Systematic review

What is the evidence base of used aggregated antibiotic resistance percentages to change empirical antibiotic treatment? A scoping review

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ABSTRACT

Objectives: Antibiotic resistance requires continuous monitoring by experts to decide whether empirical antibiotic therapies (EATs) should be replaced by alternative antibiotics. The exact moment and criteria for this change are unclear and generally based on consensus between experts. This scoping review aims to identify from the literature the resistance thresholds used for a change in EAT and the criteria on which they are based.

Methods: Scoping review for which a comprehensive structured literature search was conducted. Rayyan, software for systematic reviews, was used for the screening of abstracts and titles. Data sources were Pubmed and a hand-search of reference lists and grey literature. Papers were eligible if they concerned any type of bacterial infectious disease and mentioned or defined antibiotic resistance thresholds for decision-making purposes for EAT. The inclusion and analysis of articles was done by two researchers; any conflicts were resolved through discussion or by consulting a third reviewer.

Results: We identified 3146 unique papers. Following title/abstract screening, 125 papers were comprehensively read, and 16 papers were included. The included papers gave thresholds for urinary tract infections, respiratory tract infections, meningitis, skin and soft tissue infections, gonorrhoea, and bone and joint infections. Six criteria were found that were commonly used to base the thresholds on. These were: disease severity, efficacy of treatment, adverse drug events, risk of *Clostridioides difficile* infection, costs, and increased resistance. The number of criteria used to define each threshold varied from one to six between papers.

Conclusions: The thresholds used for EATs are few, commonly based on expert opinion estimates, and can therefore have broad ranges. Used criteria underlying reported thresholds are heterogenous and require standardization. Considering the rising trend in resistance, there is a clear need for rigid tools to determine thresholds in order to support guideline development with the best and timely evidence.
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Introduction

One major challenge in the field of medical microbiology and infectious diseases is antibiotic resistance (ABR). Most infections requiring antibiotic therapy are treated empirically with antibiotics covering the likely causative pathogens of the infection before laboratory results (if any) are known. Empirical antibiotic treatment (EAT) should be effective against the majority of microorganisms causing infections. If the causative pathogen is resistant to the administered EAT, the infection may progress and lead to a lengthened hospital stay and an increase in morbidity and mortality. If microbiological testing is done, the EAT can be switched and directed towards the detected pathogen (directed therapy) in individual patient care. At an aggregated (e.g. regional or national) level, resistance data are continuously monitored to verify whether local or national selected EATs for specific infectious disease syndromes are still appropriate. Recommendations for EATs are published in local and (inter)national guidelines, using available evidence and expert consensus. Recommendations are usually based on several criteria, including epidemiology and the susceptibilities of the causative organisms, efficacy of antibiotic options, disease severity, adverse drug events, and costs [1–3].

Infectious diseases are dynamic, and resistance levels change over time, possibly requiring regular changes in EAT recommendations. The optimal timing of such epidemiologically based adjustments is unknown and depends on the judgement of guideline committees who should monitor whether their recommendations are still valid. Clear guidance and tools are needed for these committees to ensure that empirical choices are optimal and timely. We need a definition of an antibiotic-resistance threshold in surveillance data above which EAT recommendations should be adjusted for specific infections. Although thresholds are used, consensus is lacking concerning their objective determination. As a result, EAT adjustment might be initiated too late, or experts might arrive at different recommendations.

This study presents a systematic scoping review of the existing literature on the use and estimation of resistance thresholds used for EAT recommendations, if any. It describes the thresholds that are applied for various infectious diseases, as well as the evidence on which they are based and the criteria that are used to determine them. The insights generated by this review could contribute to the improvement and standardization of selecting the most optimal EAT.

Methods

This scoping review follows in part the guidelines of the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement for the search strategy [4], Prospero ID: CRD42020147888.

Information sources and search strategy

The MEDLINE database was screened for articles published between 1st January 1976 and 3rd May 2021 using a search strategy combining terms relating to "antibiotic or antibacterial agents", "bacterial infections", and "thresholds, level, or rates". The full list of search terms is presented in the Supplementary Material. References were processed using Endnote x9 (Clarivate Analytics, Philadelphia, Pennsylvania, USA). The references of full-text articles were searched manually for additional potential studies. For articles not available online, they were obtained by contacting the authors.

Eligibility criteria

The review considered published articles that (a) concerned any type of bacterial infectious disease syndrome (IDS) and (b) mentioned or defined resistance thresholds/levels for decision-making purposes for empirical antibiotic treatment. If an abstract suggested that the article contained data on thresholds, the paper was included for full-text screening. Studies were included after full-text screening if they (a) were written in English, (b) were published in full, and (c) defined the threshold through expert consensus or other means (e.g. modelling studies). The eligibility criteria were intentionally broad in order to maximize the sensitivity of the search, given the expected paucity of available literature on the subject. A manual search was conducted of grey literature (e.g. guidelines mentioning ABR thresholds), and relevant sources were included. A manual search was also conducted of antibiotic policy documents regarding IDS (e.g. urinary tract infections (UTIs), bacterial respiratory tract infections (RTIs), bacterial meningitis, bacterial skin and soft tissue infections (SSTIs)). Infections for which the primary intervention was not antibiotic treatment and for which antibiotics were supportive (e.g. abscess, cholecystitis) were not considered. As a prerequisite, policy documents were required to have been compiled by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), the Infectious Diseases Society of America (IDSA), or other prominent international guideline-makers. National guidelines were not considered.

Study selection

Study selection was performed using Rayyan (http://rayyan.qcri.org/), and all duplicates and non-English studies were excluded. The titles and abstracts of all records were screened independently by two reviewers (AMA and MS) to asses full-text eligibility. Disagreements were resolved by involving a third reviewer (HFLW).

Assessment of study quality

Study quality was assessed independently by two reviewers (AMA and MS) using various tools developed by the Critical Appraisals Skills Program (CASP). Disagreements were discussed in meetings and, if not resolved, a third reviewer was involved (HFLW).

Data extraction

Data were extracted independently by two reviewers (AMA and MS), and all results were cross-checked. The data extracted by the two reviewers contained descriptive data such as study characteristics. The data concerning the threshold were categorized as follows: the threshold, the evidence base, IDS/pathogens, antibiotics, and criteria used.

Results

The inclusion and exclusion processes are presented in Fig. 1. Of 3146 unique papers identified in the initial database search, 112 met the criteria for full-text review, and six defined thresholds and were included for the review. In addition, 13 guidelines on various infections were screened: UTIs (uncomplicated (uUTI) and complicated (cUTI) (*n* = 2) [3,5], RTIs (*n* = 4) [1,6–8], bacterial meningitis (*n* = 3) [9–11], SSTIs (*n* = 2) [12,13], prosthetic joint infections (*n* = 1) [14], and sepsis (*n* = 1) [15]. Four guidelines mentioned thresholds and were included [1,3,5,6]. References of
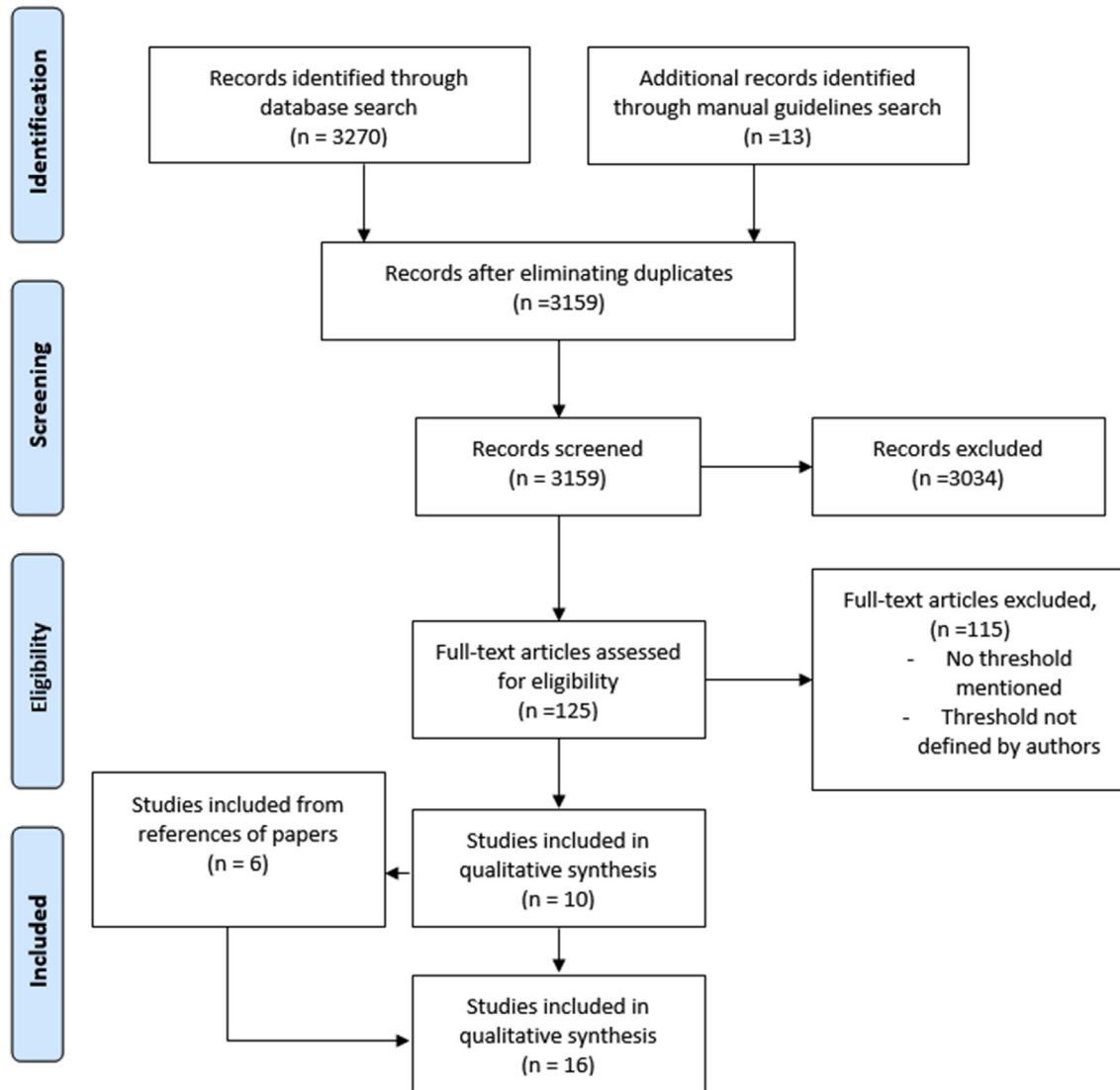
Fig. 1. Flow chart showing the inclusion and exclusion processes.

eligible papers identified an additional six papers that defined thresholds and were included.

The 16 papers that were included yielded a total of 19 thresholds, four of which concerned the same threshold and were excluded. We thus identified 16 unique thresholds for the following syndromes: UTI (*n* = 8) [2,3,5,16–20], RTI (*n* = 3) [1,6,21], meningitis (*n* = 1) [22], SSTI (*n* = 1) [23], bone and joint infections (*n* = 2) [24,25], and gonorrhoea (*n* = 1) [26] (Table 1).

Urinary tract infections

Thresholds in guidelines and review

For UTIs thresholds were determined for two antibiotics: cotrimoxazole and ciprofloxacin. The IDSA guideline recommends cotrimoxazole if resistance among *Escherichia coli* strains causing uUTI is <20% [3]. This threshold was first defined in 1999 [2] and based on expert opinion, taking clinical studies into account [27–30]. The 2010 updated IDSA guideline adds a >10% ciprofloxacin threshold for complicated UTI, although no scientific evidence for this threshold is provided.

The 2018 European Agency for Urology (EAU) guideline recommends the same thresholds of 20% (uUTI) for cotrimoxazole and 10% (cUTI) for fluoroquinolones (FQs) for empirical treatment [15]. The same thresholds are mentioned in a 2020 review [20].

Cost-effectiveness studies to determine thresholds

Four cost-effectiveness studies pertained to UTIs. Although the thresholds vary, all studies define thresholds for cotrimoxazole or FQs, and all use similar methodologies (Supplementary Material).

In 2001, Le et al. found that FQ is more cost-effective when cotrimoxazole resistance in *E. coli* exceeds 22% [16], based primarily on the cure rates for cotrimoxazole and FQ. Perfetto et al. performed a similar study in 2004, considering several case scenarios with varying resistance rates for ciprofloxacin and cotrimoxazole in *E. coli* isolates. If the cotrimoxazole resistance rate exceeded 4.3%, ciprofloxacin was more cost-effective at the resistance rate of 1% for ciprofloxacin in *E. coli*. The resistance rate of ciprofloxacin had a significant impact on the variation of the threshold, as the threshold for switching to ciprofloxacin became 13.3% when a resistance rate of 10% was applied for ciprofloxacin [18]. In a 2007

Table 1
Characteristics of articles and thresholds defined

Author	Year	Infectious disease syndrome	Document type	Antibiotics	Bacteria	Threshold	Comments
Warren et al. [2]	1999	UTI	IDSA Guideline	Cotrimoxazole/ trimethoprim	E. coli	Cotrimoxazole/trimethoprim threshold of 10% or 20% indicates switch to FQ	Recommendation based on expert opinion
Le TP et al. [16]	2001	UTI	Cost minimization and sensitivity analysis	Cotrimoxazole and fluoroquinolones.	E. coli	Cotrimoxazole threshold of 22% indicates switch to FQ	Modelling study. Fluid threshold, changing according to FQ resistance and cure rates
Bonkat G et al. [5]	2018	UTI	EAU guideline	Cotrimoxazole, fluoroquinolones	Uropathogens	Uncomplicated UTI: cotrimoxazole 20% Pyelonephritis: FQ resistance 10%	Recommendation based on expert opinion.
Perfetto E et al. [18]	2004	UTI	Cost minimization	Cotrimoxazole	E. coli	Depending on FQ resistance, 1% FQ resistance equals threshold of 4.3%; 10% FQ resistance equals threshold of 13.3%	Modeling study. Recommendations according to IDSA guidelines are cost-effective
Gupta K et al. [3]	2011	UTI	IDSA Guideline	Cotrimoxazole/ trimethoprim	E. coli	Cotrimoxazole/trimethoprim threshold of 20% indicates switch to FQ	Recommendation based on expert opinion
McKinnell JA et al. [17]	2011	UTI	Cost minimization and sensitivity analysis	Nitrofurantoin, cotrimoxazole, ciprofloxacin	E. coli	Switch to nitrofurantoin: 17% (cotrimoxazole), 12% (ciprofloxacin) Switch from cotrimoxazole to ciprofloxacin: 10%	Emphasizes 2011 IDSA guideline decision to use nitrofurantoin as first-line drug in many communities
Sadler S et al. [19]	2017	UTI	Cost-effectiveness	Trimethoprim, fosfomycin, nitrofurantoin	E. coli	Trimethoprim 30% fosfomycin becomes cost-effective At a trimethoprim threshold of 35%, both fosfomycin and nitrofurantoin become cost-effective	Modelling study
Bader et al. [20]	2020	UTI	Review	Cotrimoxazole, fluoroquinolones	Uropathogens	Cotrimoxazole threshold of 20% in uUTI, FQ resistance 10% in cUTI	Recommendation based on expert opinion
Mandell LA et al. [6]	2007	RTI/CAP	IDSA and ATS Consensus guideline	Macrolides	S. pneumoniae	Macrolide-resistant Streptococcus pneumoniae threshold of 25%	Recommendation based on expert opinion
Kalil et al. [1]	2016	RTI/HAP/VAP	IDSA and ATS Consensus guideline	Antibiotics with activity against MRSA Anti-pseudomonal antibiotics	MRSA P. aeruginosa	HAP: MRSA prevalence >20% or unknown VAP: MRSA prevalence >10−20% or unknown, anti-MRSA antibiotic should be considered Prevalence of Gram-negative isolates resistant to the agent being considered for monotherapy >10% or unknown, two anti-pseudomonal antibiotics from different classes should be considered	Recommendation based on expert opinion
Babela RT et al. [21]	2017	RTI/Sinusitis	Cost minimization and sensitivity analysis	Macrolides	S. pneumoniae	Macrolide resistant Streptococcus pneumoniae threshold of 13.8%	Modelling study
Kaplan SL [23]	2005	CA-MRSA	Review	Antibiotics with activity against MRSA	MRSA	MRSA prevalence of 10−15%	Recommendation based on expert opinion
Bradley JS et al. [22]	1997	Meningitis	Review	Cephalosporins	S. pneumoniae	Complete penicillin resistance combined with >5% cephalosporin resistance or unknown resistance prevalence, then vancomycin or rifampicin should be added to empirical treatment	Recommendation based on expert opinion
WHO [26]	2012	Gonorrhoeae	WHO global action plan to control the spread and impact of antimicrobial resistance in Neisseria gonorrhoeae	Ceftriaxone	N. gonorrhoeae	If proportion of tested samples is 5% or more, steps should be taken to review and modify the national guidelines for STI treatment and management	Recommendation based on expert opinion
Nada et al. [24]	2014	Osteomyelitis in children	Review	Anti-staphylococcal penicillin or cefazolin Clindamycin	CA-MRSA	≥10% CA-MRSA, switch to vancomycin or clindamycin (only when clindamycin resistance ≤25%)	Recommendation based on expert opinion
Saavedra-Lozano et al. [25]	2017	Bone and joint infections in children	European Society for Paediatric Infectious Diseases guideline	Anti-staphylococcal penicillin or cefazolin	CA-MRSA	≥10−15% CA-MRSA switch to empirical therapy that includes this pathogen	Recommendation based on expert opinion

UTI, urinary tract infection; EAU, European Agency for Urology; IDSA, Infectious Diseases Society of America; RTI, respiratory tract infection; CAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia; FQ, fluoroquinolone; CA-MRSA, community-acquired methicillin-resistant Staphylococcus aureus; STI, sexually transmitted infection.

cost-effectiveness study comparing nitrofurantoin and FQ, McKinnell et al. demonstrated that the EAT with nitrofurantoin is more cost-effective when the prevalence of FQ-resistant *E. coli* exceeds 12% [17]. Both studies were performed in the USA.

In a 2017 cost-effectiveness study for cystitis comparing trimethoprim, fosfomycin, pivmecillinam, and nitrofurantoin in a UK setting, Sadler et al. found that fosfomycin became more cost-effective when the prevalence of trimethoprim-resistant *E. coli* exceeded 30%, with nitrofurantoin becoming cost-effective when the prevalence of trimethoprim-resistant *E. coli* exceeds 35% [19].

Respiratory tract infections

Thresholds in guidelines

The joint consensus guidelines of the American Thoracic Community and IDSA recommend thresholds for community-acquired pneumonia (CAP, 2007), and for hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP, 2016). The resistance threshold of 25% for macrolide-resistant *Streptococcus pneumoniae* was defined, likely based on expert opinion, for CAP in outpatient settings, specifically for high-level macrolide resistance (MIC ≥16). The use of macrolides for the treatment of CAP is discouraged above this threshold [6].

In hospital settings, thresholds have been defined for methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* for HAP and VAP. The threshold for MRSA prevalence in HAP is set at 20%, above which the EAT should be changed to an agent with activity against MRSA [1].

The published VAP threshold for MRSA is broad (10–20%) as compared to that for HAP, above which it is advised to change to an antibiotic with activity against MRSA [1]. Similarly, a threshold is recommended for the EAT in VAP regarding Gram-negative microorganisms, using *P. aeruginosa* as a proxy. When the prevalence of Gram-negative bacteria with resistance to an agent rises more than 10% in ICU settings, the EAT should be changed to a treatment containing two antibiotics from different classes with activity against *P. aeruginosa* [1].

For all HAP and VAP recommendations, the EAT should be changed when the prevalence is unknown or when the patient has risk factors for antibiotic resistance. However, more concrete tools are needed to do this. The reasoning behind the lower threshold for Gram-negatives is that they are more frequently implicated in VAP than are Gram-positives.

All three of these thresholds are based on low-grade evidence (i.e. expert opinion) involving a compromise between appropriate antibiotic coverage and avoidance of superfluous treatment, potentially leading to undesirable effects [1].

Cost-effectiveness study to determine thresholds

One cost-effectiveness study was found regarding ABR thresholds in RTI (Supplementary Material). In this 2017 study, Babela et al. compared oral cephalosporins and macrolides for the treatment of *S. pneumoniae* in rhinosinusitis, describing the ABR threshold of 13.8% prevalence of macrolide-resistant *S. pneumoniae* for rhinosinusitis. Above this threshold, treatment with cephalosporins was more cost-effective [21]. The threshold of 13.8% is subject to change in a manner similar to that reported in the previous cost-effectiveness studies. Similar to the previous cost-effectiveness studies, the following criteria were considered: cost, antibiotic coverage, and treatment efficacy.

Meningitis

In a 1997 review on meningitis, Bradley et al. discussed the treatment options that were current at that time, including a

suggestion for a resistance threshold for meningitis [22]. The threshold for meningitis cases in communities with complete penicillin resistance in *S. pneumoniae* combined with intermediate or complete resistance to ceftriaxone or cefotaxime was set at >5%, although the exact criteria are unclear. The authors state that either vancomycin or rifampicin should be added to the EAT when resistance exceeds the threshold. The threshold appears to be based on *in vitro* studies and expert opinion [22]. The fact that this threshold is lower than those for UTI and HAP is likely due to the severity of the disease and risk of mortality in case of EAT mismatch.

Gonorrhoea

In its global action plan concerning the spread and impact of antimicrobial resistance in *Neisseria gonorrhoeae* (2012), the WHO states that a 5% resistance to cephalosporins warrants a change in treatment guidelines and more intensive surveillance. They further state that a sudden and unexpected increase in key population groups (e.g. sex workers, men who have sex with men) where the disease is more prevalent is also a trigger for change, even if resistance remains below the 5% threshold [26].

Community-acquired MRSA (CA-MRSA) infections

For SSTIs, a threshold of 10–15% prevalence of CA-MRSA was determined by expert opinion [23]. Above this threshold, clindamycin or cotrimoxazole is recommended for suspected CA-MRSA SSTI. Local clindamycin and cotrimoxazole resistance levels should allow for this. The same threshold is applied to the prevalence of clindamycin resistance in CA-MRSA, recommending to not use clindamycin above this threshold.

The 2017 guideline of the European Society for Paediatric Diseases advise a threshold of 10–15% for CA-MRSA for bone and joint infections in children. Nada et al. advise a threshold of 10% for CA-MRSA in children with osteomyelitis. They also advise using clindamycin only when the resistance to this antibiotic is ≤ 25%. These thresholds are based on expert opinion, with weak supporting evidence.

Criteria for thresholds

Seven criteria for thresholds were considered by various papers: efficacy, antibiotic coverage, disease severity, increase in ABR, adverse drug events, risk of *Clostridioides difficile* infections, and cost (see Table 2). One paper contained three different thresholds, which we assessed separately [1]. The cotrimoxazole threshold of 20% for UTIs was based on expert opinion (1999 IDSA guidelines) and used in both the updated 2011 guidelines and the subsequently published EAU guidelines. We treated them as identical, because they use the same criteria.

The majority of the papers (8/12) mentioned three or fewer criteria. No papers used all the criteria identified. The most prevalent criterion was antibiotic coverage (11/13 thresholds), followed by cost (8/13), efficacy (6/13), disease severity (6/13), increase in ABR (5/13), adverse drug events (5/13), and *C. difficile* infections. The number and type of criteria used to define thresholds were quite heterogenous, even when defined for the same infection and antibiotic combination.

Discussion

This scoping review systematically reports on the literature on antibiotic resistance thresholds that should trigger a change in EAT recommendations. In general, the evidence base is weak. Most thresholds (n = 11) were found in expert opinion/consensus-based

Table 2
Overview of criteria used to define thresholds

Source	Threshold	Criteria used[a]					
		Efficacy[b]	Disease severity	Increase in ABR[c]	Adverse drug event	C. difficile	Costs
IDSA guidelines 1999 [2], 2011 [3], EAU guideline 2018 [5], Bader et al. [31]	Cotrimoxazole (UTI) > 20%	Yes	Yes	Yes	Yes	Not mentioned	Not mentioned
IDSA guidelines 2011 [3], EAU guideline 2018 [5], Bader et al. [20]	Ciprofloxacin (UTI) > 10%	Yes	Yes	Yes	Not mentioned	Not mentioned	Not mentioned
Le et al. [16]	Cotrimoxazole (UTI) > 22%	Yes	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Yes
Perfetto et al. [18]	Cotrimoxazole (UTI) > 4.3%	Yes	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Yes
McKinnell et al. [17]	Cotrimoxazole (UTI) > 10%	Yes	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Yes
Sadler et al. [19]	Trimethoprim (UTI) > 30%	Yes	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Yes
IDSA and ATS consensus guideline CAP 2007 [6]	Macrolides (CAP) > 25%	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
IDSA and ATS consensus guideline HAP/VAP 2016 [1]	MRSA (HAP) > 20%	Not mentioned	Yes	Yes	Yes	Yes	Yes
IDSA and ATS consensus guideline HAP/VAP 2016 [1]	MRSA (VAP) > 10–20%	Not mentioned	Yes	Yes	Yes	Yes	Yes
IDSA and ATS consensus guideline VAP 2016 [1]	Gram-negatives (VAP) > 10%	Not mentioned	Yes	Yes	Yes	Yes	Yes
Babela et al. [21]	Macrolides (rhinosinusitis) > 13.8%	Yes	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Yes
Kaplan et al. [23]	MRSA (SSTI) > 10–15%	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Bradley et al. [22]	Cephalosporins (meningitis) > 5%	Not mentioned	Yes	Not mentioned	Not mentioned	Not mentioned	Not mentioned
WHO [26]	Ceftriaxone (gonorrhoea) 5%	Yes	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Nada et al. [24]	Anti-staphylococcal penicillin/ cefazolin (CA-MRSA) 10%	Yes	Not mentioned	Not mentioned	Yes	Not mentioned	Not mentioned
Saavedra-Lozano et al. [25]	Anti-staphylococcal penicillin/ cefazolin (CA-MRSA) 10–15%	Yes	Yes	Not mentioned	Not mentioned	Not mentioned	Not mentioned

ABR, antibiotic resistance; UTI, urinary tract infection; CAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia; CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*; SSTI, skin and soft tissue infection.
[a] Only criteria explicitly mentioned in the text.
[b] Efficacy: the maximum response that can be achieved with a drug or treatment.
[c] Increase in ABR: the potential impact on antibiotic resistance associated with the use of the selected antibiotic treatment.

papers, consisting largely of various antibiotic policy documents, with high variation in the number of criteria considered. No clinical trials assessing thresholds were found. Just five cost-effectiveness modelling studies defined thresholds and were the most scientific approaches we were able to find. However, in contrast to the expert-opinion-based papers, the modelling studies considered only cost, efficacy, and antibiotic coverage, in line with their methodology. Antibiotic coverage is, nevertheless, self-evident and actually a prerequisite. Efficacy of any alternative empirical choice would be more relevant. If the coverage is sufficient but efficacy inferior for other reasons, this needs to be weighed against the reduction in efficacy due to resistance.

The heterogeneity in the criteria used in the different papers posed a problem when comparing thresholds. The criteria that experts considered for their thresholds were: disease severity, antibiotic coverage, efficacy of treatment (cure and failure rates), adverse drug events (e.g. allergies), risk of *C. difficile* infection, costs, and increased resistance. The use of these criteria varied between papers, even concerning the same IDS/threshold combination, thus complicating the comparison of these thresholds for a given IDS. The question is raised whether thresholds for the same IDS would have differed if the different authors had considered the same criteria. Uniformity in the use of criteria is thus essential when determining thresholds for common syndromes and commonly used antibiotics to ensure that thresholds are defined uniformly.

Disease severity is an important criterion for determining thresholds: the greater the severity the lower the threshold. In severe disease the consequences of treatment failure are greater. This is confirmed by the observations that thresholds are higher for non-severe diseases like cystitis (20% for cotrimoxazole), decreasing for more severe illnesses like pyelonephritis/cUTI (10% for ciprofloxacin) and meningitis (5% for ceftriaxone). The low threshold of 5% for *N. gonorrhoeae* could be explained by the high communicability of this specific pathogen in certain populations (or subpopulations), instead of the disease severity; a considerable public health problem is another key criterion. It should be noted that multi-resistant pathogens like *N. gonorrhoeae* generally have few alternative options.

More than half of the thresholds identified were for UTI as UTIs are common and sufficient surveillance data are available. Of all thresholds identified in this review, the threshold for cotrimoxazole has the most solid evidence base in clinical studies [3,5,31], in which the clinical failure rate in the group with resistance to cotrimoxazole was relatively high (40–50%). These studies demonstrated that when cotrimoxazole resistance is 10–15%, cure rates of cotrimoxazole EAT are comparable to EAT with ciprofloxacin or nitrofurantoin [22,27–29].

The role of MICs in the definition of thresholds needs more consideration. The 25% threshold for high-level macrolide resistance in *S. pneumoniae* (MIC ≥ 16 μg/mL) was defined through expert opinion with no explicit mention of criteria (see Table 2) [6]. The effect of low-level resistance (MIC of 1–8 μg/mL) was not considered. In a 2019 theoretical modelling study of low-level resistance [32], Daneman et al. argue that some studies have called the difference in clinical failure rate between high-level and low-level macrolide resistance into question [33]. In addition, when the resistance rate of high-level and low-level macrolide resistance are combined for *S. pneumoniae*, they could exceed the 25%

Fig. 2. Recommendations to consider when defining thresholds.

threshold defined in the guideline. Therefore, the 'hidden' clinical failures due to low-level macrolide resistance should also be considered when determining resistance thresholds. Moreover, clinical breakpoints and the definition of susceptibility/resistance could potentially be different when using different sources (European Committee on Antimicrobial Susceptibility Testing (EUCAST) or National Committee for Clinical Laboratory Standards (NCCLS)).

Preferably, thresholds should be well-defined and as accurate as possible. The 10−20% for MRSA in VAP is rather broad, and it is unclear in which scenarios the threshold of 10% versus 20% should be applied [5]. The threshold for MRSA and Gram-negatives in VAP patients is important, given the severity of the infection and the potentially substantial impact of a poor EAT choice on mortality. Broad thresholds are a challenge to implement; more precise estimates for various syndromes and settings are needed to really improve patient outcomes. For individual patient care you need 'wiggle room' to decide on antibiotic change. However, on a population level and for guideline development to decide on empirical antibiotic choice, this is should be as precise as possible.

Considering the above, we propose considering a composite resistance threshold that covers the most common pathogens and their susceptibilities for specific infections with known efficacies of various antibiotic treatments. The context surrounding a threshold becomes complete when a clear recommendation is given for one or more alternative antibiotics, based on a clear set of criteria. Any threshold and EAT recommendation should include de-escalation indications for when the antibiogram becomes available. A small set of recommendations for antibiotic policymakers to consider when defining thresholds, based on our review, is presented in Fig. 2.

In conclusion, EAT thresholds are sparse while there is a multitude of infectious disease syndromes. Most thresholds are based on weak evidence, if any at all, and are usually based on expert opinion drawing on heterogeneous set of criteria. Considering the rising trend in antibiotic resistance, there is a clear need to provide tools for determining thresholds to support guideline development. We propose developing a systematic multidisciplinary approach to determine various thresholds for various classes of antibiotics for a range of prioritized IDSs. This approach should be supported by high-quality clinical datasets on ABR and surveillance at the local, national, and international levels. The need for well-defined thresholds suggests the importance of epidemiological and clinical surveillance of ABR [34].

Author contributions

AA: methodology, investigation, drafting of the manuscript. MS: investigation, approval of the manuscript. ET, JR-B and AV: funding acquisition, supervision, editing and approval of manuscript. MH and EA: methodology, supervision, editing and approval of manuscript. HW: conceptualization, methodology, investigation, supervision, drafting, editing and approval of the manuscript.

Transparency declaration

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2021.12.003.

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