 60%
The National Institute for Health and Care Excellence (NICE)	2018	The National Institute for Health and Care Excellence (NICE)	Europe	Primary, secondary and tertiary (in primary, secondary or other care settings (for example walk-in-centres, urgent care, and minor ailment schemes)	Pharyngitis	One EtD criteria reported: 1. Resource use

World Health Organization (WHO)	2016	World Health Organization (WHO)	International	low- and middle-income countries	Tuberculosis	Recommendations do not consider resistance
Public Health Agency of Canada (PHAC)	2014	Public Health Agency of Canada (PHAC)	North America	n/a	Gonorrhoea	Had a scaled domain score of < 60%
The National Institute for Health and Care Excellence (NICE)	2019	The National Institute for Health and Care Excellence (NICE)	Europe	Primary care settings (for example walk-in-centres, urgent care, and minor ailment schemes) either by prescription or by any other legal means of supply of medicine (for example patient group direction).	Community-acquired pneumonia	No EtD criteria reported
Centers for Disease Control and Prevention (CDC)	2013	National Institutes of Health, Centers for Disease Control and Prevention, the HIV Medicine Association of the Infectious Diseases Society of America and the Pediatric Infectious Diseases Society	North America	Primary care; high-resource settings	Tuberculosis	One EtD criteria reported: 1. Resource use
Ministry of Health Singapore	2016	Ministry of Health, Singapore	Asia	(primary secondary and tertiary) various (all healthcare practitioners)	Tuberculosis	Had a scaled domain score of < 60%

University of Michigan Health System	2013	Michigan Medicine. University of Michigan	North America	Primary care	Pharyngitis	Had a scaled domain score of < 60%
AHRQ - Agency for Healthcare Research + Quality,	2008	The National Institute for Health and Care Excellence (NICE); National Collaborating Centre for Women's and Children's Health (NCC-WCH)	Europe	Primary care and secondary care setting (including both community and hospital settings).	Otitis media	Three EtD criteria reported: 1. Resource use 2. Acceptability 3. Equity
British Columbia Centre for Excellence in HIV/AIDS	2015	British Columbia Centre for Excellence in HIV/AIDS	North America	Primary care	Tuberculosis	Had a scaled domain score of < 60%
Kawaguchi, R. et al.	2019	Japan Society of Obstetrics and Gynecology (JSOG) and Japan Association of Obstetricians and Gynecologists (JAOG)	Asia	Primary care (gynecological outpatient care.)	Gonorrhoea	Recommendations do not consider resistance
Mandell, L. A. et al.	2007	Infectious Disease Society of America (IDSA)	North America	Emergency medicine physicians, hospitalists, and primary care practitioners	Community-acquired pneumonia	Had a scaled domain score of < 60%
Public Health Ontario	2018	Public Health Ontario (PHO)	North America	Primary care	Gonorrhoea	Unable to provide supplementary materials
Wiersinga, W. J. et al.	2017	The Dutch Working Party on Antibiotic Policy or Stichting	Europe	This guideline is meant for the treatment of adult patients who	Community-acquired pneumonia	Had a scaled domain score of < 60%

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

		Societies of Southern Africa (FIDSSA).				
Chaves NJ. et al.	2016	The Australasian Society for Infectious Diseases (ASID) National Tuberculosis Advisory Committee (NTAC) Royal Australasian College of Physicians (RACP) The Australasian Chapter of Sexual Health Medicine (AChSHM – RACP)	Oceania	Primary, secondary and tertiary intended for healthcare providers who care for people from refugee-like backgrounds, including general practitioners, refugee health nurses, refugee health specialists, Infectious Diseases (ID) physicians	Tuberculosis and gonorrhoea	Had a scaled domain score of < 60%
Chiappini, E. et al.	2013	Italian Society of Preventive and Social Pediatrics	Europe	Primary care (primary care pediatricians and general practice physicians)	Pharyngitis; sinusitis; community acquired pneumonia; otitis media	Had a scaled domain score of < 60%
Di Comite, A. et al.	2016	Italian Pediatric TB Study Group	Europe	primary and secondary care	Tuberculosis	Recommendations do not consider resistance
Jereb, J. A.; Goldberg, S. V.; Powell, K.; Villarino, M. E.; Lobue, P.	2011	Centre for Disease Control and Prevention (CDC)	North America	Primary and secondary care	Tuberculosis	Had a scaled domain score of < 60%
Ricardo de Amorim Corrêa. et al.	2009	Scientific Board and Respiratory Infection Committee of the Brazilian Thoracic Association	South America	Primary and secondary care	Community-acquired pneumonia	Had a scaled domain score of < 60%

Z.A. Memish. et al.	2007	THE GCC CAP WORKING GROUP (GCC-CAPWG)	Asia	Primary and secondary care	Community-acquired pneumonia	Had a scaled domain score of < 60%

Supplemental Table 5S: Number of GRADE Evidence to Decision Frameworks criteria reported in guidelines developed Internationally and regionally

Author	Guideline developer	Year	Focus area	Number of EtD criteria reported	Values	Resource use	Acceptability	Feasibility	Equity
Chow AWB et al.	IDSA	2012	Sinusitis	1	Not reported	Reported	Not reported	Not reported	Not reported
Abdul Rahaman JAK et al.	Malaysian Family Physician	2012	Tuberculosis	2	Reported	Reported	Not reported	Not reported	Not reported
World Health Organization	WHO	2014	Tuberculosis	3	Not reported	Reported	Reported	Reported	Not reported
National Institute for Health and Care Excellence	NICE	2016	Tuberculosis	4	Reported	Reported	Reported	Reported	Not reported
World Health Organization	WHO	2019	Tuberculosis	5	Reported	Reported	Reported	Reported	Reported

British Infection Association	British Thoracic Society	2009	Community-acquired pneumonia	1	Not reported	Reported	Not reported	Not reported	Not reported
Spanish Society for Epidemiology, Spanish Society of Primary Care, Physicians, etc.	Spanish Society for Epidemiology, Spanish Society of Primary Care, Physicians, etc.	2010	Tuberculosis	3	Reported	Reported	Not reported	Reported	Not reported
American Academy of Pediatrics	American Academy of Pediatrics	2013	Otitis media	2	Reported	Reported	Not reported	Not reported	Not reported
National Institute for Health and Clinical Excellence	NICE	2014	Community-acquired pneumonia	2	Reported	Not reported	Not reported	Reported	Not reported
World Health Organization	WHO	2015	Tuberculosis	5	Reported	Reported	Reported	Reported	Reported
Richard M. Rosenfeld et al.	American Academy of Otolaryngology—Head and Neck	2015	Sinusitis	3	Reported	Reported	Reported	Not reported	Not reported

	Surgery Foundation								
World Health Organization	WHO	2015	Tuberculosis	5	Reported	Reported	Reported	Reported	Reported
Richard M. Rosenfeld et al.	American Academy of Otolaryngology—Head and Neck Surgery Foundation	2016	Otitis media	3	Reported	Reported	Reported	Not reported	Not reported
World Health Organization	WHO	2016	Gonorrhoea	5	Reported	Reported	Reported	Reported	Reported
P. Nahid et al.	IDSA	2016	Tuberculosis	0	Not reported	Not reported	Not reported	Not reported	Not reported
Institute for Clinical Systems Improvement	Institute for Clinical Systems Improvement	2017	Pharyngitis and sinusitis	1	Not reported	Reported	Not reported	Not reported	Not reported
Stanford T. Shulman et al.	IDSA	2012	Pharyngitis	1	Not reported	Reported	Not reported	Not reported	Not reported
Ministry of Health Malaysia	Ministry of Health Malaysia	2012	Otitis media	0	Not reported	Not reported	Not reported	Not reported	Not reported

Heidemann CL et al.	Danish Health and Medicines Authority and the Danish Society of Otorhinolaryngology, Head and Neck Surgery	2016	Otitis media	0	Not reported	Not reported	Not reported	Not reported	Not reported
The Scottish Intercollegiate Guidelines Network	SIGN	2010	Pharyngitis	2	Reported	Reported	Not reported	Not reported	Not reported
World Health Organization	WHO	2011	Tuberculosis	4	Reported	Reported	Reported	Reported	Not reported
Richard M. Rosenfeld et al.	American Academy of Otolaryngology	2015	Sinusitis	2	Reported	Reported	Not reported	Not reported	Not reported
World Health Organization	WHO	2018	Tuberculosis	5	Reported	Reported	Reported	Reported	Reported
World Health Organization	WHO	2012	Otitis media	4	Reported	Reported	Reported	Reported	Not reported
The National Institute for Health and Care Excellence	NICE	2018	Pharyngitis	1	Not reported	Reported	Not reported	Not reported	Not reported

The National Institute for Health and Care Excellence	NICE	2019	Community-acquired pneumonia	0	Not reported	Not reported	Not reported	Not reported	Not reported
National Institutes of Health, Centers for Disease Control and Prevention, et al.	NIH, CDC	2013	Tuberculosis	1	Not reported	Reported	Not reported	Not reported	Not reported
The National Institute for Health and Care Excellence; National Collaborating Centre for Women's and Children's Health (NCC-WCH)	NICE, NCC-WCH	2008	Otitis media	3	Not reported	Reported	Reported	Not reported	Reported
United States Preventative Task Force	USPTF	2019	Gonorrhoea	2	Not reported	Not reported	Not reported	Reported	Reported