Public consultation on the draft WHO Essential Medicines List Antibiotic Book

RESPONSES TO COMMENTS RECEIVED DURING THE PUBLIC CONSULTATION PERIOD 18 NOVEMBER 2021 TO 30 JANUARY 2022

This document is a summary of the responses received from all contributors during the online consultation on the draft text on *The WHO Essential Medicines List Antibiotic Book* and is being made available for the purpose of transparency. The views expressed in this document are those of the contributors concerned and do not in any way represent the views, decisions or policies of the World Health Organization.

Comments may be considered by WHO in the revision and finalization of the publication and infographics, but WHO makes no guarantee that the comments will be included in the final published materials.

Preamble

A draft of the WHO Essential Medicines List Antibiotic Book was published online for public consultation from 18 November 2021 to 30 January 2022. During this time, comments were received from more than 30 contributors. All comments received during the consultation period have been reviewed and considered. This document provides the responses to the comments received and outlines the changes that were made to the Book as a result of the consultation process.

We thank all contributors for having taken the time to review the draft and for providing their considered comments, feedback, and suggestions.

Responses to the comments received were initially reviewed and elaborated by Dr Veronica Zanichelli (WHO consultant), Dr Benedikt Huttner (Team Lead, WHO Essential Medicines Team) and Prof Mike Sharland (Chair, EML Antimicrobial Working Group), and were thereafter discussed and finalized by the WHO EML Antimicrobial Working Group, and WHO staff members in the EML team and AMR division.

Please note that the text presented here reflects the first edition of the Book (available at https://www.who.int/publications/i/item/9789240062382). Later versions of the Book might have different text.

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1 General

Comment: *"It would be important to include a short section on antimicrobial stewardship and then signpost to the two WHO AMS documents – policy guidance and toolkit. At the very least, consider mentioning the importance of surveillance for antimicrobial use, assessment of appropriate use and implementation of relevant guidelines, or perhaps a summary of the key aspects within the handbook where it has for example stated "from an antibiotic stewardship perspective".*

(UK Health Security Agency)

Comment: *"Further guidance is given on how the Handbook could be used to improve the use of antibiotics based on general antibiotic stewardship principles" is an example of a statement that can be confusion as there is e.g. no WHO antibiotic stewardship principles and the document has not summarised what it means by antibiotic stewardship principles.*

(UK Health Security Agency)

Response: Further elaboration of antibiotic stewardship principles is needed and is an important area of future work. The sentence (page 3, lines 62-63) has been replaced with the following:

"General antibiotic stewardship principles have been included throughout all the AWaRe Book. These include guidance on a risk-based prescribing approach with the no antibiotic care option, short standard durations across infections, rapid oral step down from intravenous antibiotics and standardized dosing to improve medicine purchasing and program delivery".

Comment: *"Colouring of the AWaRe categories in RAG (i.e., red, amber and green) on the infographics has real potential for error given that we routinely use this colour code to apply to safe use of antibiotics in allergy. There are real safety implications with someone misunderstanding this so would suggest they choose other colours."*

(British Society for Antimicrobial Chemotherapy)

Response: This comment refers to the AWaRe colour codes used throughout the Book and in the infographics. Each time these colours are present in the Book a legend is also present to clarify their meaning. The AWaRe Book is intended for an international audience, and it is probably not possible to avoid overlap with other colour coding schemes, but the traffic light approach is probably the most widely used and understandable. The colour coding is intended to sensitive prescribers against the overuse and inappropriate use of Watch and Reserve antibiotics.

Comment: *"The colour coding is a great idea and could be incorporated in the app version using a traditional red-yellow-green traffic light icon known across the world"*

(Prof J. Conly, Department of Medicine (Infectious Diseases), Cumming School of Medicine, University of Calgary and Alberta Health Services)

Comment: *"Would add the AWARe colour coding to the Infographics so text and infographics match re the AWARe categories"*

(Prof J. Conly, Department of Medicine (Infectious Diseases), Cumming School of Medicine, University of Calgary and Alberta Health Services)

Response: The AWaRe colour coding for antibiotics (Green-Access, Orange-Watch and Red-Reserve) is applied to all contents of the AWaRe Book including the infographics.

In the Book, antibiotics are highlighted using the corresponding AWaRe colour e,g, Amoxicillin (Green=Access). In the infographics, with an AWaRe colour-coded pill beside the name of the antibiotic:

Comment: *"Need to make users aware to check local susceptibility patterns where available"*

(Prof J. Conly, Department of Medicine (Infectious Diseases), Cumming School of Medicine, University of Calgary and Alberta Health Services)

Response: The need to consider the local epidemiology has been stressed throughout the AWaRe Book as an important thing to consider especially for infections that could be caused by resistant Gram-negative bacteria or methicillin-resistant *Staphylococcus aureus* but also for infections such as enteric fever where the risk of resistance to first line treatments is particularly high in certain settings.

Comment: "Suggest adding an appendix on HOW TO INTERPRET AN ANTIBIOGRAM. In some instances where cultures may have been obtained, clinicians may not appreciate that sensitivity to an antibiotic does not automatically mean it is the drug of choice. There may also be a need to introduce the concept of how antibiograms indicate multi drug resistance and emphasize that such patterns require specialist consult."

(Dr Anna Ong-Lim, Chief division of infectious and tropical disease in pediatrics, Philippine general hospital)

Response: Giving guidance on how to interpret an antibiogram is something that could be considered as an addition for future updates of the AWaRe Book. It was not included in this version since the key focus of the Book is to provide guidance on empiric and not targeted treatment.

Comment: *"I suggest inserting a table with antibiotic classes, their spectrum and common/severe drug interactions."*

(Dr Mireille A. Mpalang Kakubu, University of Pittsburgh (USA) and Ministry of health and social services of Namibia)

Response: For now, this is outside the scope of the AWaRe Book, but it may be reconsidered in the future.

Comment: *"While I recognize that this will broaden the scope of this document significantly, further iterations could consider changing to "antimicrobials" rather than "antibiotics" and including antiviral and antifungal agents. This might not be approbated for this version as would involve a significant amount of work but will be much more comprehensive. These agents are also not always used appropriately and can also contribute to burden of resistance globally."*

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Response: Covering antiviral and antifungal treatment is beyond the scope of this current AWaRe Book which is focused on antibiotics in the WHO Essential Medicines Lists and the AWaRe classification. Extension to antimicrobials other than antibiotics may, however, be considered in the future.

Comment: *"Did not see some agents eg the pleuromutilins so may need indicate some Abs not included and similarly other newer oxazolidinones and quinolones etc so some mention not meant to be completely comprehensive."*

(Prof J. Conly, Department of Medicine (Infectious Diseases), Cumming School of Medicine, University of Calgary and Alberta Health Services)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the Book (including adding new alternative antibiotic options such as pleuromutilins, newer oxazolidinones and fluoroquinolones) would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process).

Comment: *"INTRO For Table 3 line 178 for patients - should include information about discarding used medications (if they have old meds at home for some reason) safely (in other words don't dump on the street, feed to animals, put into water system)."*

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Response: The following text has been added to Table 3 in the Introduction (page 11 of the draft version) to address this aspect, as suggested.

Return any expired, unwanted or unused antibiotic to a pharmacy or health centre for safe disposal.

Comment: *"Is the handbook intended for both LMICs and HICs or it primarily focused for LMICs? Please clarify in the document."*

(Commonwealth pharmacists association)

Response: While recognising that many countries, especially high-income countries, already have guidance, page 1 of the Introduction (draft version) notes that the AWaRe book *"is intended for all health care workers who prescribe and dispense antibiotics in high-, middle- and low-income settings in both the primary health care and the facility/hospital setting."* There is no specific reason why the guidance provided in this Book should be applicable only to specific countries.

Comment: *"Whilst this information added to the introduction is GREAT, it would be important to promote widely and also include in the introduction "The WHO EML antibiotic book is not intended to replace local or national guidelines but rather to supplement gaps in existing guidance documents and provide a resource for adaptation of guidance documents in line with WHO's AWaRe classification".*

It will be essential to mention that the handbook is not a substitute for the already established national guidelines but can be used to support any gaps or needs."

(Commonwealth pharmacists association)

Response: This aspect is mentioned in the Introduction (page 1, lines 15-17 of the draft version) as follows: *"The AWaRe Book is not intended to replace existing local and national antibiotic prescribing guidelines and clinical judgment, but to provide simple guidance where currently none is available."*

Comment: *"We were surprised that the commonly used term by WHO and several countries "antimicrobial stewardship" was not used; rather antibiotic stewardship. We wonder if this increases the risk of confusion and non-specialist colleagues believing that antibiotic stewardship requires different approaches to those recommend through antimicrobial stewardship. One alternative would be to include a statement at the start which explains AMS and then state for the purposes of this handbook will call it antibiotic stewardship. Preferred option is to use the broader term AMS."*

(Commonwealth pharmacists association)

Comment: *"The formal term for stewardship used by WHO and several countries is antimicrobial stewardship (AMS); we believe it would be important that the same term is used within the handbook rather than antibiotic stewardship. This would reduce the risk of confusion and non-specialist colleagues believing that antibiotic stewardship requires different approaches to those recommended through antimicrobial stewardship. Alternatively, consider having a statement at the start which explains AMS and then state for the purposes of this handbook will call it antibiotic stewardship. Preferred option is to use the broader term AMS"*

(UK Health Security Agency)

Response: The WHO EML Antimicrobial Working Group that collaborated on preparing the AWaRe Book, agreed to avoid the term antimicrobial stewardship and to use the term antibiotic stewardship instead to be coherent with the fact that the Book only addresses antibiotic treatment and not antifungals, antivirals or antiparasitic medicines. This has been clarified in the introduction to avoid

confusion since antimicrobial stewardship is a term that is widely used including at WHO.

Comment: *"MSF recommends including the very widely used terms "de-escalate" and "targeted antibiotic therapy" in the sentence "simplify empiric treatment to a more narrow spectrum antibiotic based on culture results" (throughout the draft)"*

(Médecins Sans Frontières - MSF)

Response: There is no universally accepted definition of de-escalation, which is the reason why the term was not used preferentially. It is agreed, nevertheless, that it is a commonly used term, and the text has been amended as follows: "*simplify empiric treatment to a more narrow-spectrum antibiotic (often also called de-escalation) based on culture results (targeted treatment)*". This comment originally referred to the meningitis chapter, but this change has been applied throughout the Book.

Comment: *"From p5, the focus on 'no antibiotic use/care' is important, but our research suggests it is important to avoid having a 'no action' implication here - this is both difficult for clinicians and patients. Instead, action should be taken to show the illness is being taken seriously and the likely trajectory of symptoms should be explained to patients, with an action plan for if things worsen or do not improve in a particular time point."*

(Clara Chandler, London school of hygiene and tropical medicine, London, UK)

Response: In the section titled *"No Antibiotic Care - safely reducing antibiotic use"*, "no antibiotic" does not mean to suggest "no action needs to be taken" but tries to give general guidance and emphasize the importance of providing symptomatic care without antibiotics when it is safe to do so. Unfortunately, unlike in high-income countries where the normal rates of symptom recovery for common infections (e.g. respiratory tract infections) are reasonably well described, there is very little literature currently from low-and middle-income countries to inform normal rates of recovery and concerning symptoms that can provide danger flags. To clarify that "No antibiotic care" does not imply an underestimation of the clinical presentation, a point has been added to the key messages (page 5 of the draft version).

1. Most otherwise healthy patients with mild common infections can be treated without antibiotics as these infections are frequently self-limiting and the potential medicine-related adverse events outweigh the clinical benefits.
2. The risks of taking antibiotics when they are not needed should always be considered, such as side effects, allergic reactions, *Clostridioides difficile* infection and selection of resistant bacteria.
3. Patients treated with symptomatic care only (no antibiotic care) should be clearly informed of what danger signs to monitor and what to do if they occur.

Comment: *"Suggest to add to the subtitle "No antibiotic Care "Management so it is very clear it is still being managed but just without Abs"*

(Prof J. Conly, Department of Medicine (Infectious Diseases), Cumming School of Medicine, University of Calgary and Alberta Health Services)

Response: This has not been changed as it was felt that the current version of the title is sufficiently clear therefore these paragraphs throughout the AWaRe Book remained titled "No antibiotic care".

Comment: *"Generally the AWaRe classification should be different for LMIC as the level of practice and availability of antimicrobials is not the same as developed countries."*

(David Banda, Clinical pharmacy specialist, Senior lecturer, Chreso University, Nursing department, Lusaka, Zambia)

Response: The principles used to classify an antibiotic as Access, Watch or Reserve (propensity to select for and contribute to dissemination of resistance, safety and activity against priority multidrug-resistant pathogens) are not influenced by the setting but we recognize that some countries may choose to adapt the AWaRe classification (see next comment). It is recognized that the availability of antibiotics varies markedly by country due to many different factors, including costs, shortages etc. Generally, where appropriate, the AWaRe Book emphasises the importance of the use of Access antibiotics in empiric treatment recommendations.

Comment: Page 3 / lines 64-66: *"Several countries have adapted the WHO AWaRe categories for local use, suggest clarifying this in the introduction to avoid confusion."*

(UK Health Security Agency)

Response: This comment refers to the following sentence: *"Further guidance is given on how the AWaRe Book could be used to improve the use of antibiotics based on general antibiotic stewardship principles."* The AWaRe Book uses the medicines that are on the Model Lists of Essential Medicines. Countries adapt the Model EML to produce national essential Medicines Lists that are relevant to their setting. While some countries have decided to adapt the AWaRe classification of antibiotics to their setting, this approach is discouraged as AWaRe categories are based on the potential for the development of resistance and on the antibiotic spectrum of activity and these characteristics of antibiotics do not change by setting. Therefore, the content of the text remained the same.

"General antibiotic stewardship principles have been included throughout all the AWaRe book. These include guidance on a risk-based prescribing approach with the no antibiotic care option, short standard durations across infections, rapid oral step down from intravenous antibiotics and standardized dosing to improve medicine purchasing and programme delivery".

Comment: Page 5 / Key message 1 – *"Would add "and the potential adverse events outweigh the benefits".*

(UK Health Security Agency)

Response: The key messages (page 5 of the draft version) have been updated accordingly.

Comment: Page 5 / Lines 104 and following – *"Would suggest clarifying that there is a spectrum on infection severity and that while some infections are caused by bacteria, they do not require antibiotic treatment, e.g. otitis media in otherwise healthy child aged 2 years and older."*

(UK Health Security Agency)

Response: The AWaRe Book repeatedly states different clinical presentations and treatment approaches based on disease severity (mild versus severe) and for infections managed in primary care clearly states that the "No antibiotic care" approach is for mild cases most likely of viral origin in otherwise healthy individuals. However, this is now highlighted even more clearly in the Infection chapters where appropriate.

Comment: *"To optimise antibiotic use, we need to promote and educate the health workers in LMIC on the use of WBC for infection treatment and monitoring of treatment."*

(David Banda, Clinical pharmacy specialist, Senior lecturer, Chreso University, Nursing department, Lusaka, Zambia)

Response: The AWaRe Book tries to emphasize the importance of making a correct diagnosis (including which minimal set of laboratory tests may be helpful) and to carefully assess the need for antibiotic treatment for each patient.

In the introduction, clear key messages are also pointed out in Box 5 (pages 6-7 of the draft version) "Think D8 – before prescribing!" It is recognized that making guidance alone is often not sufficient to change behaviour and that other interventions, such as education of health care workers, are necessary. The comment about the use of WBC (white blood cell count) to help in the diagnosis of infection is important and the AWaRe Book gives guidance on those situations where this test may be of particular help and when it may not be necessary.

Comment: *"PAGE 4 Improving the use of antibiotics: Acknowledging the challenges of antibiotic drug shortages and the need for necessary strategies to address them as part of an EML programme*

Recommendation: A valuable addition would be to add a sub-section in this handbook on strategies to tackle the challenge of antibiotic shortages, globally."

"The lack of access to safe and effective antibiotics, including essential antibiotics on the Access and Reserve WHO category is being increasingly compromised by shortages (Shafiq et al., 2021). One of the unintended consequences of these shortages is using sub-optimal therapeutic options and substandard quality antibiotics, leading to treatment failure and emergence of antimicrobial resistance. The EML handbook should acknowledge this threat and engage with the discourse in identifying global strategies to forecast, manage, and address essential antibiotic shortages. This includes identifying the gaps in manufacture and supply chain of antibiotics; and, for the most common antibiotics at risk of shortages due to problems with procuring active pharmaceutical ingredients, or inadequate licensing agreements

working for more equitable and fair licencing and manufacturing rights in low-resource settings to enable sustainable access routes."

"Currently, there is a gap in gathering sufficient data on the extent of antibiotic drug shortages and their consequences, particularly the impact on available therapeutic options. In addition to greater collaboration between public-private sector and governments, we need to move to developing regional and global partnerships for forecasting and advocacy to address the underlying issues that drive antibiotic supply and access. This will have consequences for the recommended agents in the WHO EML list. Furthermore, the role of the WHO EML in relation to the national EMLs needs careful consideration. Particularly in tracking the supply and access of recommended agents in the EML and the consequences in terms of supply and demand as a result of these agents featuring in the EML."

(Dr Esmita Charani, Honorary associate professor university of Cape Town and research lead at NIHR HPRU in HCAI and AMR, Imperial college London, UK)

Response: This is a critically important issue. The need for global access to quality-assured essential antibiotics whenever needed is a key concept underlying the AWaRe Book. This is a complex area as summarised in recent publications and beyond the scope of the practical guidance provided by the AWaRe Book at this time. However, detailed guidance of exactly which antibiotic, dose and duration should be available at the facility when required provides a template to define more specifically what should be accessible / available at the facility level.

The next phase of this process is to develop a more detailed implementation process, including the potential for the AWaRe Book to inform future assessment of drug shortages and progress towards universal health coverage goals.

Comment: *"PAGE 9 Reducing the use of Not Recommended antibiotics*

Recommendation: Recognise the need to invest in social science research that provides contextual insight into the challenges of adhering to the AWaRe guidelines and helps identify solutions for optimising antibiotic use in human populations in different contexts."

"Incorporating a social science approach to better understanding the socio-cultural and economic drivers for antibiotic use, demand, and prescribing.

Antibiotic use remains a social process, influenced by sociocultural and economic drivers. Interventions to reduce demand, and use of not recommended antibiotics will not succeed if we do not consider the contextual factors which are influencing behaviours and attitudes. Research into this aspect of antibiotic prescribing is lacking from different contexts. Unless we can achieve sustained optimisation of use of existing agents, no number of new drugs will solve the problem of AMR (Charani et al., 2021). To this end, there needs to be a greater understanding of the contextual drivers for antibiotic use. Utilising qualitative approaches alongside the epidemiological and quantitative streams of research tackling AMR will enable:

1. Data collection on the feasibility and effectiveness in applying the AWaRe system in low- and middle-income countries as well as their relevance in high income countries

2. Identify knowledge gaps on implementing WHO guidelines on AMR stewardship by collecting data on the perception of clinicians and caregivers on the WHO EML book for specific populations such as paediatric/neonatal in LIMCs

3. Better understand the context specific drivers for change in different settings to inform hypotheses and research design"

Charani E, McKee M, Ahmad R, et al. Optimising antimicrobial use in humans - review of current evidence and an interdisciplinary consensus on key priorities for research. Lancet Reg Health Eur. 2021 Jun 29;7:100161. doi: 10.1016/j.lanepe.2021.100161."

(Dr Esmita Charani, Honorary associate professor university of Cape Town and research lead at NIHR HPRU in HCAI and AMR, Imperial college London, UK)

Response: It is agreed that considerably more attention needs to be given to a fuller understanding of social and cultural contexts that influence decision making around prescribing AWaRe antibiotics. This will be an important component of the implementation phase of the Book.

Comment: *The statement "It aims to complement WHO's Policy Guidance on Integrated Stewardship Activities and the Toolkit for health care facilities in low- and middle-income countries (LMIC)" does not accurately reflect the name of the WHO policy guidance on integrated antimicrobial stewardship activities. Also, the reference for the policy guidance [1] is not provided, only the toolkit for low and middle-income countries. (UK Health Security Agency)*

Response: This comment refers to the "Aim and scope" paragraph (page 1 of the draft version). The reference to the WHO policy guidance on integrated antimicrobial stewardship activities has been added and the title of the document has been corrected.

Comment: *"Include an anticipated duration of symptoms – see NICE Common Infection Guidelines visual summary for an example. NG120 Cough (acute): antimicrobial prescribing visual summary (nice.org.uk)"*

(British Society for Antimicrobial Chemotherapy)

Response: This aspect is not covered in detail in the AWaRe Book and it is currently somewhat beyond its scope which is primarily to give guidance on the appropriate empiric choice of antibiotics for common infections. However, for some infections, the Book mentions when clinical improvement should be expected after starting an appropriate treatment or when a complication should be suspected. This is something that can be considered for future editions.

Comment: *Page 1 / Box 1: Simplification: this might encourage the use of newer agents (e.g. carbapenems) instead of combinations of agents used in the treatment of acute appendicitis, neonatal sepsis, and similar conditions. Suggest adding "while prioritising antimicrobial stewardship/the principles above".*

(UK Health Security Agency)

Response: The principle of Simplification in this context refers to the fact that the WHO Essential Medicines Lists (and therefore the AWaRe Book which is closely aligned with the Lists) favour the use of a limited number of antibiotics if these can be effective for the treatment of different infections. For example, Amoxicillin is recommended as first choice for several community-acquired infections in the AWaRe Book. Therefore, Simplification in this context does not refer to monotherapy versus

combination treatments (e.g. using carbapenems instead of ceftriaxone co-prescribed with metronidazole for intra-abdominal infections).

The point about simplification has been clarified as follows (page 1 of the draft version):

Box 1 – Principles of the AWaRe framework

1) Maximizing clinical effectiveness

2) Minimizing toxicity

3) Minimizing unnecessary costs to patients and healthcare systems

4) Reducing the emergence and spread of antibiotic resistance (i.e. prioritizing antibiotics that are less likely to lead to antibiotic resistance in an individual patient and the community)

5) Parsimony (i.e. avoiding the inclusion of many similar antibiotics)

6) Simplification (i.e. same Access antibiotics for multiple indications)

7) Alignment with existing WHO guidelines

Comment: *"Would consider softening the dichotomy "viral vs bacterial" across the document."*

(UK Health Security Agency)

Response: The dichotomy "viral vs bacterial" is a simplification which should be seen in the context of the aim to provide simple to use guidance.

Comment: *"We would suggest adding a section in the manual, perhaps in the Introduction, regarding the lack of requirement for intravenous antibiotics as long as the treatment is not for bacteraemia (including possible sepsis) or meningitis, or there is concern about absorption/distribution of enteral antibiotics. Most inappropriate antibiotic use is probably related to clinicians believing that intravenous treatment is somehow better than its enteral equivalent."*

(UK Health Security Agency)

Response: The AWaRe Book is focused on the choice of empiric antibiotic treatment rather than route, frequency of administration and treatment duration. However, from an antibiotic stewardship perspective, it is important to of encourage oral treatment whenever it is safe and appropriate. For each infection, general recommendations for timing of intravenous to oral step down are given where appropriate. The following paragraph has been added to the Introduction:

"Most non-severe infections can be safely treated with oral antibiotics and this approach is encouraged as it has several advantages for example less risk of line-associated infections and avoidance of hospitalizations. However, this is provided that there is no risk of poor enteral absorption (e.g. no vomiting) or need to treat pathogens for which effective oral options are not available, for example in the case of infections caused by certain multidrug-resistant pathogens.

When intravenous treatment is started (e.g. for severe infections), rapid oral step down should be considered as soon as this can be safely done."

Comment: *"Ensure the ADG in AMR Dr H Balkhy aware of this work"*

(Prof J. Conly, Department of Medicine (Infectious Diseases), Cumming School of Medicine, University of Calgary and Alberta Health Services)

Response: The WHO AMR division has been involved in this project and the AWaRe Book is aligned with their publications and work.

Comment: *"Reserve AB list is great – can it be also be a standalone"*

(Prof J. Conly, Department of Medicine (Infectious Diseases), Cumming School of Medicine, University of Calgary and Alberta Health Services)

Response: The AWaRe Book is meant to be a single comprehensive source of information, encompassing all antibiotic categories. The infographics are integrated into the book but have also been developed to be used as standalone guides. Users are free to select, mix and optimize contents to suit their needs.

Comment: *"Page 120 (line 32) – Line 32 mentions diabetic foot infection and surgical site infections could it be elaborated why this has not been included? It would be very useful to have these infections covered as well." (Stephanie Kohl, Policy and advocacy officer at the European association of hospital pharmacists)*

Response: The WHO EML Antimicrobial Working Group went through a detailed scoping exercise based on the frequency, public health relevance and the evidence base for recommending antibiotic treatment. Concerning skin and soft tissues infections, this first edition of the AWaRe book focuses on impetigo / erysipelas / cellulitis, recognising that other conditions such as diabetic foot infections and surgical site infections could be added in the future. Many surgical site infections will require targeted treatment, which was not the focus of the first edition of the AWaRe Book.

Style / typographic errors

Comment: *"The exact titles should be in both the infographics and the main body of the text and not always the case so some harmonization would be helpful. As an aside I prefer "Most Likely Pathogen" over Microbiology Epidemiology".*

(Prof J. Conly, Department of Medicine (Infectious Diseases), Cumming School of Medicine, University of Calgary and Alberta Health Services)

Response: The AWaRe Book and infographics have been revised for consistency of terminology including the titles of each section. Concerning the specific suggestion to align the titles of the microbiology sections between the Book (where this section is called "Microbiology epidemiology") and the infographics (where it is called "Most likely pathogens"), the decision was to use the term "Most likely pathogens" in the Book and infographics.

Comment: *"The subtitle Microbiology Epidemiology seems redundant and could just say Microbiology"*

(Prof J. Conly, Department of Medicine (Infectious Diseases), Cumming School of Medicine, University of Calgary and Alberta Health Services)

Response: See previous comment. The final decision was to align with the infographics and use the term "Most likely pathogens" for these sections throughout the Book.

Comment: "Some refs are in italics and others not so will need to fix that"

(Prof J. Conly, Department of Medicine (Infectious Diseases), Cumming School of Medicine, University of Calgary and Alberta Health Services)

Response: The format and final layout has been revised to be consistent with WHO publication style.

Comment: Page 9 / line 172 Key message 1 - Would use "to improve" or "in improving".

(UK Health Security Agency)

Response: This comment refers to the following sentence: "*All prescribers have a responsibility to improving the use of antibiotics*". The sentence has been corrected as suggested.

Comment: Page 14 / line 267 – Perhaps use of "non-self" rather than "foreign" would be a more appropriate term.

(UK Health Security Agency)

Response: This comment refers to the following sentence: "*An allergy is a reaction of the immune system to a "foreign" substance*". The sentence has been corrected as suggested.

Comment: Suggest all abbreviations to be expanded in the first instance for the non-specialist reader, for example see Page 15 / line 299 – suggest writing out EBV in full as "Epstein Barr virus". Non-common abbreviations may be worth repeating.

(UK Health Security Agency)

Response: The document has been revised to make sure all abbreviations are expanded the first time they are used.

Format

Comment: *"Can the TOC be hyperlinked for ease of finding sections?"*

(Prof J. Conly, Department of Medicine (Infectious Diseases), Cumming School of Medicine, University of Calgary and Alberta Health Services)

Response: The Table of Contents in the PDF version have hyperlinks to facilitate access to the different sections of the Book.

Comment: *"The AWARE addition is a major advance. Infographics are outstanding and would suggest they be in the text and available as a standalone– could the colour photos be added or hyperlinked to the infographics – need EDI so people from different backgrounds other than only Caucasian. Suggest to link the infographics and its proposed digitization to garner more support from within WHO."*

(Prof J. Conly, Department of Medicine (Infectious Diseases), Cumming School of Medicine, University of Calgary and Alberta Health Services)

Response: The infographics are available as a separate PDF document downloadable from the WHO website that end-users could print if needed but they have been integrated in the Book with each corresponding chapter. An electronic application of the AWaRe Book's contents (including the infographics), freely accessible from a smart device on- and offline, has been developed (https://app.firstline.org/en/clients/276-world-health-organization). Photographs have been selected to ensure people from different backgrounds are represented.

Comment: *"The infographics should be made iOS and android available in an algorithmic "app".*

(Prof J. Conly, Department of Medicine (Infectious Diseases), Cumming School of Medicine, University of Calgary and Alberta Health Services)

Response: The AWaRe Book's contents are also available in a smartphone application format. It is hoped that the content will be taken up by different antibiotic smartphone applications.

The content is presented in a way that should help the reader in deciding how to manage a patient presenting with common infections both in the primary health care and hospital settings (what lab tests to do, imaging, symptomatic treatment, empiric treatment) and how Reserve antibiotics should be used. The infographics were specifically designed as simple, visual algorithms containing the key information and professionals with expertise in infographics and algorithms were involved in designing this section.

Of note, developing algorithms for associations of symptoms (e.g. cough and fever, headache and fever, undifferentiated fever) was also discussed in the early stages of preparation of the Book however due to their complexity (many possible differential diagnoses need to be taken into account) it was decided to discard the idea for the moment. This may however be considered in the future.

Comment: *"Colour photos add a great deal and very helpful – would add a few more of them in some sections eg the dental infections section"*

(Prof J. Conly, Department of Medicine (Infectious Diseases), Cumming School of Medicine, University of Calgary and Alberta Health Services)

Response: The number of pictures has been kept to a minimum. The choice was to rather having illustrations for conditions such as dental or eye infections.

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2 Dosing

Comment: *"INTRO For line 230 would consider adding in for "different sites of infection" for example for a CNS infection for children we would use 100 mg/kg/day divided q12 versus for non-CNS we use 50-75mg/kg/day once daily. We do not need to use that specific example but I know serious infections are included but CNS infections in particular might be worth mentioning here."*

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Response: It is agreed that there are a range of conditions where doses that differ from the ones suggested in the AWaRe Book may be required. This first edition aims to provide standard dosing guidance for the most common infections. The potential need for higher doses and / or more frequent administration is already mentioned on page 13, lines 230-234 (draft version). The text in bold has been added:

"Even though this dosing is not covered in the AWaRe book, higher doses or more frequent administration may be required in certain situations such as: patients with very severe infections (including sepsis / septic shock) ***or infections of certain body sites such as infections of the central nervous system;*** *patients with significant underlying disease (e.g. severe immunosuppression); and overweigh patients.*

Comment: *"The WHO essential medicines list antibiotic book is very good. But all antibiotic dosages are for normal renal and hepatic function in the WHO essential medicines list antibiotic book, can give WHO antibiotic dosages guidelines for abnormal renal and hepatic function?"*

(Chen Zhi-dong, pharmacist, Shanghai, China)

Response: Although this is an important area, it is outside the current scope of the AWaRe Book, which focuses on providing doses that are considered appropriate for most patients for specific infections at the time of first empiric prescribing. The importance to always consider "the individual circumstances of the patient" including "renal or hepatic insufficiency which may require dose adaptation of antibiotics" is mentioned in Box 2 "General considerations about the AWaRe Book" (page 2 of the draft version).

Comment: *Page 378: "Please list maximum dose for all medicines to avoid adverse events where children have a high weight." (UK Health Security Agency)*

Response: Maximum doses have been added for all antibiotics in the children's formulary.

Comment: *"Page 2 (line 36; box 2): For quinolones, it should be reiterated that the patient's renal function is supposed to be normal. More information about this topic can also be found via* https://www.ema.europa.eu/en/medicines/human/referrals/quinolone-fluoroquinolone-containing-medicinal-products."

(Stephanie Kohl, Policy and advocacy officer at the European association of hospital pharmacists)

Response: As the AWaRe Book aims to be a short practical guide, detailed dosing guidance for patients with altered renal or hepatic function is not currently given for individual medicines. However, general guidance is provided in Box 2 (Page 2 of the draft version) and this important area will be considered for future editions.

2.1 Formulary for adults

Gentamicin

Comment: *"Page 376: Gentamicin EUCAST breakpoints are based on 7mg/kg, not 5mg/kg. Might need to specify the option of 5-7mg/kg?"*

(UK Health Security Agency)

Response: Even though gentamicin can be dosed at 5-7 mg / kg per day, the decision in the AWaRe Book was to avoid giving ranges and always suggest the lowest therapeutically effective dose especially considering renal and ear toxicities that can be associated with its prolonged use. Therefore, no changes to the text were made.

Piperacillin-tazobactam

Comment: *"Page 377: Piperacillin-tazobactam is primarily dosed at every 8 hours in the UK, which is where EUCAST breakpoints are based on."*

(UK Health Security Agency)

Response: Different dosing regimens can be used and the AWaRe Book does not "recommend" doses but only gives suggestions on what would be considered appropriate in most cases. Therefore, no changes to the text were made. Of note, v 12.0 of the EUCAST Clinical Breakpoints – bacteria also includes dosing at every 6 hours.

2.2 Formulary for children

Amoxicillin

Comment: *"The table (for pharyngitis treatment) says "40-50 mg/kg/dose given every 12 hours" and then, the dosages in different age bands.*

For 20-30 kg, it says 1,000 mg every 12 hours and for more than 30 "use adult dose". And, adult dose is 500 mg every 8 hours. Then a 30 kg child will receive 2,000 mg per day and a 32 kg child, 1500 mg per day. Perhaps there is a mistake with the "every 12 hours", and it should be "40-50 mg/kg per day (it can be divided in two or three doses per day)?"

(Dr Albert Figueras, Department of pharmacology, Autonomous University of Barcelona, Spain)

Comment: Page 56 / line 311 (Table): *"Recommendations for Amoxicillin dosing schedule seem to recommend a higher dose for children who weigh 20-30kg (2g over a 24 hour period) than for adults (1.5g over a 24 hour period). [1,2]"*

References:

1. UK guidance for Amoxicillin: https://bnf.nice.org.uk/drug/amoxicillin.html

2. UK guidance for Phenoxymethylpenicillin: https://bnf.nice.org.uk/drug/phenoxymethylpenicillin.html

(UK Health Security Agency)

Response: These comments include two important points:

- Total daily dose of amoxicillin in children. The AWaRe Book has been revised to suggest 80-90 mg/kg/day for all infections where amoxicillin is recommended. This dose is aligned with what is suggested in the "*Report on consensus guidance on paediatric dosing regimens for antibiotics on the Essential Medicine List for Children*" which indicates a total daily dose of 80-100 mg/kg of amoxicillin (divided every 12 hours).
- When to switch to adult dosing in children. This aspect is not harmonised across international guidelines. In the AWaRe Book, the general approach of suggesting adult dosing for children that weigh 30 kg and more has been taken. This cut-off is arbitrary and has limitations (e.g. overdosing small children, underdosing large children) but offers the chance of harmonizing dosing guidance across infections and is in line with the overall idea of the AWaRe Book to give simple guidance for the management of common infections especially where none is available. For amoxicillin, the suggested children's oral weight band dosing has been revised as follows:
    - 3 - <6 kg: 250 mg given every 12 hours
    - 6 - <10 kg: 375 mg given every 12 hours
    - 10 - <15 kg: 500 mg given every 12 hours
    - 15 - <20 kg: 750mg given every 12 hours
    - ≥ 20 kg: 500 mg given every 8 hours or 1 g given every 12 hours

In both cases, it is important to note that, as mentioned on page 12 (lines 216-219 of the draft version), the AWaRe Book does not provide formal recommendations for dosage but offers a general guidance on what would be considered appropriate in most clinical cases. Therefore, adaptation based on national / local guidelines may be needed.

Ceftriaxone

Comment: Page 380 / *Ceftriaxone: "Please use consistent description for lower dose and higher dose (mg/kg/dose given once daily or mg/kg given once daily)." (UK Health Security Agency)*

Response: The terminology has been harmonized (mg/kg/dose given once daily).

Comment: Page 380 / Ceftriaxone: *"Would consider listing 50 mg/kg as standard dose (= bacteraemia + other conditions), with higher dose = 80-100 mg/kg once daily (this depends on countries and is usually 80 or 100) if needed for penetration, e.g. CNS or bone." (UK Health Security Agency)*

Response: The 80 mg/kg daily dose of ceftriaxone (or 100 mg/kg daily for meningitis) is based on the Pocket book of hospital care for children, therefore no changes to the text were made.

Clindamycin

Comment: Page 380 / *"For severe infections such as the ones listed, an appropriate dose would be 10 mg/kg/dose every 6 hours (with max)."*

(UK Health Security Agency)

Response: Different dosing regimens can be used and the AWaRe Book does not "recommend" doses but only gives suggestions on what would be considered appropriate in most cases. Therefore, no changes to the text were made.

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3 Allergies

Comment: *"I see that alternatives to first line are not in the scope of this book. I would consider adding this for next iteration since allergy could be one reason but drug interactions, non-IgE mediated issues (eg SJS etc) could also be relevant so this might be helpful to consider. I see some reactions are mentioned in line 323 which is good but alternative agents might be useful to suggest."*

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Comment: *"Not having Recommendations for penicillin allergic patients in some sections is unhelpful as systems are not yet widely in place in de-label patients with incorrect allergy labels."*

(British Society for Antimicrobial Chemotherapy)

Comment: *"The rationale for not including alternatives for penicillin allergy is understood. However, we suggest it would be worthwhile including an alternative to penicillin for situations where the patient has had a previous anaphylactic reaction to penicillin. This could be placed in chapter 5: "Appropriate antibiotic dosing and duration" as a general guideline, rather than for each individual clinical indication.*

For instance:

- *for amoxicillin or phenoxymethylpenicillin, recommend cefalexin*
- *for co-amoxiclav, recommend cefuroxime*
- *for piperacillin & tazobactam, recommend ceftriaxone."*

(UK Health Security Agency)

Comment: Pages 44-57 (Dental infections chapter): *"We think that the presentation of advice on allergies could be improved. We acknowledge the detailed information on allergies and the rationale of not including information on alternatives. However, accepting that true allergies may be rare, the consequences of not considering allergies every time medication is prescribed could be life threatening. To ensure that a safe approach is given, we would suggest that alternatives (due to allergies and/or contra-indications) are published for every condition on the same page as the preferred drugs. This would help prompt practitioners to always consider an allergy. At the very least, a prompt which has been designed (perhaps in bold or larger font) on the same page as prescribing data to consider allergies (as well as other contra-indications) would be helpful to help minimise issues."*

(UK Health Security Agency)

Comment: Penicillin allergy:

a. offer alternatives for anaphylaxis history
b. add to chapter 5 (Allergies to antibiotics) appropriate cephalosporin alternatives

e.g. Pen V / amoxicillin – cefalexin
co-amoxiclav – cefuroxime
pip-taz – ceftriaxone

(The UK Paediatric Antimicrobial Stewardship)

Response: The recommendation for antibiotics in the Book is based on antibiotics listed in the WHO Essential Medicines Lists for each indication. Therefore, alternative options (that are not specifically mentioned in the WHO Essential Medicines Lists) are not reported. This may, however, be considered for future updates of the Book. There is a certain risk that these alternatives could be overused which may have negative consequences e.g. if the alternatives are less effective, less safe and have a higher potential for resistance (e.g. alternatives may often be non-beta-lactam Watch group antibiotics). Therefore, no changes to the text were made about offering alternative options to those already recommended.

Comment: Page 17 (line 363) *"The statement that "routine skin testing is not needed…" is an oversimplification and potentially harmful."*

(British Society for Antimicrobial Chemotherapy)

Response: This comment refers to the following statement: *"Routine skin testing before prescribing a beta-lactam antibiotic (e.g. penicillin, amoxicillin) is not needed in children or adults and should not be recommended in guidelines as this is an unnecessary barrier to the use of Access antibiotics"*. This statement is based on the fact that true severe allergy to antibiotics is rare, and allergies (especially to beta-lactams) are often over-reported and over-diagnosed resulting in the unnecessary use of alternative antibiotics. Therefore, instead of "moving" directly to a second line option with a different class of antibiotics, the AWaRe Book suggests that patients with a history of allergy to antibiotics should be evaluated to confirm the existence (or persistence) of the allergy and their risk level if re-exposed.

The Key messages (page 13 of the draft version) have been amended as shown:

1. True severe allergy to antibiotics is rare and allergies are often over-reported.
2. Beta-lactam antibiotics (penicillins and cephalosporins) of the Access group are among the most effective and safe medicines for many infections, and they should only be avoided when there is a high suspicion of true allergy.
3. Cephalosporins and carbapenems can be safely used in most cases of non-severe penicillin allergy.
4. All patients who are labelled as allergic should be carefully evaluated and their antibiotic allergy risk level should be determined.
5. Routine skin testing before prescribing a beta-lactam antibiotic (e.g. penicillin or amoxicillin) is not needed, and direct oral challenge can be performed in carefully selected low-risk phenotypes.

However, management of allergies to antibiotics goes beyond the scope of the Book and other guidance documents on the topic of allergies to antibiotics should be checked for more detail.

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4 Primary health care

4.1 Acute otitis media

Comment: *"Add some additional upper resp viruses that are common or simply indicate other resp viruses in the appropriate sections eg parecho, enterovirus etc".*

(Prof J. Conly, Department of Medicine (Infectious Diseases), Cumming School of Medicine, University of Calgary and Alberta Health Services)

Response: This comment did not refer specifically to the "Acute otitis media" chapter but was a general consideration. As suggested, "Other respiratory viruses" have been added in the Microbiology (now "Most likely pathogens") sections of the following chapters: bronchitis, acute otitis media, pharyngitis, acute sinusitis, mild and severe community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP) and chronic obstructive pulmonary disease (COPD) exacerbations.

Comment: *"Consider explaining why culture of pus is unhelpful (presumably due to specimen contamination)."*

(British Society for Antimicrobial Chemotherapy)

Response: This comment refers to the following statement in the "Microbiology tests" section (page 26 of the draft version): *"In uncomplicated cases, microbiological tests are usually not needed and cultures of pus from perforated ear drums should not be used to guide treatment"*. The most common causative pathogen in these cases is *Streptococcus pyogenes* (group A *Streptococcus*) which is universally still very susceptible to amoxicillin (first line antibiotic for this indication).

Comment: "*Consider anaesthetic ear drops in addition to oral analgesia where no perforated ear drum before antibiotics* – Anaesthetic analgesic ear drops to reduce antibiotic consumption in children with acute otitis media: the CEDAR RCT (nihr.ac.uk)"

(British Society for Antimicrobial Chemotherapy)

Response: Analgesic ear drops are not listed in the WHO Essential Medicines Lists (with which the AWaRe Book is closely aligned), therefore no changes to the text were made.

Comment: *"When saying "Antibiotics should be considered if: …severe ear pain…", would you consider "….if severe ear pain despite analgesics…"?*

(British Society for Antimicrobial Chemotherapy)

Response: The text has been amended accordingly (page 27 of the draft version).

Comment: *Page 26 / Lines 51-57 on Otoscopy: "Would suggest adding that tympanic membranes often appear red when a child is crying, and this does not necessarily indicate infection."*

(UK Health Security Agency)

Response: This comment refers to the sentence: "In settings where otoscopy is available, classic findings include bulging, inflamed/congested tympanic membrane that may be opaque and show decreased mobility". The text has not been changed as evidence to support this statement has not been provided.

Comment: Page 28: *"alternative for penicillin allergy of clarithromycin or erythromycin."*

(British Society for Antimicrobial Chemotherapy)

Comment: *"MSF recommends reserving macrolides for penicillin-allergic patients to avoid increasing macrolide resistance"*

(Médecins Sans Frontières - MSF)

Response: Macrolides (e.g. clarithromycin) are not included in the WHO Essential Medicines Lists for the treatment of acute otitis media and therefore the AWaRe Book (which is closely aligned with the WHO lists) does not include them for this indication. The AWaRe Book currently does not provide alternative regimes in case of allergy, partly because antibiotic allergy is over diagnosed in many settings potentially leading to treatment with antibiotics that are less effective, less well tolerated and have a higher risk of selection of resistance (e.g. Watch macrolides instead of Access beta-lactams). Real-world experience shows for example that prescribers tend to over diagnose presumed allergic contraindications to beta-lactams.

Comment: *"Main document Table 3 Line 88-90 for AOM treatment of 5 days - for younger age groups would consider 10 days. Reference: https://cps.ca/documents/position/acute-otitis-media".*

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Comment: *"Table 3 line 88-90 on acute otitis media treatment. I don't see high dose amoxicillin listed anywhere in this treatment diagram. Would add this in for those with risk factors for resistance or based on local antibiograms."*

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Response: Both comments refer to Table 3 in the otitis media chapter (page 28 of the draft version).

Concerning antibiotic treatment duration: While acknowledging that certain guidelines / position statements of professional societies suggest a longer treatment duration for children <2 years of age (e.g. The American Academy of Pediatrics, the American Academy of Family Physicians and the

Canadian Pediatric Society), other guidelines which have reviewed the evidence base in detail (e.g. The National Institute for Health and Care Excellence) suggest 5-7 days in all age groups. The decision to suggest a treatment duration of 5 days irrespective of the age of the child is based on the strategy of providing effective treatment for the shortest appropriate period of time.

Concerning dosing of amoxicillin: The dose provided in the chapter is 80-90 mg/kg of amoxicillin per day which overlaps with the dose indicated by most guidelines (including those of the Canadian Pediatric Society).

Comment: Page 28 / Table 3: *"The three references (36-38) point to a higher incidence of treatment failure when a 5-day course is used (compared to 7-10 days). Please clarify why 5 days were chosen as standard total treatment duration."*

(UK Health Security Agency)

Response: Two of the three referenced studies (ref 37-38 of the draft version) pose the problem of longer antibiotic courses for children <2 years of age while ref 36 concludes whether *"the minimal short-term benefit from longer treatment of antibiotics is worth exposing children to a longer course of antibiotics"* leaving the debate on optimal treatment duration open.

While it is correct that certain guidelines / position statements of professional societies suggest a longer treatment duration for children <2 years of age (e.g. The American Academy of Pediatrics, the American Academy of Family Physicians and the Canadian Pediatric Society), other guidelines which have reviewed the evidence base in detail (e.g. The National Institute for Health and Care Excellence) suggest 5-7 days in all age groups. The decision to suggest a treatment duration of 5 days irrespective of the age of the child is based on the strategy of providing effective treatment for the shortest appropriate period of time.

Comment: *"We need to bear with developing countries when we are classing the AWaRe list, as most drugs are difficult to be provided by government hospitals. An example is the first line for otitis media, the amoxicillin combination with clavulanic acid is not provided by government stores in Zambia".*

(David Banda, Clinical pharmacy specialist, Senior lecturer, Chreso University, Nursing department, Lusaka, Zambia)

Response: This context-specific comment raises the important issue of how the AWaRe Book may need to be adapted for the treatment of certain infections at the local / national level based on availabilities of antibiotics. However, in the specific example (treatment of acute otitis media), amoxicillin + clavulanic acid is listed in the AWaRe Book not as first-line but as a second-choice option (amoxicillin is first line). Furthermore, local availability of antibiotics may be subject to relatively rapid changes over time, making it difficult to suggest specific alternatives. Consideration will be given to potentially including indication alternatives based on antibiotic class (ATC codes) in future editions.

Comment: *"MSF recommends the 8:1 or 7:1 formulation of amoxicillin-clavulanic acid (rather than 4:1) to increase the dose of amoxicillin while maintaining the same dose of clavulanic acid (therefore limiting risk of gastrointestinal side effects, such as diarrhoea, with minimal benefits in terms of efficacy against beta-lactamases"*

(Médecins Sans Frontières - MSF)

Response: Users of the AWaRe Book should be aware of the limited evidence underlying many antibiotic prescribing strategies and particularly the very poor evidence for dosing guidance, which may explain some of the variation in international recommendations. The Book therefore does not provide formal recommendations for dosage but rather provides general guidance on what would be considered appropriate in most clinical cases. In general, for simplicity and wherever appropriate, the same dose is given in the Book for each antibiotic for all infections to help local procurement and prescribing. In the case of amoxicillin-clavulanic acid in adult patients, the higher dose (875 mg + 125 mg) suggested by the reviewer is only used in the Book for community-acquired pneumonia and for intra-abdominal infections while for all other indications a standard dose (500 mg + 125 mg) is suggested.

Therefore, while acknowledging the rationale of the suggestion, and agreement that a higher dose may be needed in patients that are systemically very unwell, it is considered that in most patients presenting to primary care, a standard formulation (500 mg + 125 mg) would be adequate.

This is also the formulation used in other guidance documents (e.g. the UK guidelines by the National Institute for Health and Care excellence, the guidelines by the Africa CDC & Center for Disease Dynamics, Economics & Policy). Of note, the AWaRe Book always suggests doses based on formulations included in the WHO Essential Medicines Lists and the 8:1 formulation of amoxicillin-clavulanic acid (1000 mg + 125 mg) is not currently included.

4.2 Pharyngitis

Comment: Page 32 & 33: *"Centor score validated with small numbers of patients in an emergency department setting – would FeverPAIN not be a more valid score to use?"*

(British Society for Antimicrobial Chemotherapy)

Comment: Page 32 / Line 73 / Scoring symptoms - Centor criteria: *"would suggest clarifying these were not validated in the paediatric population. Would suggest mentioning FeverPAIN criteria"*. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4781545

(UK Health Security Agency)

Response: Despite its limitations (e.g. it has not been validated in LMIC settings and was developed for adults), the Centor score remains one of the most used systems to evaluate the risk of streptococcal pharyngitis in patients presenting with sore throat. The Book is not meant to comprehensively cover all aspects of management, especially those not related to antibiotic treatment, therefore no changes to the text were made.

Comment: *"More prominence to use GAS rapid antigen tests where available to further reduce antibiotic prescribing."*

https://academic.oup.com/jac/advance-article/doi/10.1093/jac/dkab470/6509366?guestAccessKey=667049c6-37da-4d41-b168-7b75c68bbfd3

(British Society for Antimicrobial Chemotherapy)

Response: Microbiological confirmation and targeted treatment of sore-throat patients with antigen-positive tests is an option in settings where this is feasible. However, in LMIC settings where rheumatic fever and rheumatic heart disease are important problems, strategies based on microbiological diagnosis of sore throat are unfortunately still very difficult to implement. Therefore, no changes to the text were made.

Comment: *"Line 1 I see there is mention in this section of the GAS - that is good that it is here (My previous comment was just on the summary table and still applies but it is good that this is explained in detail here)."*

"Table 1 line 50-52 - arcanobacterium is not listed and should be considered, diphtheria could also be considered (though it has other identifying features).

I wouldn't say that bacterial pharyngitis is rare (particularly in children) however can test for it easily".

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Response: This comment refers to Table 1 in the Pharyngitis chapter (page 32 of the draft version). The table indicates that most cases have a viral origin, including in children. Since the table is meant to only report "Pathogens most frequently associated with pharyngitis", *Arcanobacterium* spp. (a Gram-positive bacillus) was not added as this is a rare cause of sore throat.

Concerning *Corynebacterium diphtheriae* (the causative pathogen of diphtheria), even though this became a rare condition (due to vaccination programmes) and usually has a clinical presentation that differs from viral (or even streptococcal) pharyngitis, a comment has been added to the text in the "Most likely pathogens" section (page 31 of the draft version) as follows:

"Other infectious causes that need to be considered are acute HIV-infection and other sexually transmitted infections such as syphilis and gonorrhoea, acute toxoplasmosis and diphtheria – consider diphtheria if fever and greyish-white membranes covering the tonsil(s) are present in a child not vaccinated against diphtheria".

Comment: Page 35 / Lines 125 – 138 / Antibiotic treatment -*"Would clarify that, while rare, some cases of pharyngitis are caused by Lemierre's syndrome (Fusobacterium necrophorum and other bacteria), a severe condition that should be considered if the symptoms progress despite antibiotic use."*

(UK Health Security Agency)

Response: This comment refers to the following sentence: "*Most cases of pharyngitis are of viral origin and do not benefit from antibiotics"* (page 35 of the draft version). Lemierre's syndrome is a serious and potentially life-threatening condition, but it is rare and not always associated with pharyngitis (e.g it can be associated with other infections of the head / neck anatomical region) therefore, in line with the scope of the AWaRe Book to focus on the treatment of common infections, no changes to the text were made.

Comment: *"INTRO For Table 1 Line 113 for pharyngitis I would add the caveat about Streptococcus pharyngitis (GAS/strep throat) in that the standard of care of this is still to treat with antibiotics particularly for children re: Rheumatic fever risk"*.

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Response: This comment refers to Table 1 in the Introduction (page 6 of the draft version). The purpose of the table is to describe which common infections in primary health care can be safely treated with "No Antibiotic Care" for mild cases, and pharyngitis (which is usually caused by viruses) is one of these infections. It was therefore decided not to change the table to keep the message concise. However, situations where antibiotics are needed for the treatment of pharyngitis are indicated in the pharyngitis chapter. A footnote has been added to the table to refer to the pharyngitis chapter.

Comment: *"Recommend phenoxymethylpenicillin 1st line in countries where available, and amoxicillin where it is not as penicillin exerts less selection pressure for resistance (e.g. ESBL) compared with amoxicillin. Alternative for penicillin allergy of clarithromycin or erythromycin."*

(British Society for Antimicrobial Chemotherapy)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the AWaRe Book (including alternatives for allergic patients) would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process).

Comment: *"MSF recommends that intramuscular benzathine benzylpenicillin can be used when patient adherence to the 10-day oral phenoxymethylpenicillin regimen is unlikely, oral therapy is not tolerated, or a single-dose treatment is preferred"*

(Médecins Sans Frontières - MSF)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the AWaRe Book (e.g. adding benzathine benzylpenicillin for this indication) would first require changes to recommendations in the Model Lists (which must be requested through the

standard submission process). Therefore, no changes to the text were made.

Comment: *"Line 53 - would add in similar comment about macrolide in with clindamycin."*

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Response: The WHO Essential Medicines Lists do not include pharyngitis as an indication for the use of clindamycin while clarithromycin (a macrolide) is listed as a second-choice option for this indication. This is the reason why only resistance to macrolides is mentioned in the text. Because the AWaRe Book is based on the WHO Essential Medicines Lists, no changes to the text were made.

Comment: *"For penicillin allergic patients: MSF recommends azithromycin as a first choice over clarithromycin in view of adverse effects and observer lower compliance with clarithromycin" (Médecins Sans Frontières - MSF)*

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the AWaRe Book (including alternatives for allergic patients) would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process). Therefore, no changes to the text were made.

Of note, although azithromycin could be used as an alternative (e.g. when clarithromycin is not available) it is also acknowledged that there are increasing concerns about its potential for the emergence and spread of antibiotic resistance because of its long half-life.

4.3 Acute sinusitis

Comment: *"Table 1 line 27-28 consider adding in chronic situations anaerobes might be more predominant. Recently we have seen several chronic sinusitis all presenting ultimately with brain abscess/meningitis/orbital cellulitis over the last 2 years".*

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Response: This comment refers to Table 1 in the Sinusitis chapter (page 39 of the draft version). The focus of the chapter is on acute sinusitis and causes of chronic infections are not addressed therefore no changes to the text were made.

Comment: p 11-13. *"Consider recommending amoxicillin as first choice and co-amoxiclav as second choice because amoxicillin exerts less selection pressure for resistance (e.g. ESBL) compared with co-amoxiclav. Alternative for penicillin allergy of clarithromycin or erythromycin." (British Society for Antimicrobial Chemotherapy)*

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the AWaRe Book (including alternatives for allergic patients) would first require changes to recommendations in the Model Lists (which must be requested through the standard

submission process).

4.4 Dental infections

Comment: *"FDI stands ready to support WHO as it continues to finalise the oral and dental infections chapter and moves towards dissemination of this Antibiotic Book."*

(World Dental Federation)

Response: The support by FDI is appreciated.

Comment: *"Because the text refers to more than just teeth, a better title for this chapter would be 'Oral and dental infections'."*

(World Dental Federation)

Response: The title of the chapter has been amended as suggested.

Comment: *"It is important that this chapter is cross-referenced with the Book's other chapters (in particular periorbital cellulitis, cellulitis and sepsis, acute lymphadenitis and osteomyelitis). Some of these conditions can have a dental origin, but this is not mentioned in the relevant chapters."*

(World Dental Federation)

Response: Changes have been made to the specific chapters as suggested. Reviewers sent us specific comments for these chapters and answers to these comments are presented elsewhere in this document (see sections referring to cellulitis, acute lymphadenitis, osteomyelitis and sepsis).

Comment: *"As dentists are responsible for up to 10% of antibiotic prescribing worldwide, we appreciate consideration of the appropriateness of prescribing antibiotics in the management of dental infections. However, we believe it pertinent to mention that in some countries (such as the United States) prescriptions issued by dentists are mostly for surgical prophylaxis rather than dental infections. As there are significant differences in guidelines for the prophylactic use of antibiotics between countries a reminder for clinicians to review national guidance documents would be helpful, not least from a medicolegal perspective."*

(World Dental Federation)

Response: This point has been added to the following sentence in the "Antibiotic treatment" section (page 55 of the draft version):

"Up to 10% of antibiotic prescribing in the outpatient setting can be ***by dentists for the treatment of oral and dental infections or prophylaxis of surgical procedures,*** *of which a large proportion have been shown to be unnecessary or inappropriate. Efforts should be made to restrict the use of antibiotics only to situations when their use is strictly necessary".*

Comment: *"FDI supports the idea of focusing the chapter and infographic only on the four dental infections which may be appropriate for antibiotic treatment: abscess, pericoronitis, necrotizing periodontal disease and noma. Specifically dental pain is not an indication for antibiotics and should be removed throughout the document to avoid confusion. Similarly, dental conditions such as dental caries, gingivitis and chronic periodontitis should not be treated with antibiotics and should, therefore, be excluded from this chapter to assist clarity."*

(World Dental Federation)

Response: The few dental conditions that may require antibiotic treatment have been highlighted more clearly, as well as the key message that antibiotics are not appropriate for inflammatory conditions with the purpose of reducing inflammation or pain. The chapter has been reorganized, separating "Conditions that may require antibiotic treatment" from "Conditions that do not require antibiotic treatment". The first group includes abscesses, pericoronitis, necrotizing periodontal disease and noma.

Comment: *"Finally, in reference to non-severe penicillin allergy and the fact that "antibiotics are the most common cause of life-threatening immunologically-mediated reactions", as mentioned in the introductory chapter (lines 290, 291), FDI suggest to consider recommending the prescription of cephalosporin for a non-severe penicillin allergy."*

(World Dental Federation)

Response: The recommendation for antibiotics in the Book is based on antibiotics listed in the WHO Essential Medicines Lists for each indication. Therefore, alternative options (that are not specifically mentioned in the WHO Essential Medicines Lists) are not reported. This may, however, be considered for future updates of the AWaRe Book. There is a certain risk that these alternatives could be overused which may have negative consequences e.g. if the alternatives are less effective, less safe and have a higher potential for resistance (e.g. alternatives may often be non beta-lactam Watch group antibiotics).

Comment: *"We appreciate the strong emphasis on antibiotic stewardship and the specific mention that dental treatment is generally more appropriate than antibiotics in the management of dental infection."*

(World Dental Federation)

Comment: *"We appreciate the emphasis on dental treatment being generally more appropriate than antibiotics in the management of dental infection."*

(World Dental Federation)

Response: This comment refers to Table 1 (page 5 of the draft version) and Table 2 (page 8 of the draft version) of the Introduction and the positive feedback is appreciated.

Comment: *"Severe dental pain is not an indication for antibiotics. References to dental pain in relation to clinical indications for antibiotics should be removed."*

(World Dental Federation)

Response: It is agreed that severe dental pain is not an indication for antibiotic treatment and this is clearly stated in the chapter with sentences such as *"Dental pain is often due to inflammation rather than infection and careful diagnosis is required to ensure optimal treatment is provided and antibiotic use minimised"* (page 48 of the draft version) or again *"Antibiotics should not be used to cure toothache (pain relief is best achieved by a dental procedure not a dental prescription)"* (page 55 of the draft version). Reference to dental pain is made in the Clinical presentation sections where appropriate (e.g. Dental abscess – "*Tooth tenderness stimulated by chewing or food trapping is common*") and this was retained because pain is a common symptom of oral conditions.

Comment: *"Typical signs and symptoms of selected oral conditions. This chapter is about the use of antibiotics for dental infections not the diagnosis and treatment of dental pain. A statement to this effect early in the chapter will help clarify this chapter by removal of superfluous detail."*

(World Dental Federation)

Response: Reviewers suggest focusing the chapter only on those oral conditions that require antibiotic treatment (abscess, pericoronitis, necrotizing periodontal disease and noma) while removing references to other conditions that should not be treated with antibiotics (dental caries, pulpitis, dry socket / alveolar osteitis, gingivitis, non-necrotizing periodontitis). The decision was not to delete any section (including those referring to conditions that do not require antibiotics) but to reorganize the chapter separating "Conditions that may require antibiotic treatment" from "Conditions that do not require antibiotic treatment". The first group includes abscesses, pericoronitis, necrotizing periodontal disease and noma.

Comment: *"Cross linking to other chapters on periorbital cellulitis, cellulitis and sepsis is essential in relation to spreading infection which can quickly become life-threatening – _also cross links to chapters on acute lymphadenitis and osteomyelitis are essential."*

(World Dental Federation)

Response: Cross references have been made in the relevant chapters as suggested here and in other comments.

Comment: *"Replace 'not addressed in this chapter' with 'addressed in the surgical prophylaxis chapter'."*

(World Dental Federation)

Response: This comment refers to the initial disclaimer *"Antibiotic prophylaxis prior to dental procedures is not addressed in this chapter"*. The chapter on surgical prophylaxis does not address dental surgery but this could be considered in the future.

Comment: Key message 1: *"Mild or severe is irrelevant – dental pain is not treated with antibiotics. References to dental pain in relation to clinical indications for antibiotics should be removed. 'Symptomatic care' is a confusing term in this box."*

(World Dental Federation)

Comment: Key message 4: *"Replace 'Prevention of dental caries is key to maintain good dental health and includes…' with 'Key to prevention of dental infection is to maintain good oral health and includes…'. It is not correct to use caries in that sentence."*

(World Dental Federation)

Response: These comments refer to the Key messages presented at the start of the dental chapter (page 44 of the draft version). Key messages have been updated as suggested. Of note the final version of the Oral and dental infections chapter has been revised by a representative of the World Dental Federation and the final version of the "key messages" now includes additional changes and is presented below.

1. Untreated tooth decay is the most common global health condition. Dental caries and periodontal disease are largely preventable.
2. Key to prevention of dental infection is to maintain good oral health; this includes reducing sugar consumption, regular toothbrushing and interdental cleaning and stopping tobacco smoking.
3. Antibiotics are not needed for dental pain, which can be treated with analgesics or a dental procedure if appropriate.
4. Antibiotics should not be used before a dental procedure to decrease inflammation or to cure toothache.
5. Antibiotics are not needed before most dental procedures to prevent surgical site infections.
6. For people with a severe spreading dental infection, effective antibiotics and surgical management are vital. Sepsis and the spread of infection may block the upper airway or move to the brain and are life-threatening so should be managed promptly.

Comment: *"Add a link to one of the numerous WHO documents about tobacco control/cessation: https://www.euro.who.int/en/health-topics/disease-prevention/tobacco"*

(World Dental Federation)

Response: Link has been added for the "*WHO monograph on tobacco cessation and oral health integration*", (page 44 of the draft version).

Comment: *"Please ensure that all of these definitions are correct – FDI is happy to assist with this. We are not convinced this chapter on dental infections needs so many definitions about other dental conditions which are not caused by an infection. It would be clearer for the reader to focusing this chapter only on conditions for which antibiotics are appropriate (abscess, pericoronitis, and necrotizing periodontal disease and noma). Hence omit definitions for: apical periodontitis, dental caries, dry socket, gingivitis, periodontitis, plaque and pulpitis. A simple statement early in the chapter is required which states that other dental conditions (eg caries, gingivitis and chronic periodontitis) are not covered in this chapter as antibiotics are not indicated for their treatment."(World Dental Federation)*

Response: All definitions have been revised in consultation with a representative of the World Dental Federation.

Comment: *"Need to be clear in this section about the difference between the oral microbiome (of which plaque is part) and dental infections. Suggest outlining that many dental conditions relate to the microbiome/host response and are not appropriate for antibiotics." (World Dental Federation)*

Response: This comment refers to the pathophysiology section in particular the part about the role of dental plaque. The text (page 46 of the draft version) has been amended as shown:

"Most dental conditions relate to the oral microbiota in dental plaque and do not require antibiotic treatment. Dental plaque is a microbe rich biofilm which sticks to surfaces within the mouth, including teeth, dentures and orthodontic appliances. In the presence of free sugars, especially sucrose from the diet, plaque bacteria can create an environment that favours tooth decay (dental caries). Acid produced by plaque bacteria in the presence of sugar causes this destruction, which is reversible only when confined to the outer enamel layer. Unless it is removed, the progression of caries is hard to stop once it enters the deeper parts of the tooth.

Comment: *"Focus just on the main four conditions which may be appropriate for antibiotics: abscess, pericoronitis, necrotizing ulcerative gingivitis and noma (as highlighted in the first line of the infographic)." (World Dental Federation)*

Response: The chapter has been updated as suggested.

Comment: *"Include references to acute cervical lymphadenitis and periorbital cellulitis (often from infection of an upper canine tooth) as a sign of dental infection and cross refer to relevant chapter."*

(World Dental Federation)

Response: This comment refers to the sentence "*Please also refer to the chapter on sepsis if suspected*" (page 48 of the draft version). The sentence has been updated as shown:

"Please also refer to the chapter on sepsis if suspected. Oral and dental infections commonly involve the lymph nodes and can also spread through the fascial spaces of the head and neck to block the airway, move into the brain through the periorbital area and can present as osteomyelitis. Please refer to the chapters on sepsis, lymphadenitis and osteomyelitis if these sequalae are suspected".

Comment: *"Add 'without the need for antibiotics.' (line 140, page 49)"*

(World Dental Federation)

Response: This comment refers to the following sentence which has been modified as follows:

"A periodontal abscess is less common than an apical abscess. It is usually a localised accumulation of pus in the periodontal tissues (gums and alveolar bone supporting the tooth) which can be readily drained by professional cleaning of the periodontal pocket or by extraction of the tooth ***without the need for antibiotics"***.

Comment: *"Replace 'usually presents as….they are' (it doesn't usually present with visible holes) and replace with 'is' (line 142, page 48)"*

(World Dental Federation)

Response: This comment refers to the following sentence: *"Dental caries (tooth decay) usually presents as cavities (holes in the tooth), although they are often hidden in the space between the teeth"*. The sentence has been modified in consultation with a representative of the World Dental Federation and now reads as follows:

"Dental caries is the localized destruction of dental hard tissue (enamel or dentine) by acid-producing plaque bacteria in the presence of dietary sugar. This process can be reversible in early lesions. Caries can sometimes lead to the formation of cavities (i.e. holes in the tooth) which are often hidden in the space between the teeth".

Comment: *"The diagrams are confusing and in places inaccurate – _FDI can help refine the diagrams but suggest focus only on the four infective conditions (line 150)"*

(World Dental Federation)

Response: The chapter has been revised by a representative of the World Dental Federation and the conditions that may require antibiotic treatment have been more clearly highlighted.

Comment: *"Redraft as 'basic oral hygiene, diet supplementation with protein and nutrients, and antibiotics' (as per WHO guidelines on noma)"*

(World Dental Federation)

Response: The section on noma has been updated and the sentence mentioned in the comment has been amended as shown:

"If detected early, its progression can be rapidly halted, through basic oral hygiene rules, diet supplementation with proteins and nutrients and with antibiotics"

The link to the WHO document on noma has been added.

Comment: *"Add 'as it can quickly become life-threatening.' (line 183)"*

(World Dental Federation)

Response: This comment refers to the following sentence (page 50 of the draft version) which has been amended as shown"

"Cellulitis of the neck (e.g. Ludwig's angina) is a medical emergency ***as it can quickly become life-threatening"****.*

Comment: *"This section is confused about non-vital tooth and pulpal necrosis – _it appears the narrative discusses the same condition but uses different terms. Neither is a necessarily an infective condition but may be associated with a dental abscess. To avoid confusion, please focus only on diagnosing a dental abscess. Periodontal probing can identify a periodontal abscess if pus exudes from a pocket greater than 3mm – or necrotizing ulcerative disease if extremely tender gingival tissue and grey sloughing. (line 230)"*

(World Dental Federation)

Response: This comment refers to the paragraph on point-of-care test and investigations to assist diagnosis (page 52 of the draft version), which has been updated in consultation with a representative of the World Dental Federation as follows:

"Establishing the source of the dental pain/infection is an important element of accurate diagnosis and is essential to make appropriate treatment decisions. Sensitivity of the tooth to a cold stimulus indicates a vital pulp; depending on the intensity and duration of the stimulated pain this may indicate pulpitis. ***No response to cold may indicate a non-vital/necrotic pulp and tenderness to percussion (tapping the tooth) indicates that the pain originates in the supporting bone and may be due to an abscess. Periodontal probing can identify a periodontal abscess if pus exudes from a pocket greater than 3 mm or necrotizing ulcerative disease if there is extremely tender gingival tissue and grey sloughing"****.*

Comment: *"add ', and location of the radiolucency relative to the tooth helps differentiate between an apical, periodontal or perioendo abscess.' (line 238)"*

(World Dental Federation)

Response: This comment refers to the following sentence (page 52 of the draft version) which has been modified as follows:

"Radiographs are important for differentiating between the various causes of dental pain, including how far caries (decay) has progressed and where tenderness to percussion is associated with a radiolucency (i.e. black area on radiographic image) in the alveolar bone suggesting an abscess. ***Location of the radiolucency relative to the tooth helps differentiate between an apical or periodontal abscess"****.*

Comment: *"add 'occurs at 2-3 days after extraction and can last for up to 10 days' (line 253); add 'but no antibiotics unless osteomyelitis is suspected (refer to chapter on osteomyelitis)' (line 254)"*

(World Dental Federation)

Response: This comment refers to the following sentence (page 53 of the draft version) which has been modified as shown:

*"Dry socket (alveolar osteitis) is an extremely painful and common occurrence following dental extraction. **It occurs 2-3 days after extraction and can last for up to 10 days**. This condition requires optimum pain management but no antibiotics are needed **unless osteomyelitis is suspected; please refer to the chapter on osteomyelitis if this is suspected.***

Comment: *"After 'hypersensitivity to aspirin' add in brackets '(such as people with asthma)' (line 262); delete 'Not recommended for ..... such an effect.' (line 263)"*

(World Dental Federation)

Response: This comment refers to two footnotes to Table 2 (page 53 of the draft version). No changes to the text were made as not all patients with asthma have hypersensitivity to acetylsalicylic acid and the footnote already mentions to avoid the use of NSAIDs (including acetylsalicylic acid) in case of known hypersensitivity. As it is correct that paracetamol (acetaminophen) does not have an anti-inflammatory effect, the requested deletion was not made.

Comment: *"add treatment of noma as per WHO guidance (line 278)* https://apps.who.int/iris/handle/10665/254579*"*

(World Dental Federation)

Response: The link to the WHO document on the management of noma has been added to Table 3 (page 55 of the draft version). This includes the recommended antibiotic treatment to use for the different stages of disease.

Comment: *"Delete 'Acute' – the rest of the document uses the more up to date term 'Necrotizing ulcerative gingivitis' – although the most up-to-date terminology is 'necrotizing periodontal disease' (line 279)"*

(World Dental Federation)

Response: The footnote (Table 3 page 55 of the draft version) has been amended, as shown:

*"**Necrotizing periodontal disease** can often be resolved by procedures alone – antibiotics are often not required"*

Comment: *"This statistic about dental infections is incorrect – whilst dentistry is responsible for 10% of antibiotics prescriptions worldwide, in many countries (including the USA) these antibiotics are mostly for surgical prophylaxis rather than for the treatment of dental infections. Some other countries, such as the UK, take a different view of the evidence and prophylaxis is not routinely recommended. (line 282)"*

(World Dental Federation)

Response: Irrespective of the indication for use (prophylaxis or treatment), 10% of total antibiotics being used for dental conditions in the outpatient setting represents an important finding of which not all readers of the AWaRe Book may be aware (including dentists) therefore this statement is retained as it is an important reminder of the need to improve antibiotic use in this setting.

Comment: "Redraft 'Effective antibiotic treatment (along with a procedure for source control) is essential….' (line 292)"

(World Dental Federation)

Response: This comment refers to the following sentence (page 55 of the draft version) which has been modified as shown:

*"**Effective** antibiotic treatment (along with a procedure for source control) is essential in patients with severe, spreading dental infections".*

Comment: *"Delete 'severe pain' (line 294)"*

(World Dental Federation)

Response: This comment refers to the following sentence (page 55 of the draft version) which has been modified, as shown:

"Severe cases include those with systemic signs of infection, for example, facial swelling, inability to open the mouth, fever > 38.0 °C and tachycardia".

Comment: *"Redraft as 'Noma is usually the only indication for dual antibiotic therapy (using two antibiotics such as amoxicillin and metronidazole).' (lines 299-300)."*

(World Dental Federation)

Response: This comment refers to the following sentence: *"Using two antibiotics (e.g. amoxicillin and metronidazole) as adjunctive treatment is not necessary in the vast majority of cases", which has been amended as shown:*

"Using two antibiotics (e.g. amoxicillin and metronidazole) as adjunctive treatment is not necessary in the vast majority of cases and noma is usually the only indication for dual antibiotic therapy (using two antibiotics such as amoxicillin and metronidazole)".

Comment: *"Full stop after 'antibiotics' and then the next sentence 'Only penicillin options are recommended in this handbook for dental infections, which may be considered problematic by some prescribers and medicolegal advisors in urgent or emergency dental contexts.'*

For routine situations in which dentists prescribe antibiotics as surgical prophylaxis, the WHO approach is arguably reasonable. For urgent and emergency dental contexts, in which patients are already at high risk of airway compromise, however, adding swelling from an anaphylactic reaction could quickly become devastating and indefensible medicolegally. (line 303)"

(World Dental Federation)

Response: This comment refers to the sentence (page 55 of the draft version): *"The Handbook does not include alternative antibiotic options in cases of allergy to first-choice antibiotics which in the case of dental infections, where only penicillin options are recommended by this Handbook, may be considered problematic by some prescribers"*.

The recommendation for antibiotics in the Book is based on antibiotics listed in the WHO Essential Medicines Lists for each indication. Therefore, alternative options (that are not specifically mentioned in the WHO Essential Medicines Lists) are not reported. This may, however, be considered for future updates of the Book. There is a certain risk that these alternatives could be overused which may have negative consequences e.g. if the alternatives are less effective, less safe and have a higher potential for resistance (e.g. alternatives may often be non-beta-lactam Watch group antibiotics). Real-world experience shows for example that prescribers tend to overdiagnose presumed allergic contraindications to beta-lactams. Therefore, no changes to the text were made in regard to offering alternative options to those already recommended. However, the text acknowledges that it is important to assure that whenever possible a detailed history about allergies is sought and that in certain situations other options may be necessary.

Comment: *"Infections of the soft tissues make up around 50% of dental infections which are appropriate for antibiotic therapy. It is curious, therefore that these conditions are covered only as a footnote. This element gets more profile in the infographic than in the main paper. (line 314)"*

(World Dental Federation)

Response: This comment refers to a footnote to Table 4 (page 56 of the draft version) and to the corresponding infographic.

The footnote reads as follows: *"For the treatment of infections of the dental soft tissues (e.g. pericoronitis or necrotizing periodontal disease), metronidazole is an option"*.

The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the Book would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process).

Comment: *"Line 3 - key messages, I really like these. Commonly we hear no dental intervention will be done until they get antibiotics (and where I work IV antibiotics). Point 2 in the key messages is great and for point 3 in someone who is sick I agree antibiotics are necessary but even more so urgent dental intervention. Often, I know when there is so much trismus it is hard to perform the procedures but even significant periorbital cellulitis 2nd to dental infection can rapidly improve with this. In other words, this would be an extension of what is said for the mild cases and also apply to more significant ones".*

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Response: It is agreed and hoped that the importance of dental procedures as a form of source control is sufficiently clear.

Comment: *"INTRO For Table 2 line 156 - for the dental infections I agree with Amoxicillin, is there consideration for adding things like A) alternatives if allergic and B) DO NOT use list of antibiotics? I know this makes it more complicated but for example clindamycin is almost always used by community dentists where I practice. Something to consider for education perspective. As I read further in line 256 I see that alternatives to first line are not in the scope of this book. I would consider adding this for next iteration since allergy could be one reason but drug interactions, non-IgE mediated issues (eg SJS etc) could also be relevant so this might be helpful to consider. I see some reactions are mentioned in line 323 which is good but alternative agents might be useful to suggest".*

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Response: Please refer to the section "Allergies to antibiotics" for the response on the rationale of the approach used in the AWaRe Book.

Comment: *In the chapter "Dental infection" (page 44) I would insert a specific section for surgical site infection (SSI) in the key message. Many overprescriptions are related to this aspect and antibiotics are often prescribed pre- and post-operative or only post-operative for 5/6 days for this purpose even in procedures with low risk of infectious complications (e.g. extractions of erupted teeth). I would add as follows:*

"Antibiotic prophylaxis for the prevention of surgical site infection is only useful in particular types of procedures (e.g. bone graft) or with patients susceptible to infections (immunocompromised, uncontrolled diabetes etc.). If indicated, a single preoperative dose is enough".

(Gianluca Pingitore, Department of oral and maxillofacial sciences, Sapienza university of Rome, Italy)

Response: The issue of avoiding the use of antibiotics to prevent surgical site infections is already mentioned in the key messages of the Dental infections chapter.

In particular:

- *Antibiotics should not be used before a dental procedure to decrease inflammation or to cure toothache*
- *Antibiotics are not needed before most dental procedures to prevent surgical site infections.*

Of note, the AWaRe Book does not address antibiotic prophylaxis prior to dental procedures as this is beyond the scope of the Book.

Comment: *"Key messages (page 44). The first key message should focus on prevention*

1. Untreated tooth decay is the most common global health condition (1). Prevention of dental caries and periodontal disease is largely preventable and includes reducing sugar consumption, regular toothbrushing with interdental cleaning and stopping tobacco smoking.

2. Antibiotics are not usually needed for mild dental pain or infection, which can be treated by a dental procedure to remove the source of the infection such as, extraction or root canal therapy.

3. Antibiotics should not be used before a dental procedure to "calm an infection", to "decrease inflammation", to cure toothache or to prevent surgical site infections.

4. For people with a spreading severe dental infection and sepsis, effective antibiotics and surgical management are essential. Sepsis and spread of infection to block the upper airway are life threatening and should be managed promptly.

Reference:

1. Lancet Oral Health Series 2019 https://www.thelancet.com/series/oral-health"

(Andrew Smith, Professor and consultant microbiologist, chair of the Scottish antimicrobial prescribing group – dental)

Response: The order of the key messages (page 44 of the draft version) was changed and the content updated (including giving more prominence to prevention). The wording used for the key messages has been amended as shown:

1. Prevention of dental caries is key to maintain good dental health and includes reducing sugar consumption, regular toothbrushing and interdental cleaning and stopping tobacco smoking. (ORIGINAL TEXT)

   Updated text:

   1. Untreated tooth decay is the most common global health condition. Dental caries and periodontal disease are largely preventable.
   2. Key to prevention of dental infection is to maintain good oral health; this includes reducing sugar consumption, regular toothbrushing and interdental cleaning and stopping tobacco smoking.

2. Antibiotics are not needed usually for mild dental pain or infection, which can be treated with symptomatic care (or a dental procedure to remove the source of the inflammation or infection). (ORIGINAL TEXT)

   Updated text:

   3. Antibiotics are not needed for dental pain, which can be treated with analgesics or a dental procedure if appropriate.

3. Antibiotics should not be used before a dental procedure to "calm an infection", to "decrease inflammation", to cure toothache or to prevent surgical site infections.

Updated text:

4. Antibiotics should not be used before a dental procedure to decrease inflammation or to cure toothache
5. Antibiotics are not needed before most dental procedures to prevent surgical site infections.

4. For people with a spreading severe dental infection, effective antibiotics are vital; sepsis and the spread of infection toward vital structures may occur rapidly. These conditions can be life-threatening. (ORIGINAL TEXT)

Updated text:

6. For people with a severe spreading dental infection, effective antibiotics and surgical management are vital. Sepsis and spread of infection may block the upper airway or move to the brain and are life threatening so should be managed promptly.

Comment: *"Laboratory tests (page 51)- Patient microbiology tests: Access to routine microbiology testing in dental practice is very limited, so unavailable to assist in the management of most cases. However, for severe odontogenic infections in the presence of sepsis the collection of pus aspirates for culture and susceptibility testing is considered good clinical practice (see chapter on sepsis). In addition to providing a rational basis for changes to empirical antibiotic therapy, such data can be of use in surveillance to inform empiric antibiotic choice for dental infections".*

(Andrew Smith, Professor and consultant microbiologist, chair of the Scottish antimicrobial prescribing group – dental)

Response: An amendment in the text has been made, as shown:

"Routine microbiology tests are not required in most cases of dental infection but can be considered in severe cases requiring hospitalization, when culture and sensitivity testing ***(e.g. blood and / or pus aspirates culture)*** *can help in the selection of an appropriate antibiotic for example if cellulitis (e.g. Ludwig's angina) is spreading to vital structures or if sepsis is suspected. Please also refer to the chapter on sepsis if suspected."*

Comment: *"Using microbiology surveillance data: Historically, the collation of surveillance data linked to severe odontogenic infections has been confounded by a lack of consensus on bacterial isolation and characterisation methods, antimicrobial susceptibility testing methodology and definitions of resistance (2). International consensus on methodology and reporting for severe odontogenic infections is urgently required to monitor changes in bacterial susceptibility patterns and inform empiric antibiotic prescribing. As a minimum, patients admitted to secondary care facilities for management of severe infections should have high quality specimens (pus aspirates) taken for microbiology culture and susceptibility testing according to local protocols."*

(Andrew Smith, Professor and consultant microbiologist, chair of the Scottish antimicrobial prescribing group – dental)

Reference:

2. Robertson D, Smith AJ. The microbiology of the acute dental abscess. J of Med Micro 58: 155-162, 2009.

Response: The chapter on oral and dental infections belongs to the Primary health care section therefore it is focused on mild cases for which microbiology surveillance data are usually not available as mentioned in the text ("*Routine microbiology surveillance of oral microbiota does not generally take place, so such data are unavailable for clinical guidance*"). The management of severe cases of dental infections is not covered in the AWaRe Book except for when sepsis of dental origin is present in which case the reader is referred to the sepsis chapter (including for considerations on microbiology surveillance).

Comment: *"Antibiotic treatment (page 55) Lines 282 – 284: Up to 10% of total antibiotic prescribing in the outpatient setting can be for oral infections, with dental prescriptions for metronidazole accounting for the majority of the total metronidazole prescribed in healthcare (3). It has been shown that approximately 80% of dental prescriptions are unnecessary or inappropriate. Efforts should be made to restrict the use of antibiotics only to situations when their use is strictly necessary".*

(Andrew Smith, Professor and consultant microbiologist, chair of the Scottish antimicrobial prescribing group – dental)

Reference:
3. Smith AJ. Metronidazole resistance: a hidden epidemic? British Dental Journal March 2018 DOI: 10.1038/sj.bdj.2018.221"

Response: The text (page 55 of the draft version) has been amended as shown, focussing on the general concepts rather than specific antibiotics, which will vary globally.

"Up to 10% of antibiotic prescribing in the outpatient setting can be ***by dentists for the treatment of oral and dental*** *infections or prophylaxis of surgical procedures, of which a large proportion have been shown to be unnecessary or inappropriate. Efforts should be made to restrict the use of antibiotics only to situations when their use is strictly necessary".*

Comment: *"Lines 297-301: When antibiotic treatment is considered necessary, empiric use of phenoxymethylpenicillin or amoxicillin as indicated in Table 4 is considered appropriate.*

Phenoxymethylpenicillin (penicillin V) has a narrower spectrum of antimicrobial activity than amoxicillin but has equivalent efficacy and clinical outcomes in acute dento-alveolar infections (4). Limiting unintended consequences of antimicrobial use is a key principle of antimicrobial stewardship and since amoxicillin has a broader spectrum of activity than penicillin V, it has a greater impact on selection of resistance in the host micro-flora (5).

Phenoxymethylpenicillin (penicillin V) should be used as first line therapy with amoxicillin reserved for patients where compliance is likely to be more challenging.

There is no evidence that for the management of infections in the primary care setting, the combined use of two antibiotics such as amoxicillin and metronidazole is associated with an improved clinical outcome and is more likely to drive antimicrobial resistance".

(Andrew Smith, Professor and consultant microbiologist, chair of the Scottish antimicrobial prescribing group – dental)

References:
4. Martins JR, Chaga OL Jr, Velasques BD, Bobrowski AN, Correa MB, Torriani MA. The use of antibiotics in odontogenic infections: What is the best choice? A systematic Review. J Oral Maxillofacial Surg 75: 2606.e1–2606.e11, 2017.
5. Zimmerman P, Curtis N. The effect of antibiotics on the composition of the intestinal microbiota - a systematic review. J Infect 79:471-489, 2019."

Response: The WHO Essential Medicines Lists (on which the Antibiotic Book is based) list amoxicillin and phenoxymethylpenicillin as alternative first choice options for dental infections and the order in which they are presented in Table 4 (page 56 of the draft version) is alphabetical, this has been clarified in the table.

Comment: *"References to dentistry should not be restricted to the dental chapter but should also be included elsewhere as appropriate. For example:*

- *In some countries, dentists prescribe antibiotics more commonly for surgical prophylaxis than for dental infections.*
- *Periorbital cellulitis is a recognised consequence of some severe dental infections".*

(Arianne Matlin, British dental association and Wendy Thompson, lead on antimicrobial resistance, College of general dentistry)

Response: References to dentistry have been added to the periorbital cellulitis section of the "Eye infections" chapter (page 81 of the draft version). In particular, the possibility that a severe dental infection may be the source of infection for periorbital cellulitis has been added in the epidemiology section as follows:

*"Most cases [of periorbital cellulitis] are exogenous and result from adjacent infection (hordeolum, dacryocystitis, infection of the periorbital sinuses, **severe dental infection**) or follow animal and insect bites or trauma of the eyelid."*

The chapter on "Surgical prophylaxis" does not address antibiotic prophylaxis prior to dental procedures and this has been clarified (the chapter on "Dental infections" already states that this aspect is not addressed although it could be considered as an addition for future updates of the AWaRe Book).

Comment: *"We recommend substantial revision of the dental chapter, which currently contains inaccuracies. In particular, a clear distinction should be made between conditions such as caries, gingivitis and periodontitis that do not require antibiotics and dental infections for which antibiotics may be indicated".*

(Arianne Matlin, British dental association)

Comment: *"Significant revision of the dental chapter is required for it to be accurate, including ensuring that there is clarity between the normal host response to the microbiome (which does not require antibiotics eg gingivitis/periodontitis/caries) and frank dental infections (which may require antibiotics)".*

(Wendy Thompson, lead on antimicrobial resistance, College of general dentistry)

Response: The few dental conditions that require antibiotic treatment have been highlighted, and greater emphasis has been made in the key message that antibiotics are not appropriate for inflammatory conditions with the purpose of reducing inflammation or pain.

The chapter has been revised in collaboration with a representative of the World Dental Federation.

Comment: p15 & p17. *"Consider offering penicillin as first choice and amoxicillin as second choice because penicillin exerts less selection pressure for resistance (e.g. ESBL) compared with amoxicillin."*

(British Society for Antimicrobial Chemotherapy)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the AWaRe Book would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process).

Comment: *"The UK has a number of guidelines for prescribing dental antibiotics, including SDCEP and CGDent [1, 2]; but we welcome the development of this book and recognise its value, particularly in countries without existing guidance. It would be useful to consider how the book and infographics will be accessed (electronically versus hard copy); if electronically then what device is likely to be used (e.g. via a mobile. tablet device or laptop) to inform formatting. If an electronic format is useful (which we think it will be) then embedded web links to resources would be useful, rather than written references. We think it is particularly pertinent to design the book and infographics to support safe prescribing and designing of this information in such a way that the practitioner always considers contra-indications and potential allergies.*

In addition, it is unlikely that individual will read a whole book in detail when looking for guidance so care should be taken to ensure that important information is easily seen and weblinks to recommended reading are provided rather than just referencing 'the chapter on allergies' etc. "

References:

1. SDCEP guidance: https://www.sdcep.org.uk/published-guidance/drug-prescribing

2. CGDent guidance: https://cgdent.uk/wp-content/uploads/2021/08/Antimicrobial-Prescribing-in-Dentistry-2020-online-version.pdf

(UK Health Security Agency)

Response: The AWaRe Book and infographics are accessible on the WHO website as downloadable pdf documents (https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2022.02) and also as an app for electronic devices (e.g. smartphones, tablets) with weblinks for referenced documents (https://app.firstline.org/en/clients/276-world-health-organization). As to safe prescribing in terms of designing the information to consider contra-indications and allergies, this is beyond the scope of the AWaRe Book / app and it is not going to be part of the information provided in each chapter / infographic. This is made clear in the Introduction (Box 2, page 2 of the draft version) where general considerations about prescribing are made.

4.5 Lymphadenitis

Comment: *"Table 1 - line 34-36 I recognize that this is not an exhaustive list and the bacterial list there is great, though more frequently inguinal might be worth adding bubonic plague into the table. TB is also mentioned above in the text but NTM (MAC etc) should definitely be mentioned explicitly as it is presents occasionally in children in particular. I like all the other on the ddx. Inclusion of non-infectious causes in the text above the table as is done is also good".*

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Response: Table 1 (page 59 of the draft version) has been amended to include *Yersinia pestis* (the causative pathogen of bubonic plague), although it is a very rare cause of acute lymphadenitis. Concerning nontuberbulous mycobacteria (NTM), the footnote of the table has been updated as shown:

"Pathogens associated with chronic lymphadenitis such as mycobacteria (including nontuberculous) are not included in the table."

Comment: *"Table 1 LN treatment empiric line 85 - while I do not disagree that Amoxicillin-clavulanic acid can be used for this treatment, if we saw that anaerobes are rare then why is this the first choice provided? Consider putting in cephalexin or cloxacillin first (and also provisions for MRSA covering drugs) and Amox-Clav as a non-first choice. Others often add aerobic coverage in paediatrics in young children + metronidazole. That is not my regular practice but several of my colleague do add this".*

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Comment: P18-20. *"Put cloxacillin or flucloxacillin above others and only consider amoxicillin-clavulanate as 2nd line."*

(British Society for Antimicrobial Chemotherapy)

Response: This comment refers to the empiric treatment table (pages 61-62 of the draft version).

The order with which multiple antibiotic options for a certain indication are presented in the Book is always alphabetical. For this reason, the three alternative first choice options listed in the WHO Essential Medicines Lists for the treatment of mild skin and soft tissue infections (from which the recommendations for acute lymphadenitis are extrapolated) are listed as follows, potentially giving the impression that amoxicillin-clavulanic acid should be used first:

- Amoxicillin-clavulanic acid
- Cefalexin
- Cloxacillin

However, a note indicates that among the three options, cloxacillin and cefalexin have a narrower spectrum of antibacterial activity compared to amoxicillin clavulanic acid and would at least theoretically be preferable to use from an antibiotic stewardship perspective (the exact impact on selection and spread of antibiotic-resistant bacteria of different antibiotics being understudied). In 2017, the Expert Committee responsible for updating the WHO Essential Medicines Lists, recommended amoxicillin-clavulanic acid and cloxacillin for reasons of parsimony because both antibiotics provide good coverage

for staphylococcal (non-MRSA) and streptococcal infections, which are the leading causes of mild to moderate community-acquired skin and soft tissue infections worldwide. The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the AWaRe Book (including alternatives for allergic patients or for MRSA) would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process).

Comment: *"Penicillin allergy option required eg doxycycline (adults) or clarithromycin / erythromycin in children."*

(British Society for Antimicrobial Chemotherapy)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the AWaRe Book (including alternatives for allergic patients) would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process).

Comment:: *"Cervical lymphadenopathy is commonly associated with dental infections and the chapters should be cross-referenced; Add 'Dental infections are rarely self-limiting and will normally require treatment. (See Chapter on Dental Infections)'; Consider modify to – 'HIV infection, tuberculosis, spreading dental infection and head and neck cancer should always be considered in the differential diagnosis'"*

(World Dental Federation)

Response: These comments refer to the Key messages in the acute bacterial lymphadenitis chapter (page 58 of the draft version).

To limit the number of key messages in alignment with the other chapters, some of the suggested text has been added in the main body of the chapter instead than in the Key messages.

1. Antibiotics are not needed for the great majority of cases of enlarged lymph nodes as they are caused by viral infections.
2. A watchful waiting approach is reasonable when the patient is not severely ill and bacterial lymphadenitis or a malignancy is not suspected, because the condition is usually self-limiting.
3. HIV infection, tuberculosis and spreading dental infection should always be considered in the differential diagnosis.
4. If a bacterial lymphadenitis is suspected, empiric antibiotic treatment should cover *Staphylococcus aureus* and *Streptococcus pyogenes* with Access group antibiotics

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Comment: *"Dental causes need to be added to the list (line 10-11, page 58)"*

(World Dental Federation)

Response: This comment refers to the Definition and in particular to the sentence *"Lymphadenitis has several infectious and non-infectious causes, including skin infections, cancer or lymphoproliferative disorders"*, the sentence has been amended as shown:

"Lymphadenitis has several infectious and non-infectious causes, including skin infections, ***dental infections****, cancer or lymphoproliferative disorders".*

Comment: *Dental infections are probably a far more likely cause of cervical lymphadenopathy than sexually transmitted disease. Palpation of lymph nodes is one of the chairside tests undertaken to determine the diagnosis of a dental infection which will usually require prompt clinical intervention to avoid the inappropriate use of antibiotics.*

(World Dental Federation)

Response: This comment refers to the Clinical presentation and in particular to the sentence (page 60 of the draft version) *"As the first step, it is important to identify the cause of the enlargement. Location of the enlarged lymph node and accompanying signs and symptoms of infection (e.g. skin lesion, pharyngitis, signs and symptoms of a sexually transmitted disease) can help establishing the diagnosis. History and physical examination usually help in the diagnosis and guide the investigation and treatment"*.

The sentence has been amended as shown:

"As the first step, it is important to identify the cause of the enlargement. Location of the enlarged lymph node and accompanying signs and symptoms of infection (e.g. ***symptoms of a dental infection****, skin lesions, pharyngitis, signs and symptoms of a sexually transmitted disease) can help establishing the diagnosis. History and physical examination* ***(including palpation of lymph nodes)*** *usually help in the diagnosis and guide the investigation and treatment"*

The comment also refers to the Antibiotic Treatment section (line 78-81, page 60-61 of the draft version) and in particular to the following sentence, which has been amended as shown:

"This approach (watchful waiting) is reasonable because the condition is frequently self-limiting – for example, mild cervical lymphadenitis is usually caused by a viral infection of the upper respiratory tract, especially in children ***but could also be associated with a dental infection.****"*

4.6 Eye infections

Conjunctivitis

Comment: *"Table 2 conjunctivitis line 83/84 would consider adding in VZV together with HSV".*

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Response: Table 2 (page 68 of the draft version) has been updated adding Varicella-zoster virus to the list of common pathogens that can cause viral conjunctivitis.

Comment: *"Page 69 (line 90/91) – In relation to viral and allergic conjunctivitis would it be possible to add that viral conjunctivitis may present also with watery discharge? The reason for including this clarification is that the sentence currently included in the document could mislead the clinician that the patient has bacterial and not a viral infection and start unnecessary treatment with antibiotics. More information about this topic can also be found via the following two sources:*

1. https://www.ncbi.nlm.nih.gov/books/NBK470271/

2.https://www.uptodate.com/contents/conjunctivitis?search=viral%20conjunctivitis&source=search_result&selectedTitle=1~19&usage_type=default&display_rank=1#H362487768"

(Stephanie Kohl, Policy and advocacy officer at the European association of hospital pharmacists)

Response: The sentence (page 68-69 of the draft version) has been amended as shown:

"Patients may refer to all discharge as pus; however, in bacterial conjunctivitis, the complaint of discharge predominates, while in viral and allergic conjunctivitis patients report a burning and gritty feeling or itching ***and the eye usually presents with a watery discharge****."*

Comment: p21-22. *"Chloramphenicol eye drops as an alternative."*

(British Society for Antimicrobial Chemotherapy and The UK Paediatric Antimicrobial Stewardship)

Comment: Page 63: *"For cases which require the use of topical antibiotics we would suggest: Chloramphenicol 0.5% eye drop OR 1% ointment to continue until 48 hours after the resolution of symptoms; instead of tetracycline. [1,2]"*

References:

1. College of Optometrists, 2021, Clinical Management Guidelines: Conjunctivitis (bacterial). https://www.college-optometrists.org/clinical-guidance/clinical-management-guidelines/conjunctivitis_bacterial

2. Medicines and Healthcare products Regulatory Agency, 2021. Chloramphenicol eye drops containing borax or boric acid buffers: use in children younger than 2 years. https://www.gov.uk/drug-safety-update/chloramphenicol-eye-drops-containing-borax-or-boric-acid-buffers-use-in-children-younger-than-2-years#review-of-the-interpretation-of-eu-guidance-on-boric-acid-and-borates-as-excipients

(UK Health Security Agency)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines and chloramphenicol (eye drops) is not included in the lists, therefore no changes to the text were made. Changes to

recommendations in the AWaRe Book would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process).

Ophthalmia neonatorum (Conjunctivitis of the newborn)

Comment: Page 156 *"For ophthalmia neonatorum we would suggest:*

- *1st line: Cefotaxime single dose IV plus chloramphenicol eye drops; instead of ceftriaxone*
- *2nd line: Gentamicin; instead of spectinomycin"*

References:
Workowski, K.A. and Bolan, G.A., 2015. Sexually transmitted diseases treatment guidelines, 2015. MMWR. Recommendations and reports: Morbidity and mortality weekly report. Recommendations and reports, 64(RR-03), p.1.

(UK Health Security Agency)

Comment: *"Spectinomycin IM Gonococcus: gentamicin"*

(The UK Paediatric Antimicrobial Stewardship)

Response: The AWaRe Book is closely aligned with other WHO guidelines, in this case WHO guidelines for the treatment of Gonorrhoea and Chlamydia (references below) and with the WHO Essential Medicines Lists. Changes to recommendations in the AWaRe Book would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process).

For more detail:

- Guideline for the treatment of *Neisseria gonorrhoeae* (2016) https://apps.who.int/iris/handle/10665/246114
- Guideline for the treatment of *Chlamydia trachomatis* (2016) https://apps.who.int/iris/handle/10665/246165
- Guidelines for the management of symptomatic sexually transmitted infections (2021) https://apps.who.int/iris/handle/10665/342523

Comment: *"MSF recommends ceftriaxone IV/IM for both gonococcal and chlamydial infections, as it is clinically difficult to distinguish the cause of neonatal conjunctivitis, unless maternal infection is confirmed (which is not often the case).*

MSF recommends mentioning erythromycin as an alternative to azithromycin (as azithromycin is often not available). MSF recommends adding a precaution for increased risk of pyloric stenosis with macrolides, which is higher with erythromycin"

(Médecins Sans Frontières - MSF)

Response: While it is acknowledged that without laboratory confirmation it would be nearly impossible to distinguish clinically gonococcal and chlamydial conjunctivitis in a neonate, no changes were made to treatment recommendations in alignment with WHO guidelines for the treatment of Gonorrhoea

and Chlamydia (references below). However, the following text has been added in the clinical presentation section (page 69 of the draft version):

"In neonates, conjunctivitis can be caused by a range of pathogens. In general gonococcal or staphylococcal infection is more likely to present early with symptoms in the first 5 days of life, with chlamydial infection generally presenting later (>5 days after birth)".

Of note, ophthalmia neonatorum (i.e. conjunctivitis of the neonate) is not covered in the 2021 syndromic WHO guidelines and therefore treatment recommendations are based on the 2016 WHO guidelines and should always be targeted (e.g. maternal infection confirmed).

Regarding the use of erythromycin (as an alternative to azithromycin) for Chlamydial conjunctivitis, this is mentioned in a footnote (Table 3 pages 147-148 of the draft version) because erythromycin is not listed in the WHO Essential Medicines Lists for this indication (except as topical eye treatment).

For more detail:

- Guideline for the treatment of *Neisseria gonorrhoeae* (2016) https://apps.who.int/iris/handle/10665/246114
- Guideline for the treatment of *Chlamydia trachomatis* (2016) https://apps.who.int/iris/handle/10665/246165
- Guidelines for the management of symptomatic sexually transmitted infections (2021) https://apps.who.int/iris/handle/10665/342523

Endophthalmitis

Comment: *"Table 4 endophthalmitis is usually broken into ddx via mechanism of injury and if foreign body in place. Would consider modifying to the same."*

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Response: Table 4 (page 71 of the draft version) has been updated and pathogens have been separated as suggested by mechanism of injury.

Comment: *"Table 5 line 55/text for endophthalmitis should really emphasize that the standard of care is intravitreal treatment - I don't disagree with systemic antibiotics but it needs to be a bold statement and that this is a surgical emergency".*

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Response: The text already highlights the importance of urgent referral to an ophthalmologist, where available (Lines 39-41, page 73 of the draft version): *"This condition should be treated by an ophthalmologist where available. Urgent referral of the patient to an ophthalmologist, if available, should be considered when endophthalmitis is suspected because this condition could potentially threaten the patient's sight."*

Concerning the importance of intravitreal treatment, the text (page 73 of the draft version) has been amended as shown:

"With bacterial endophthalmitis ***the cornerstone of treatment is intravitreal injection of antibiotics.*** *There are two common approaches:*

- *"tap and inject": first a sample of vitreous humour is collected for culture (through vitreous aspiration) and then antibiotics are injected into the vitreous*
- *vitrectomy is performed – that is, eye surgery to remove some or all the inflamed vitreous from the eye as a form of source control and during the procedure, the antibiotic is injected into the vitreous*

Systemic antibiotics *(in combination with intravitreal antibiotics)* ***should also be considered given the severity of this condition****, especially when referral to an ophthalmologist is not readily available (Table 6 of the draft version). In cases of endogenous infections, systemic antibiotics should always be given.* ***However, evidence of their added benefit (e.g. on visual acuity) compared to intravitreal antibiotics alone is still controversial****. The ability to rapidly reach adequate concentrations in the eye varies by antibiotic."*

Comment: *"Endophthalmitis in immunocompetent patient p23 – If current or recent central venous catheter, injecting drug user or known candidaemia add: intravitreal amphotericin 0.005mg in 0.1ml AND oral Fluconazole 400mg 24-hourly.*

Endophthalmitis in immunocompromised patient and penetrating eye injury: intravitreal Vancomycin 1mg in 0.1ml AND Ceftazidime 2mg in 0.1ml AND amphotericin 0.005mg in 0.1ml AND Oral Voriconazole 400mg 12-hourly for two doses then 200mg 12-hourly."

(British Society for Antimicrobial Chemotherapy)

Response: The AWaRe Book is focused on antibiotic treatment and does not provide guidance on the use of antifungals. Therefore, even though the text acknowledges that endophthalmitis may be caused by fungi, no changes to the text were made. Of note, the intravitreal injection of vancomycin and ceftazidime is already recommended in the Book for this condition.

Orbital cellulitis

Comment: *"Why are no treatment options given? I only ask because it is inconsistent with all the other sections where treatment choices are given. This is seen commonly in pediatric ID practice. Would suggest adding treatments in. This can be nicely contrasted and compared to the next chapter which is periorbital cellulitis and their differences in presentation and treatment as well as management".*

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Response: In the initial phase of preparation of the AWaRe Book, antibiotic options for this infection were listed. They had been extrapolated from options recommended in the WHO Essential Medicines Lists for mild skin and soft tissues infections (i.e., amoxicillin-clavulanic acid, cefalexin and cloxacillin). However, while this decision was maintained for preseptal cellulitis, it was finally decided not to address the antibiotic treatment of orbital cellulitis because this is a potentially severe condition for which there currently is no antibiotic listed the WHO Essential Medicines Lists. A thorough review of the evidence will be required if this condition is to be included in the future.

Periorbital cellulitis

Comment: p27&28 *"flucloxacillin / cloxacillin do not have activity against respiratory Gram-negative pathogens so why are they recommended with equal prominence to co-amoxiclav and cefalexin?"*

(British Society for Antimicrobial Chemotherapy)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines and recommendations for the empiric treatment of periorbital cellulitis are extrapolated from those for mild skin infections. Changes to recommendations in the AWaRe Book would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process). However, as suggested a comment has been added as follows:

"Cloxacillin has a narrower spectrum of antibacterial activity than amoxicillin+clavulanic acid and cefalexin with limited coverage of Gram-negative bacteria from the upper respiratory tract that may cause periorbital (or preseptal) cellulitis (e.g. Haemophilus influenzae, Moraxella catarrhalis). Therefore, when this infection is suspected, amoxicillin-clavulanic acid or cefalexin are the preferred options".

Comment: "Alternatives in penicillin allergy – clindamycin or levofloxacin." *(British Society for Antimicrobial Chemotherapy)*

Response: The AWaRe Book currently does not provide alternative regimes in case of allergy, partly because antibiotic allergy is overdiagnosed in many settings potentially leading to treatment with antibiotics that are less effective, less well tolerated and have a higher risk of selection of resistance (e.g. Watch macrolides instead of Access beta-lactams). Therefore, no changes to the text were made.

Uveitis

Comment: *"Table 1 add in VZV".*

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Response: Table 15 (page 85 of the draft version) has been updated to include Varicella-zoster virus.

Trachoma

Comment: p29-30. Is six weeks' treatment with tetracycline eye ointment necessary? The alternative – azithromycin – is recommended for just 3 days.

(British Society for Antimicrobial Chemotherapy)

Response: Topical treatment with tetracycline for 6 weeks is only used when azithromycin (oral or eye drops) is not available.

4.7 Community-acquired Pneumonia - Mild

Comment: *"Lines 141 & 176. I agree that GenXpert is the test of choice for TB diagnosis. I suggest mentioning TB LAM (lipoarabinomannan urine test) for severely HIV immunocompromised patients to rule in TB in settings with high TH-HIV coinfection".*

(Dr Mireille A. Mpalang Kakubu, University of Pittsburgh (USA) and Ministry of health and social services of Namibia)

Response: The test has been added as it is included in the 3rd WHO Model list of Essential *in-vitro* Diagnostics (https://apps.who.int/iris/handle/10665/339064) to aid in the diagnosis of TB in patients living with HIV. For more information on this topic, the interest reader can refer to the WHO 2019 policy update "Lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis of active tuberculosis in people living with HIV" (https://apps.who.int/iris/handle/10665/329479).

Comment: p32 mild-to-moderate cases in adults – *"please consider removing co-amoxiclav from options – the number needed to treat with co-amoxiclav to cover a beta-lactamase producing organism resistant to amoxicillin is too high to justify the risk of widespread use of this drug for this common indication and the associated selection pressure for resistant Gram-negative organisms (e.g. ESBL-producing) in the intestinal flora. Offering clarithromycin as a second-choice agent is preferable to avoid Gram-negative selection pressure."*

(British Society for Antimicrobial Chemotherapy)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the Book would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process). Therefore, no changes to the text were made. The large systematic review that directly compared exposure to antibiotics by AWaRe category and isolation of multidrug resistant bacteria (Sulis et al. 2022) did not suggest that macrolide or amoxicillin-clavulanic acid exposure had a significantly different risk of subsequent selection of resistant Gram-negative bacteria.

Comment: *"Aetiologies: MSF recommends adding some important common risk factors (e.g. GNB – advanced AIDS; C. psittaci: exposure to birds). MSF recommends considering adding "atypicals" in the case of extra-pulmonary signs"*

(Médecins Sans Frontières - MSF)

Response: Only some of the suggestions have been accepted and some text has been added to the footnotes as shown below (Table 1 page 95 of the draft version). Suggestions that have not been adopted are 1) AIDS being a risk factor for pneumonia caused by Gram-negative bacteria and, 2) the comment on extra-pulmonary signs and infections caused by "atypical bacteria". There is not enough evidence to link Gram-negative bacteria with AIDS and considering the high prevalence of patients living with HIV in certain countries, this could lead to overuse of empiric Gram-negative bacteria coverage for any patient with HIV presenting with mild CAP which would favor AMR development.

Table 1 (draft version) Pathogens most frequently associated with community-acquired pneumonia (in descending order of frequency)

Typical bacteria	Atypical bacteria[b]	Respiratory viruses	Other pathogens to consider in specific settings
Streptococcus pneumoniae[a] *Haemophilus influenzae* *Moraxella catarrhalis* *Staphylococcus aureus* Enterobacterales (e.g. *Escherichia coli, Klebsiella pneumoniae)*	*Mycoplasma pneumoniae*[b] *Chlamydophila pneumoniae*[b] *and Chlamydophila psittaci*[b] *Legionella* spp. *Coxiella burnetii*	Influenza virus (A and B) Respiratory syncytial virus[c] Metapneumovirus Parainfluenza virus Coronavirus (including SARS-CoV-2) Adenovirus Rhinovirus Other respiratory viruses	*Burkholderia pseudomallei* (South-East Asia, Australia) *Mycobacterium tuberculosis* *Pneumocystis jirovecii* (in people with HIV or other types of cellular immunosuppression)

[a]The most common bacterial cause of CAP in all age groups (beyond the first week of life) is *Streptococcus pneumoniae*.

[b]Atypical bacteria remain colourless with Gram staining. They also have intrinsic resistance to beta-lactams. *Mycoplasma pneumoniae* and *Chlamydia* spp. are more frequent in children > 5 years (compared with younger children) and in young adults. Risk factors for *Chlamydia psittaci* include exposure to birds.

[c]Up to 50% of cases of pneumonia in children < 5 years are caused by a virus, most commonly respiratory syncytial virus

4.8 Chronic Obstructive Pulmonary Disease (COPD) exacerbations

Comment: *"INTRO For Table 2 line 156 for COPD exacerbations should a comment be added of "when antibiotics are required" since earlier on in Table 1 it implied antibiotics are often not used. Some differentiation between these recommendations (severity based etc.) would be helpful".*

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Response: This comment refers to Table 2 in the Introduction (page 8-9 of the draft version). The Table clearly refers to antibiotic options to use "*when an antibiotic is indicated*" based on the clinical assessment of the patient (see footnote) and is focused on empiric treatment of mild cases usually managed in the primary health care setting. Differentiations in terms of management based on the severity of the clinical presentation are addressed in the "Antibiotic treatment" section of the "Exacerbations of COPD" chapter (page 105 of the draft version).

Comment: p35 – *"Severe cases with penicillin allergy should use levofloxacin."*

(British Society for Antimicrobial Chemotherapy)

Response: The AWaRe Book currently does not provide alternative regimes in case of allergy, partly because antibiotic allergy is overdiagnosed in many settings potentially leading to treatment with antibiotics that are less effective, less well tolerated and have a higher risk of selection of resistance (e.g. Watch macrolides instead of Access beta-lactams). Therefore, no changes to the text were made.

4.9 Acute infectious diarrhoea / gastroenteritis

Comment: *"On page 5: May read "the cornerstone of treatment is re-hydration and electrolyte replacement".*

(Commonwealth pharmacists association)

Response: This comment refers to the acute diarrhoea part of Table 1 in the Introduction (page 5 of the draft version). The text in the Table has been amended as suggested.

Comment: *"I have doubts about the place of schistosomiasis in the list of acute diarrhoeas next to Giardia and Entamoeba. The gastroenterological presentation is really very infrequent and many other parasites are much more likely, Cyclospora cayetanensis and Cryptosporidium for example. In order to remain concise, I would propose not to keep Schistosoma."*

(Dr Jean-Marc Schwob, Tropical and travel medicine unit, Geneva university hospitals, Switzerland)

Response: This comment refers to the following paragraph in the Acute infectious diarrhoea / gastroenteritis chapter (page 108 of the draft version), which has been amended as shown. The WHO website page on Schistosomiasis has been referenced.

2. *Patients with bloody diarrhoea (dysentery or invasive diarrhoea with damage to the intestinal mucosa). In these patients, the most likely cause are bacteria, mostly Shigella spp., Campylobacter spp., intestinal/non-invasive-diarrheal non-typhoidal Salmonella or enterotoxigenic Escherichia coli. These cases may benefit from antibiotic treatment. In addition to dehydration these infections can be*

*complicated by sepsis and malnutrition. **Entamoeba histolytica can rarely also cause bloody diarrhoea** weeks or months after the infection; often these infections are responsible for chronic rather than acute bloody diarrhoea. **Other protozoal parasites and very rarely Schistosoma can also cause bloody diarrhoea; only Schistosoma mansoni and Schistosoma japonicum, the intestinal species.***

Comment: *"Table 1 Line 113 (Introduction) could consider adding here that most do not need antibiotics and in some cases antibiotics can do harm (such as in shiga toxin bacteria resulting in increased risk of HUS) and also prolonged shedding for many bacterial GI pathogens particularly as it pertains to children. I think this is an important inclusion because I think many people think about resistance and C.diff but these are other specific issues. This could go into the comments section of the table beside "acute diarrhea"." AND "For diarrhea chapter please see my earlier comments about HUS and prolonged shedding of bacteria etc."*

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Response: This comment refers to the acute diarrhoea part of Table 1 in the Introduction (page 5 of the draft version). The risk of "doing harm" by giving antibiotics in certain cases of infectious diarrhoea is addressed in the "Infectious diarrhoea / gastroenteritis" chapter (page 111, lines 139-142 of the draft version) where the potential risk of worsening symptoms with the use of antibiotics in children is mentioned. The text in the Infectious diarrhoea / gastroenteritis chapter has been amended as shown:

*"Bloody diarrhoea could be caused by certain strains of Escherichia coli (Shiga toxin-producing Escherichia coli also known as enterohaemorrhagic Escherichia coli). In these cases (mostly in children) the use of antibiotics is controversial because there is a theoretical concern that it could worsen symptoms of haemolytic uraemic syndrome characterized by haemolytic anaemia, renal injury and low platelets. **However as there is clear evidence of benefit in shigellosis, empiric treatment with antibiotics should not be withheld because of a concern of causing haemolytic uraemic syndrome**".*

It was decided not to change the table in the Introduction to keep the message concise.

Comment: *"Line 144: I agree with the choice of antibiotics for treating specific causes of diarrhoea. However, I am concerned about HIV patients on sulfamethoxazole-trimethoprim as prophylaxis. This section needs clarification for this category of patients while selecting the antibiotic."*

(Dr Mireille A. Mpalang Kakubu, University of Pittsburgh (USA) and Ministry of health and social services of Namibia)

Response: The first- and second- choice antibiotic treatment options for the treatment of acute infectious diarrhoea in people living with HIV is the same as for immunocompetent patients.

However, in patients taking sulfamethoxazole-trimethoprim for prophylaxis a different molecule should be considered for treatment unless susceptibility is confirmed because of the potential risk of resistance. The following footnote has been added to Table 6 (page 112 of the draft version) to clarify this aspect.

"[e] In patients taking sulfamethoxazole+trimethoprim for prophylaxis, a different antibiotic should be used for treatment unless susceptibility is confirmed."

Comment: *"The use of ciprofloxacin in children: I agree with you on choosing this antibiotic as 1st line for treating diarrhoea. However, I suggest inserting a note on the cautious use of ciprofloxacin in children due to possible cartilage damage."*

(Dr Mireille A. Mpalang Kakubu, University of Pittsburgh (USA) and Ministry of health and social services of Namibia)

Response: The AWaRe Book aims to be a practical guide for prescribing and does not provide details of potential side effects of all the antibiotics included. However, this is an important point and FDA black box warnings and alerts (e.g. concerning quinolones and macrolides) have now been summarised where these antibiotics are mentioned.

Comment: *"MSF recommends antibiotic treatment for all causes and cases of bloody diarrhoea. MSF protocols differentiate bloody from non-bloody diarrhoea, and antibiotic treatment is not limited to only cases of severe bloody diarrhoea or in immunosuppressed patients."*

(Médecins Sans Frontières - MSF)

Response: The AWaRe Book currently suggests antibiotic treatment only in case of significant acute bloody diarrhoea and in severely immunocompromised patients. The suggestion to recommend antibiotic treatment for all cases of bloody diarrhea has been evaluated by the WHO EML Antimicrobial Working group and was considered reasonable for the management of acute cases and this has been clarified in the text (page 111 of the draft version). The main concern with this approach was considered the risk of overtreatment of diarrhea and potential negative impact in case of enterohemorrhagic *Escherichia coli*. In these cases (mostly in children) the use of antibiotics is controversial because there is a theoretical concern that it could worsen symptoms of haemolytic uremic syndrome (characterized by haemolytic anemia, renal injury and low platelets). However, this risk also exists if only selected cases of acute bloody diarrhoea are treated with antibiotics.

The text (page 111 of the draft version) has been amended as shown:

"However, in patients with significant ***acute*** *bloody diarrhoea and in severely immunocompromised patients, antibiotics may be given (see Table 6 of the draft version for empiric options based on the risk of fluoroquinolone resistance).* ***Bloody diarrhoea could be caused by certain strains of Escherichia coli (Shiga toxin-producing Escherichia coli also known as enterohaemorrhagic Escherichia coli). In these cases (mostly in children) the use of antibiotics is controversial because there is a theoretical concern that it could worsen symptoms of haemolytic uraemic syndrome, characterized by haemolytic anaemia, renal injury and low platelets. However as there is clear evidence of benefit in shigellosis, empiric treatment with antibiotics should not be withheld because of a concern of causing haemolytic uremic syndrome.***

If symptoms do not resolve after 24–48 hours of antibiotic treatment, adding a treatment course of metronidazole for possible Entamoeba histolytica could be considered".

In addition, antibiotic treatment should be considered in the context of cholera based on the Global Task Force on Cholera Control technical note on this topic, also mentioned in the chapter.

Comment: MSF specifies antibiotic treatment for specific target populations (e.g. azithromycin for all pregnant women with cholera).

(Médecins Sans Frontières - MSF)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines Lists and for adults, the list does not include specific recommendations for pregnant women. Therefore, alternative options not specifically mentioned in the lists are not reported. This may, however, be considered for future updates of the Book.

However, a single dose of azithromycin is already indicated in the Book as first line for the treatment of cholera in adults (Table 7 page 112-113 of the draft version) with a note of caution that, because of the long half-life of azithromycin, it should only be recommended for outbreak situations, where single-dose treatment is especially useful.

Comment: *"Please find attached the Global Task Force on Cholera Control document on the use of antibiotics titled Technical note on the use of antibiotics for the treatment and control of cholera"*

https://www.gtfcc.org/resources/

(Kathryn Alberti, Cholera Team, World Health Organization)

Response: As suggested, the section on cholera (page 112 of the draft version) has been adapted based on the Global Task Force on Cholera Control technical note which has also been referenced in the chapter. In particular, the part on indications for using antibiotics have been updated as follows:

"Antibiotic treatment should be considered in the context of cholera in the following cases:

- *Suspected cholera in patients hospitalized with severe dehydration*
- *Regardless of degree of dehydration:*
    - *high purging or failure of first 4-hour course of rehydration therapy or*
    - *coexisting conditions (e.g. pregnancy) or*
    - *co-morbidities (e.g. severe acute malnutrition, HIV infection) that pose elevated risk in cholera illness"*

4.10 Enteric fever

Comment: *"We have noticed that the terminology used to refer to the various Salmonella enterica serotypes is not used consistently across the handbook, i.e., sometimes Salmonella spp. refers to non-typhoidal Salmonella (e.g. p. 114, line 9-10) and sometimes it is used as an umbrella term to refer to all Salmonella serotypes including Salmonella Typhi and Paratyphi (e.g., in Table 3 p. 189). In other parts, the term non-typhoidal Salmonella is used to specifically refer to serotypes other than Typhi and Paratyphi (e.g., Table 3 p.204).*

It is important to make a clear distinction between the serotypes, as different serotypes are associated with different clinical presentations and diseases.

We therefore propose (Crump et al., 2015):

- *to use the terms Salmonella Typhi and Paratyphi when referring to enteric fever*
- *to use the term (intestinal/non-invasive/diarrheal) non-typhoidal Salmonella when referring to non-typhoidal Salmonella causing gastro-enteritis*
- *to use the term invasive non-typhoidal Salmonella when referring to non-typhoidal Salmonella causing invasive disease (bloodstream infection, meningitis, bone & joint infections) in children or HIV-infected patients, particularly in sub-Saharan Africa (see comment 2)*
- *to avoid the umbrella term Salmonella spp. and instead combine the terms described above for clearer references to the clinical presentations linked to serotypes"*

(Tropical Bacteriology, Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp; Dr. Bieke Tack, MD, PhD Candidate and Prof. Dr. Jan Jacobs, MD, PhD)

Response: The terminology has been updated throughout the AWaRe Book as suggested.

Comment: *"Non-typhi salmonella should also be listed somewhere in that most are self-limited and would not require therapy. I think it is good to differentiate between typhi and non".*

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Response: Non-typhoidal *Salmonella* is listed as a possible cause of acute gastroenteritis and invasive diseases such as bloodstream infections, meningitis (in children and adolescents) or bone and joint infections in the corresponding chapters.

In the Enteric fever chapter, it has been clarified that non-typhoidal *Salmonella* does not cause enteric fever and that information about this pathogen can be found in other chapters (acute gastroenteritis, meningitis, sepsis, bone and joint infections).

The text (page 114 of the draft version) has been updated as shown:

"Non-typhoidal Salmonella is not a cause of enteric fever but may cause infectious gastroenteritis, bloodstream infections, meningitis or bone and joint infections. Please refer to the relevant chapters if these infections are suspected."

Comment: *"MDR typhoid in Pakistan etc should also be mentioned specifically in the epi section".*

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Comment: Enteric fever: p 117 – line 84-86: *"In these settings, a third-generation cephalosporin or azithromycin are appropriate options because resistance to these antibiotics is still low in most settings (< 5% for ceftriaxone and only sporadic cases with resistance to azithromycin)."*

"Unfortunately, following an outbreak in Pakistan, third-generation cephalosporin resistance has emerged in typhoid fever. In Pakistan, >10.000 cases of extensive drug resistant (XDR) typhoid fever, i.e. combined resistance to ampicillin, cotrimoxazole, chloramphenicol, fluoroquinolones and third generation cephalosporins, have been registered, leaving only azithromycin and carbapenems as recommended treatment options. Travel-related cases with XDR typhoid fever have been reported in the US, Canada, Australia, Europe, etc. (Akram et al., 2020; Marchello et al., 2020; Saha et al., 2020)

We propose adding a sentence on the public health threat of XDR typhoid fever in Pakistan and its travel-related spread".

(Tropical Bacteriology, Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp; Dr. Bieke Tack, MD, PhD Candidate and Prof. Dr. Jan Jacobs, MD, PhD)

Response: The AWaRe Book does not aim to provide detailed guidance for outbreaks of multidrug-resistant pathogens in specific settings and throughout the Book, it was decided not to mention specific countries. The reason is that these data may become outdated within a relatively short timeframe (e.g. other countries may face the same problem in the near future), however in this specific case a footnote to mention the issue of outbreaks of enteric fever caused by extensively antibiotic-resistant *Salmonella* Typhi (e.g. in Pakistan since 2016) has been added to Table 2 (pages 117-118 of the draft version) and a sentence has been added in the text in the Antibiotic treatment section (page 117 of the draft version).

The text now reads as shown:

"When choosing empiric treatment, the local prevalence of fluoroquinolone resistance should be considered because of the increasing number of resistant isolates, mostly in Asia (ref 141 of the draft version). In these settings, a third-generation cephalosporin or azithromycin are appropriate options because resistance to these antibiotics is still low in most settings; < 5% for ceftriaxone and only sporadic cases with resistance to azithromycin.

…

In recent years, outbreaks of enteric fever caused by extensively antibiotic-resistant Salmonella Typhi have been reported, for example in Pakistan since 2016. These extensively antibiotic-resistant isolates are resistant to ampicillin, sulfamethoxazole+trimethoprim, chloramphenicol, fluoroquinolones and third-generation cephalosporins and represent a public health threat including the risk of travel/migration-related spread to other countries and regions".

The footnote to Table 2 (page 118 of the draft version) now reads as follows:

"[b]In settings where ceftriaxone-resistance is increasing, azithromycin should be prioritized. ***Outbreaks of enteric fever caused by extensively antibiotic-resistant Salmonella Typhi have been reported, for example in Pakistan since 2016 and travel-related cases across the world****. In general, when ceftriaxone is used, changing to oral treatment could be considered when there is symptomatic improvement. If available,*

the choice of oral options to use could be guided by susceptibility testing results, including the possibility of using certain first-choice options that were used in the past."

Comment: *"Oral stepdown: azithromycin or ciprofloxacin if sensitive"*

(The UK Paediatric Antimicrobial Stewardship)

Response: Oral options to use for intravenous to oral step-down are not specifically mentioned in the AWaRe Book (this level of detail is beyond the scope of the Book which is mainly focused on the choice of the initial empiric antibiotic), however oral formulations of antibiotics recommended for a certain infection could be used for this purpose if available.

Comment: *"The recommended dosage regimens for ciprofloxacin and azithromycin do not correspond with previous dosages recommended by the WHO.*

Chapter Enteric Fever: p 117 – _Table 2:

- *Ciprofloxacin (oral): 10-20 mg/kg/dose given every 12 hours*
- *Azithromycin (oral): 20 mg/kg/dose given every 12 hours*

The regimens that were previously recommended in the WHO pocketbook of hospital care for children (World Health Organization, 2013):

- *Ciprofloxacin: 15 mg/kg/dose given every 12 hours*
- *Azithromycin: 20 mg/kg/dose given every 24 hours*

Please note that similarly high ciprofloxacin doses are also mentioned to treat infectious gastro-enteritis on p. 111. We propose checking the doses and frequency of administration for these molecules and adding a reference to support the chosen regimen.

We propose checking the doses and frequency of administration for these molecules and adding a reference to support the chosen regimen."

(Tropical Bacteriology, Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp. Dr. Bieke Tack, MD, PhD Candidate and Prof. Dr. Jan Jacobs, MD, PhD)

Response: Doses have been updated as follows:

- Azithromycin: 20 mg/kg/dose given every 24 hours
- Ciprofloxacin: 15 mg/kg/dose given every 12 hours

Comment: p 118 – _line 110-116: Prevention *"For updated information on vaccines to prevent enteric fever, please refer to the most recent WHO position paper on vaccination (144). Vaccination should be prioritized in countries with the highest burden of enteric fever (especially where antibiotic resistance is high) and in response to confirmed outbreaks. A recent systematic review evaluated the effects of different types vaccines for preventing enteric fever and found that the two commonly used vaccines (Ty21a and Vi polysaccharide) overall prevent around half of typhoid cases during the first three years after vaccination (145). We think it would be appropriate to explicitly discuss the new typhoid conjugate vaccine in this paragraph, as the WHO position paper dates from 2018 and important additional evidence is meanwhile available. The more because the typhoid conjugate vaccine is mentioned in the chapter on sepsis in adults and neonates/children on p. 197 & 211.*

Compared to the previous Ty21a and Vi polysaccharide vaccines, the typhoid conjugate vaccine has improved efficacy, can be used in children from the age of 6 months onwards and has a single dose regimen with prolonged duration of protection. The typhoid conjugate vaccine has been introduced in the national routine immunisation programs of Pakistan, Zimbabwe, Liberia and Samoa; it is planned for 2022 in Nepal and Malawi. (Typhoid Vaccines - Take on Typhoid, n.d.)".

(Tropical Bacteriology, Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp; Dr. Bieke Tack, MD, PhD Candidate and Prof. Dr. Jan Jacobs, MD, PhD)

Response: the WHO 2018 position paper that is referenced in the text also includes recommendations on the use of conjugate vaccines concluding that "among the available typhoid vaccines, typhoid conjugated vaccine is preferred at all ages in view of its improved immunological properties, suitability for use in younger children and expected longer duration of protection". In general, a detailed discussion about vaccination is beyond the scope of the AWaRe Book and has not been done for other infections. However, the text has been amended as shown:

"For updated information on vaccines to prevent enteric fever, please refer to the 2018 WHO position paper on typhoid vaccines (ref 144 of the draft version). Vaccination should be prioritized in countries with the highest burden of enteric fever (especially where antibiotic resistance is high) and in response to confirmed outbreaks. ***Single-dose typhoid conjugated vaccines are also available that can be used in younger children (from the age of 6 months onwards) and confer prolonged duration of protection. Recommendations on these newer vaccines can also be found in the 2018 WHO position paper****".*

4.11 Skin and Soft Tissues Infections (SSTI)

Comment: *For skin/soft tissue infections: "recommend a more specific anti-staphylococcal agent (eg. Cloxacillin or cefazolin) rather than ceftriaxone, particularly if the risk of staph aureus bacteremia is high"*

(Médecins Sans Frontières - MSF)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the AWaRe Book would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process). Of note, ceftriaxone is NOT recommended in the Book for the treatment of skin infections (while cloxacillin is already recommended).

Comment: *"On the treatment of skin and soft tissue infections amoxicillin-clavulanic acid is first option, I would take it out and chose first generation cephalosporins."*

(Dr Pablo Rojo, Pediatric infectious diseases unit, Hospital 12 de Octubre, Madrid, Spain).

Comment: *"I think there is a general overuse of amoxicillin-clavulanate in many of the infections, and I think it is too broad antibiotic to use in several infections. For example to treat cervical lymphadenitis a much better option to cover S. aureus and GAS would be first generation cephalosporins either cephalexin or cefadroxil only, and not include amoxicillin-clavulanate".*

(Dr Pablo Rojo, Pediatric infectious diseases unit, Hospital 12 de Octubre, Madrid, Spain).

Comment: *"Line 136 I would not indicate amoxicillin-clavulanic acid as first choice - stick with S/S bugs Cloxacillin, cephalexin, for MRSA risk areas something to cover that and then amoxicillin-clavulanic acid last (we do use it but not as first line)".*

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Comment: *"INTRO For Table 2 line 156 for SSTI would not suggest amoxicillin-clavulanic acid as the first line. The rest are good. Other considerations are 2nd generation cephalosporins. I am okay with the cloxacillin & cephalexin but would move amoxicillin-clavulanic acid way down on the list (or remove all together). Obviously, it would be used in some instances particularly with human/animal bites and other but wouldn't be first line".*

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Response: These comments refer to the treatment of skin infections as indicated both in Table 2 in the Introduction (page 9 of the draft version) and in Table 4 (page 125-126 of the draft version) of the impetigo, erysipelas and cellulitis chapter.

In the AWaRe Book, when more than one antibiotic option is listed for a certain indication, antibiotics are listed alphabetically which, in this case for example, could give the impression that amoxicillin-clavulanic acid is first choice while in fact all three options are considered adequate alternatives. This has been made clearer and will be further emphasized in the document.

Impetigo

Comment: p125 *"flucloxacillin / cloxacillin preferred as 1st line to minimize Gram negative resistance in both adults and children."*

(British Society for Antimicrobial Chemotherapy)

Response: The order with which multiple antibiotic options for a certain indication are presented in the AWaRe Book is always alphabetical. For this reason, the three alternative first choice options listed in the WHO Essential Medicines Lists for the treatment of mild skin and soft tissue infections are listed as follows, potentially giving the impression that amoxicillin-clavulanic acid should be used first:

- Amoxicillin-clavulanic acid
- Cefalexin
- Cloxacillin

However, a footnote in Table 4 (page 126 of the draft version) clearly indicates that among the three options cloxacillin has the narrowest spectrum of activity and would at least theoretically be preferable to use from an antibiotic stewardship perspective (the exact impact on selection and spread of antibiotic-resistant bacteria of different antibiotics being understudied). In 2017, the Expert Committee responsible for updating the WHO Essential Medicines Lists, recommended amoxicillin-clavulanic acid and cloxacillin for reasons of parsimony because both antibiotics provide good coverage for staphylococcal (non-MRSA) and streptococcal infections, which are the leading causes of mild to moderate community-acquired skin and soft tissue infections worldwide. The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the AWaRe Book (including alternatives for allergic patients) would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process).

Comment: *"MSF recommends oral cephalexin for mild omphalitis/periumbilical impetigo in neonates, but IV cloxacillin if moderate or major infection"*

(Médecins Sans Frontières - MSF)

Response: In the AWaRe Book, when more than one antibiotic option is listed for a certain indication, antibiotics are listed alphabetically which, in the case of mild skin infections for example, could give the impression that amoxicillin-clavulanic acid is first choice while in fact all options listed (including cefalexin) are considered adequate alternatives. This has been made clearer and will be further emphasized in the document. The chapter on skin infections focuses on mild cases presenting to primary health care, for more severe presentations with a skin source, the sepsis chapter can be consulted if this is suspected.

Comment: Pathophysiology (line 33, page 120). *"It is implied throughout this section that these three situations only arise via damage to the skin. This is not true for cellulitis of dental infection origin."*

(World Dental Federation)

Response: This comment refers to the following sentence in the pathophysiology section (page 120 of the draft version) which has been amended to include a comment on facial cellulitis secondary to a dental infection as shown:

*"Damage of the skin can lead to infections of the deeper layers beneath the epidermis. When such damage occurs, both endogenous pathogens (i.e. that naturally reside in the body) and exogenous pathogens (i.e. that enter the body from the environment) can penetrate the epidermis and spread to deeper structures through the lymphatic system. Depending on the depth of the infection, different clinical diseases can occur: impetigo and erysipelas (infections of the upper layer of the skin) and cellulitis (infection of the deep dermis and subcutaneous tissue). **Cellulitis of the face can also occur as a consequence of local spreading of a dental infection, for example, dental abscess spreading to the surrounding soft tissue that results in cellulitis**"*

Cellulitis

Comment: *"Cellulitis of the face and neck can be associated with dental infections. This needs to be included in the oral and dental infections chapter and cross-referenced when needed (line 75, page 123)"*

Comment: *"After full stop add: 'Facial and/or neck cellulitis can arise as a result of dental infection and spread rapidly through the fascial spaces to become life threatening. This is a medical emergency.' (line 80, page 123)"*

(World Dental Federation)

Response: These comments refer to the following paragraph in the cellulitis section (page 123 of the draft version) which has not been amended and remains as follows:

"….Cellulitis is characterized by an acute onset of a skin lesion presenting with a combination of redness, swelling and induration, warmth and pain (or tenderness) of the affected area. The condition can occur anywhere on the body, but predominantly affects the skin of the lower part of the legs and feet or the face."

Comment: *"After full stop add: 'Facial and neck cellulitis, commonly arising from dental infection can lead to potentially fatal deep space infections such as Ludwig's angina. Cellulitis of the midface can spread to the brain and lead to serious complications such as cavernous sinus thrombosis. These are medical emergencies. (line 86, page 123)"*

(World Dental Federation)

Response: This comment refers to the following sentence in the cellulitis section (page 123-124 of the draft version) which has been amended as shown:

"The severity of the infection should always be carefully assessed, especially to exclude the possibility of involvement of the muscular fascia (fasciitis). Facial and neck cellulitis, commonly arising from dental infection can lead to potentially fatal deep space infections such as Ludwig angina. Cellulitis of the face can spread to the brain and lead to serious complications such as cavernous sinus thrombosis. These are medical emergencies but are overall rare."

Comment: *"Imaging (line 110, page 124-125). This paragraph should include a comment about imaging being necessary for diagnosis of the cause of an abscess. Drainage of a dental abscess may be the correct initial urgent procedure but further treatment will be required to eliminate the cause and prevent recurrence."*

Comment: *"(line 113-114, page 124-125). Consider modifying these lines – 'In these cases, management often requires a surgical approach (e.g. drainage of pus in the case of abscess and management of the primary dental cause)'"*

(World Dental Federation)

Response: These comments refer to the following sentence in the imaging section (page 124-125 of the draft version) which has been amended as shown:

"Routine imaging of mild cases of impetigo, erysipelas and cellulitis is not necessary. However, initial imaging (e.g. ultrasound, X-ray) may be considered if an abscess or subdermal involvement are suspected. In these cases, management often requires a surgical approach, for example, incision and drainage in case of abscess and management of the primary dental cause".

Burn wounds

Comment: *"Amoxicillin-clavulanic acid would make more sense and also pseudomonal coverage is not listed here and should be".*

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines Lists and treatment options for burn-related infections are extrapolated from what the Model Lists recommend for mild skin infections. Changes to recommendations in the AWaRe Book would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process). *Pseudomonas aeruginosa* infection is associated with treatment in burn units where hydrotherapy is used. As these are hospital-acquired skin and soft tissue infections, they are currently not covered in the AwaRe Book.

Comment: *"MSF recommends minimizing antibiotic exposure by limiting the use of prophylactic antibiotics to excision and grafting definitive surgery"*

Médecins Sans Frontières - MSF)

Response: This aspect is also briefly covered in the text ("Preventive antibiotic use" page 130 of the draft version) as follows: *"Routine use of antibiotics to prevent infection in burn wounds should be avoided if there are no signs of systemic infection or in otherwise healthy patients. Use of antibiotics as a preventive treatment is controversial because there is no clear evidence that it can prevent infection (refs). In addition, such use can lead to colonization with resistant microorganisms, so caution is needed"*. Of note, the Book only addresses the antibiotic treatment of mild cases of burn-wound-related infections presenting to primary health care and not more severe presentations requiring hospital admission (except for sepsis which is covered in a dedicated chapter). For cases requiring a surgical procedure (e.g. in this case skin excision and grafting), antibiotic prophylaxis is covered in the "Surgical prophylaxis" chapter.

Comment: "*For empiric treatment for sepsis, MSF recommends two broad spectrum antibiotics to cover main pathogens in bacteraemia: Pseudomonas, E. coli, Klebsiella, Acinetobacter, and S. aureus: e.g. cloxacillin (or cephazolin) AND ceftazidime (or ciprofloxacin/gentamicin). This needs to be informed by local reliable microbiology*"

(Médecins Sans Frontières - MSF)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the AWaRe Book would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process). Therefore, alternative options not specifically mentioned in the Model Lists are not reported and no changes to the text were made. In particular, it is understood that the reviewers are referring to the empiric treatment of sepsis in cases associated with burn-wound infections (i.e. skin source of infection). The options recommended in the Book for sepsis with a skin source is piperacillin-tazobactam (4.5 g q6h) which has good Gram-negative coverage including *Pseudomonas aeruginosa* and also has activity against methicillin-susceptible Staphylococcus aureus (MSSA) and clindamycin (which also has activity against *Staphylococcus aureus* and may have activity against MRSA). This combination treatment is presented in table 7 of the sepsis chapter (pages 195-196 of the draft version). Empiric guidance may be reviewed and adapted based on local clinically relevant microbiology surveillance data (e.g. blood culture data of significant isolates from patients with confirmed sepsis) and this has been clarified in the text.

Bite wounds

Comment: *"I would not advocate for cloxacillin or cephalexin. Amoxicillin-clavulanic acid should be the choice here (versus in the other SSTI)".*

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Response: Treatment options for bite-related infections are extrapolated from what the WHO Essential Medicines Lists recommend for mild skin infections Changes to recommendations in the AWaRe Book would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process). However, it is acknowledged that amoxicillin-clavulanic acid gives a better coverage of anaerobes (which can cause bite-related infections) and this is mentioned in the antibiotic treatment section of the "Wounds and bite-related infections" chapter (Table 4, pages 140-141 of the draft version).

Comment: "P49 *See new NICE guidance on bites visual-summary-pdf-8897023117 (nice.org.uk) Antibiotics not needed in most cases unless blood drawn, with the exception of high risk patients with human bites if the skin is broken." (British Society for Antimicrobial Chemotherapy)*

Response: This is reflected in the chapter including in the Key messages at the beginning of the chapter (page 132 of the draft version). The first key message for example reads as follows: *"In general, uninfected wounds do not require antibiotic treatment except in very selected cases".* Selected cases are those where the potential risk of infection is judged to outweigh the risk of "overusing" antibiotics such as bite-related wounds in high-risk areas (e.g. hands, near joints) and high-risk patients (severely immunocompromised). The text (page 139) has been amended as shown:

"Preventive antibiotic use may be considered in very few specific cases where the potential risk of infection is judged to outweigh the risk of "overusing" antibiotics.

This includes:

- *Wounds in high-risk clinical areas (e.g. face, hands, areas near a joint)*
- *Severely immunocompromised patients"*

Comment: *"Doxycycline as alternative in adult penicillin allergy, or co-trimoxazole in children."*

(British Society for Antimicrobial Chemotherapy)

Response: The AWaRe Book currently does not provide alternative regimes in case of allergy, partly because antibiotic allergy is overdiagnosed in many settings potentially leading to treatment with antibiotics that are less effective, less well tolerated and have a higher risk of selection of resistance (e.g. Watch macrolides instead of Access beta-lactams). Therefore, no changes to the text were made.

4.12 Sexually transmitted infections (STI)

Chlamydial urogenital infection

Comment: *"I understand that there is a difference in green and yellow status but consideration for a one time dose versus 7 days should also be considered important line 119 and given that azithromycin is given for gonorrhoea anyway (+ceftriaxone) that might be a simpler regime to consider?".*

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Response: This comment refers to Table 3 (page 147 of the draft version). Recommendations for sexually transmitted infections in the AWaRe Book are based on WHO guidelines.

In particular, *Treatment of Chlamydia trachomatis guidelines (2016)*: This guideline mentions that "*the choice of treatment may depend on convenience of dosage, the cost and the quality of medicines in different settings, and equity considerations. When high value is placed on reducing costs, doxycycline in a standard dose may be the best choice. When high value is placed on convenience, azithromycin in a single dose may be the best choice*".

In 2021, new WHO guidelines for the management of symptomatic sexually transmitted infections have been released and these recommend doxycycline as first-line option and azithromycin as an effective substitute. Therefore exceptionally, the alphabetical order (to list alternative options) has not been respected in Table 3 (draft version) and doxycycline is mentioned first. The 2023 WHO Essential Medicines List 2023 update will consider updating the EML to align with the 2021 WHO sexually transmitted infections guidelines.

Gonococcal infection

Comment: "*MSF always recommends dual treatment for Neisseria gonorrhoeae (with the assumption that in most MSF contexts there is no knowledge on antibiotic resistance prevalence). For single dose treatment, MSF recommends azithromycin over doxycycline, to maximize patient compliance, particularly for mobile populations where follow up is difficult. MSF recommends increasing dosages of ceftriaxone to 500 mg for all suspected Neisseria gonorrhoeae infection, regardless the infection localization and knowledge of local ABR resistance rate in settings where resistance rate is unknown and among population at high risk of recurrent sexually transmitted infections".*

(Médecins Sans Frontières – MSF)

Response: The AWaRe Book is closely aligned with WHO guidelines for the treatment of Gonorrhoea, and this includes the indications for dual or single treatment and the dose of ceftriaxone (250 mg single dose), therefore no changes to the text were made. Of note, the 500 mg single dose of ceftriaxone is recommended for retreatment after treatment failure (e.g. persistent or recurrent urethral discharge) but not for a first episode or reinfection. Of note, the 2021 WHO STI guidelines include the following comment "*Because of increasing antimicrobial resistance to azithromycin in N. gonorrhoeae and reduced susceptibility to cephalosporins, WHO is in the process of revising current treatment recommendations and dosages.*" Checking the WHO website regularly for possible updates on this topic is recommended and a note about this has been added to the text.

Concerning the comment *"For single dose treatment, MSF recommends azithromycin over doxycycline"*, the AWaRe Book recommends azithromycin (with ceftriaxone or cefixime) and does not include doxycycline in alignment with WHO guidelines for the treatment of Gonorrhoea.

For more detail:

- Guideline for the treatment of *Neisseria gonorrhoeae* (2016)
- Guidelines for the management of symptomatic sexually transmitted infections (2021)

Comment: *"Line 142-144. I agree with the authors on considering another diagnosis or suspicion of resistant strain if there is no improvement. However, I would suggest stating clearly that culture and drug sensitivities are needed to identify the resistant strain of gonococcus or other bacteria".*

(Dr Mireille A. Mpalang Kakubu, University of Pittsburgh (USA) and Ministry of health and social services of Namibia)

Response: This comment refers to the following sentence on page 156 of the draft version: *"If symptoms do not resolve within about 5 days of adequate antibiotic treatment, a resistant infection should be suspected, or an alternative diagnosis sought."*

Table 1 (page 153 of the draft version) in the "Microbiology tests" section mentions when cultures could be considered as follows: *"Consider if symptoms persist despite adequate treatment and for surveillance purposes"*.

Comment: *"Cefixime single dose being used in gonorrhea is no longer effective, at least in the Kenyan context".*

(Commonwealth pharmacists association)

Response: This context-specific comment raises the important issue of how the AWaRe Book may need to be adapted for the treatment of certain infections at the local / national level based on availabilities of antibiotics and surveillance data on antimicrobial resistance.

As with any general guidance document, the individual circumstances of the patients and the local context need to be considered.

The AWaRe Book is aligned with WHO guidelines, in particular:

- Guideline for the treatment of Neisseria gonorrhoea (2016), that clearly recommends that "local resistance data should determine the choice of therapy"
- Guidelines for the management of symptomatic sexually transmitted infections (2021)

The AWaRe Book recommends dual therapy with cefixime (or ceftriaxone) in combination with azithromycin (both as single doses) when no reliable data on resistance are available (Table 3, pages 156-157 of the draft version). Monotherapy should only be used if local data confirm susceptibility to the antibiotic taking also into account where the infection is located (urogenital, rectal, oropharyngeal) as not all antibiotic options are adequate for all sites of infection.

Of note, the 2021 WHO guidelines include the following comment "Because of increasing antimicrobial resistance to azithromycin in *N. gonorrhoeae* and reduced susceptibility to cephalosporins, WHO is in

the process of revising current treatment recommendations and dosages." It is therefore recommended to check the WHO website regularly for possible updates on this topic.

Comment: *"Page 54 Gonococcal Infection: - i. Gentamicin 240 mg IM- the use of this strength, with its associated toxicities, at PHC, should be reviewed. This is very important in resource limited environment where there is a shortage of qualified health personnel. A product of 280mg/2ml was once banned in Nigeria. I therefore wish to suggest that its use should be restricted to Hospital Facility".*

(Commonwealth pharmacists association)

Response: As with any general guidance document, the individual circumstances of the patients and the local context need to be considered. Local adaptation may be needed to decide if gentamicin would be better administered in an hospital setting (including when a single dose is needed as is the case of gonorrhea treatment).

Of note, the WHO Essential Medicines List, includes gentamicin for this indication, however, this option is not recommended in the WHO 2016 and 2021 guidelines (except in combination with azithromycin as an option for retreatment after treatment failure in the 2016 guidelines) and it has therefore been removed from the book. Unless new information supporting the use of gentamicin in gonococcal infections is provided, the 2023 Expert Committee might consider gentamicin for deletion for this indication.

Syphilis

Comment: *"Page 168 – I think this could be expanded significantly. This is a huge probably in HIC as well as LMIC. More on S/S, more on interpretation of serology depending on mother's stage would be very helpful. We are called clinically every week if not every day on the management here".*

Comment: *"For congenital syphilis I am not sure if it is a typo to say 10-15 days but should be 10-14 days. For LMIC the interpretation for endemic treponemal disease would also be important".*

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Response: These comments refer to the congenital syphilis row in Table 6 (pages 167-169 of the draft version) in the Syphilis chapter. All recommendations in the syphilis chapter (including the treatment duration of 10 to 15 days for congenital syphilis) are aligned with WHO guidelines.

In particular:

- Management of symptomatic sexually transmitted infections (2021)
- Treatment of treponema pallidum (2016)

These guidelines are referenced in the chapter for the interested reader.

4.13 Lower urinary tract infection (UTI)

Comment: *"INTRO For Table 1 Line 113 I am not sure that I understand why UTIs (lower) would not be treated. Should this read as asymptomatic bacteriuria? I don't think it is accurate to say that lower UTIs wouldn't be treated, no symptoms – yes (and in some groups like pregnancy even those would be treated)".*

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Response: This comment refers to urinary tract infection (lower) in Table 1 of the Introduction (pages 5-6 of the draft version). The final decision made by the WHO EML Antimicrobial Working Group was to only slightly change the text (but to keep the overall message unchanged) to make it clear that this non-antibiotic care (or delayed antibiotic-care) approach can be considered on a case-by-case basis (e.g. in young non-pregnant women). The text in the table has been updated as shown:

Urinary tract infection (lower)	Only in very selected patients with no risk factors for complicated infections	In young women who are not pregnant, with mild symptoms and who may wish to avoid or delay antibiotic treatment, symptomatic treatment alone can be considered.

Comment: p61 p63. *"Do not use dipsticks in older people (>65y) as often colonized."*

(British Society for Antimicrobial Chemotherapy)

Response: It has been assumed that this comment refers to line 80 (page 179 of the draft version) in relation to urinalysis tests. Offering a detailed guidance about how and when to use laboratory tests is beyond the scope of the AWaRe Book, therefore changes to the text were not made. However, the text (page 180 of the draft version) makes it clear that only patients with urinary symptoms should be tested. The rationale being to avoid overtreatment with antibiotics when not needed.

Reviewers have made the same comment for the upper UTI chapter, to which the above considerations can be extended.

Comment: *"Nitrofurantoin 3 days is enough for uncomplicated UTI in adults."*

(British Society for Antimicrobial Chemotherapy)

Response: The AWaRe Book does not provide formal recommendations for treatment duration but rather provides general guidance on what would be considered appropriate in most clinical cases. In the case of nitrofurantoin, 5 days of treatment for uncomplicated cystitis is what most international guidelines recommend (e.g. European 2021 guidelines of the Urology association), therefore no changes to the text were made.

Comment: *"Page 180 I wonder if we need to caveat that nitrofurantoin only for lower tract infection - I realize that is the title of this section but often it is used in febrile UTI/Pyelo and would like to avoid that".*

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Response: This comment refers to the chapter on lower UTI where the text clearly states that *"Nitrofurantoin for 5 days is the main antibiotic recommended for acute cystitis."*

Comment: *"For treatment of lower UTIs on page 61, cotrimoxazole no longer effective, at least in the Kenyan context".*

(Commonwealth pharmacists association)

Response: It has been assumed this comment refers to pages 180-181 of the draft version of the Book (Lower UTI chapter). This context-specific comment raises the important issue of how the AWaRe Book may need to be adapted for the treatment of certain infections at the local / national level based on availabilities of antibiotics and surveillance data on antimicrobial resistance. As with any general guidance document, the individual circumstances of the patients and the local context need to be considered.

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5 Hospital facility

5.1 Sepsis in adults

Comment: Microbiology _*"Likely pathogens - are these listed in prevalence order or alphabetical? Putting Acinetobacter at no. 1 in Hospital-acquired feels very odd. States only listing bacterial pathogens then lists viruses and malaria in the endemic section. Need consistency. If putting everything else then where are the fungi?"*

(British Society for Antimicrobial Chemotherapy)

Response: This comment refers to Table 3 (pages 188-189 of the draft version) which indicates pathogens most frequently identified in blood cultures of patients with sepsis by setting of acquisition (community vs hospital acquired). Because the focus of the AWaRe Book is the treatment of bacterial infections, the Table has been amended to only include bacteria (not viruses or fungi). The order in which pathogens are presented in the table is alphabetical and the proportion of each listed bacteria as a causative pathogen of hospital-acquired sepsis will vary from hospital to hospital. Of note, the focus of the Book is on community-acquired cases, and therefore the implications on antibiotic treatment of cases acquired in hospitals are not addressed and currently beyond the scope of the AWaRe Book.

The table has been updated as shown:

*Table 3 (draft version of the Book) **Bacteria** most frequently identified in blood cultures in patients with sepsis*

Setting of acquisition of the infection	Bacteria (in alphabetical order)
Community	Enterobacterales[a] (*Escherichia coli, Klebsiella pneumoniae* and others) Invasive non-typhoidal *Salmonella* (elderly patients and patients living with HIV) *Salmonella* Typhi and Paratyphi (causing enteric fever) *Staphylococcus aureus* (including MRSA) *Streptococcus pneumoniae* (including penicillin non-susceptible strains) *Streptococcus pyogenes* (group A *Streptococcus*) Other pathogens to consider *Burkholderia pseudomallei* (pathogen causing melioidosis which is endemic in South-East Asia and Australia) *Neisseria meningitidis* (including strains resistant to third-generation cephalosporins)

Hospital	*Acinetobacter baumannii*[a] Enterobacterales[a] (*Escherichia coli, Klebsiella pneumoniae* and others) *Pseudomonas aeuroginosa*[a] *Staphylococcus aureus* (including MRSA)
Maternal sepsis (additional pathogens to consider)[b]	*Listeria monocytogenes* *Streptococcus agalactiae* (group B *Streptococcus*)

[a]Including multidrug-resistant strains such as those producing ESBL and carbapenemases.
[b]In cases of maternal sepsis, however, the urinary tract represents the main source of infection (see epidemiology section).
Note: Most data on the pathogens associated with sepsis come from high-income settings.

To reflect the changes made to the table, the text (page 188 of the draft version) has also been amended as shown:

"The bacterial pathogens associated with sepsis will vary widely depending on the primary site of infection, geography and place of acquisition (community or hospital see table 3). ***Pathogens other than bacteria should be considered according to the local epidemiology. For example, certain settings are endemic for Plasmodium spp., the pathogen causing malaria, and this should always be considered where appropriate, including after travel to endemic areas. Multiple other pathogens including viruses causing viral haemorrhagic fevers, respiratory viruses such as the influenza virus and SARS-CoV-2 and fungal infections also need to be considered where appropriate (community and hospital-acquired infections)".***

Comment: p 188-189– Table 3:

- *Salmonella spp. not listed among Gram-negative bacteria*
- *Salmonella spp. refers to Salmonella Typhi, Paratyphi and non-Typhi*

The order in which the bacteria are listed, and the Salmonella terminology (see comment 1) is confusing.

We propose listing Salmonella right before or after the other Gram-negative Enterobacterales. In addition, we propose to use the following terms and specifications (see comment 1): Salmonella Typhi and Paratyphi (causing enteric fever) and invasive non-typhoidal Salmonella (mainly in HIV-patients).

(Tropical Bacteriology, Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp. Dr. Bieke Tack, MD, PhD Candidate and Prof. Dr. Jan Jacobs, MD, PhD)

Response: Table 3 (pages 188-189 of the draft version) has been updated but pathogens have been listed in alphabetical order as the proportion of each bacterium in the list as a causative pathogen of community-acquired sepsis will vary according to the local epidemiology (see updated Table in the previous comment).

Comment: Diagnosis-*"Add information on blood culture volumes."*

(British Society for Antimicrobial Chemotherapy)

Response: While it is acknowledged that this is important (the greater the volume, the greater the probability of a positive blood culture), details about correct sample collection is generally not given in the AWaRe Book, therefore for consistency and to keep the message simple (i.e. the same comment could be important in other chapters and for other types of specimens), no changes to the text were made.

Comment: *"Sepsis may result from an oral or dental infection. The chapters on sepsis should, therefore, cross refer to the chapter on oral and dental infections where appropriate. As of now, dental infections are only mentioned in table 4 of the Sepsis in Adults chapter."*

(World Dental Federation)

Comment: *"Treatment (Table 7, line 230, page 196). This table should include oral and dental infections."*

(World Dental Federation)

Response: The chapter on sepsis gives general guidance and mentions that "*Sepsis can originate from any type of infection (bacterial, viral, fungal and protozoal) in any organ system*" without going into further detail on the source of infection except for the Microbiology lab section where different laboratory tests/samples according to the source of infection are listed (dental infections are already mentioned in Table 4, page 191 of the draft version). In the Treatment section (Table 7, pages 195-196 of the draft version), where different empiric antibiotic options are presented based on the most likely source of infection, dental infections are not specifically mentioned and no changes to the text have been made as the Book has to remain a simple guidance and not all possible infectious sources can therefore be covered.

Comment: *"This section should refer to other tests in the oral and dental chapter to identify the source of infection. Please add - if a dental infection is suspected, then further tests are detailed in the oral and dental infections chapter".*

(World Dental Federation)

Response: This comment refers to the following sentence in the Laboratory tests section (II. Other tests, page 191 of the draft version) which has been amended as shown, but keeping the text more general as the same type of comment could apply to infections due to sources other than dental:

"Laboratory tests can be used to complement the clinical examination and history. Tables 5 and 6 (draft version of the Book) indicate the tests that could be considered to make an initial assessment of the patient and to help guide the duration of antibiotic treatment. Additional laboratory tests may be considered based on local availability ***and on the most likely source of infection; further tests are detailed in the corresponding chapter".***

Comment: *"Imaging (line 178, page 194). Consider including dental radiographs - 'if a dental infection is suspected then x-rays/radiographs are recommended, as detailed in…'"*

(World Dental Federation)

Response: The paragraph already mentions that *"Imaging studies should be guided by the suspected primary site of infection. Please also refer to specific chapters of the AWaRe Book based on the suspected underlying infection"; however, reference to dental infections has been added to the following paragraph (page 193 of the draft version):*

"When sepsis is suspected and respiratory distress is present, a chest X-ray (or lung ultrasound) is indicated to confirm a lower respiratory tract infection. If an abdominal source of infection is suspected, in settings where it is available, a computed tomography scan of the abdomen could be considered (e.g. to confirm an intra-abdominal infection). A low dose CT scan is an acceptable option, including in pregnant women. However, because abdominal ultrasound is more widely available, it can be a very helpful alternative depending on the exact site of infection. If sepsis caused by an infection of the urinary tract is suspected, initial imaging (e.g. ultrasound) of the urinary tract or during follow-up could be considered if an outflow obstruction (e.g. because of urolithiasis) or an abscess are suspected. If a dental infection is suspected then X-rays are recommended, as detailed in the corresponding chapter."

Comment: *"Treatment (line 189, page 194). Should refer to source control when mentioning treatment of the underlying infection"*

(World Dental Federation)

Response: This comment refers to the following sentence in the Treatment section (page 193 of the draft version) which has been amended as shown.

"Treatment of sepsis includes treatment of the underlying infection, source control and life-saving interventions such as fluid resuscitation and vital organ support which are beyond the scope of the AWaRe Book.

Comment: *"Ceftriaxone should be restricted as it is the highest level in our practice here, we would wish to be reserved for targeted treatment. Therefore, benzylpenicillin should be first line and ceftriaxone as second line. Meropenem, vancomycin and amoxicillin-clavulanic acid IV are not available in government hospitals at all levels of health care delivery, secondly they cannot be afforded by the patients".*

(David Banda, Clinical pharmacy specialist, Senior lecturer, Chreso University, Nursing department, Lusaka, Zambia)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the Book would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process). Therefore, no changes to the text were made. Context-specific comments raise the important issue of how the AWaRe Book may need to be adapted for the treatment of certain infections at the local / national level based on availabilities of antibiotics and limitations to access basic antimicrobial agents.

Comment: P67-9: *"consider piperacillin-tazobactam as an alternative."*

(British Society for Antimicrobial Chemotherapy)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the Book would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process). Therefore, no changes to the text were made. In septic patients, piperacillin-tazobactam is the recommended first choice when an abdominal or skin source of infection is identified (Table 7, pages 195-196 of the draft version).

Comment: "What's the rationale for the dosing recommendations for piperacillin-tazobactam (must be QDS) and meropenem 2g TDS?"

(British Society for Antimicrobial Chemotherapy)

Response: The AWaRe Book does not provide formal recommendations for dosage but rather provides general guidance on what would be considered appropriate in most clinical cases. Frequency of dosing for piperacillin-tazobactam (every 6 hours) and meropenem (every 8 hours) when an abdominal source of infection is identified, is aligned with other international guidelines (e.g. guidelines on the management of intra-abdominal infections by the Surgical Infection Society), and no changes to the text were made. However, different dosing strategies may be preferred based on local practices (e.g. dosing piperacillin-tazobactam every 8 hours). Providing guidance for alternative dosing strategies is beyond the scope of the AWaRe Book.

Comment: *"no mention of how to prevent HCAIs e.g. catheter / IV line care"*

(British Society for Antimicrobial Chemotherapy)

Comment: *"MSF recommends including information regarding hospital acquired sepsis and prevention of HCAI (e.g. bundles, avoidance/care of urinary and IV catheters especially CVC, VAP prevention), and IPC related to MDR bacteria transmission"*

(Médecins Sans Frontières - MSF)

Response: The AWaRe Book is focussed on community-acquired cases. Information regarding hospital-acquired sepsis including prevention of healthcare-associated infections is beyond the scope of the first edition of the Book but may be considered in the future. Hospital-acquired cases are mentioned in the Microbiology section to highlight that the list of bacterial pathogens causing sepsis varies by setting of acquisition of the infection (hospital or community). In particular, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* (including multidrug-resistant strains) are more frequently encountered in hospital-acquired infections (Table 3, page 188-89 of the draft version). However, the implications on antibiotic treatment are not addressed and currently beyond the scope of the AWaRe Book.

Comment: *"MSF recommends including information regarding important foci (for example, urinary or skin), taking into account that duration changes also with specific pathogens, as for bactaeremia, once culture/AST results come. Duration will also vary according to the antibiotic used*.

(Médecins Sans Frontières - MSF)

Response: Empiric antibiotic treatment (and duration) according to the most probable source of infection is covered in Table 7 (page 195-196 of the draft version) and a more explicit comment that *"Total treatment duration (may vary also based on degree of immunosuppression)"* has been added. However, while treatment duration may vary with specific pathogens, the Book is focussed on the choice of the initial empiric treatment and in general does not provide guidance for specific pathogens. The only exception is the treatment of bacterial meningitis where pathogen-specific indications (in terms of treatment duration) are given.

5.2 Sepsis in neonates & children

Comment : *"p 203-204 –Table 4 & p 204-205 Table 5 Salmonella spp/ non-typhoidal Salmonella not listed among Gram-negative bacteria. The order in which the bacteria are listed, and the Salmonella terminology (see Comment 1) is confusing. We propose listing Salmonella right before or after the other Gram negative Enterobacterales"*

Comment: *"As enteric fever is rare in neonates, we propose the term "invasive non-typhoidal Salmonella" for Table 4"*

Comment: *"In Table 5 (sepsis in children), we recommend the following terms and specifications (see comment 1):"Salmonella Typhi and Paratyphi (causing enteric fever) and invasive non-typhoidal Salmonella (mainly in sub-Saharan Africa in children < 5 years with recent/acute Plasmodium falciparum malaria, anaemia, malnutrition, or HIV)"*.

(Tropical Bacteriology, Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp. Dr. Bieke Tack, MD, PhD Candidate and Prof. Dr. Jan Jacobs, MD, PhD)

Response: Table 4 (neonates, pages 203-204 of the draft version) and Table 5 (older children, pages 204-205 of the draft version) have been updated (as shown) but invasive non-typhoidal *Salmonella* in neonates (Table 4) has been considered by the WHO EML Antimicrobial Working Group as rare and so it is reported at the bottom of the list. (Note, only parts of the tables with changes are shown).

Table 4 (draft version of the Book) Bacteria most frequently identified in blood cultures in neonates 28 days or younger with sepsis

Setting	Infection acquired in the community
Low- and middle-income	Most common: *Escherichia coli* (including multidrug-resistant strains such as those producing ESBL) *Staphylococcus aureus* (including MRSA) *Klebsiella* spp. (including multidrug-resistant strains) *Streptococcus agalactiae* (group B *Streptococcus*) More rarely: *Staphylococcus* spp. (other than *Staphylococcus aureus*) *Acinetobacter* spp. *Streptococcus pyogenes* (group A *Streptococcus*) *Streptococcus pneumoniae* *Listeria monocytogenes* *Haemophilus influenzae* Gram-negative bacteria other than *Escherichia coli*, *Klebsiella* spp. and *Acinetobacter* spp. *Enterococcus* spp. Invasive non-typhoidal *Salmonella*

Table 5 (draft version of the Book) Bacteria most frequently identified in blood cultures in children older than 28 days with sepsis

Setting	Infection acquired in the community
Low- and middle-income	Gram-negative bacteria (mostly *Escherichia coli, Klebsiella* spp.) (including multidrug-resistant strains such as those producing ESBL and carbapenemases) *Salmonella* Typhi and Paratyphi (causing enteric fever) Invasive non-typhoidal *Salmonella* (mainly in sub-Saharan Africa in children < 5 years with recent/acute *Plasmodium falciparum* malaria, anaemia, malnutrition, or HIV) *Streptococcus pneumoniae* *Streptococcus pyogenes* (group A *Streptococcus*) *Staphylococcus aureus* *Neisseria meningitidis* *Haemophilus influenzae* type b

Comment: p 209 – Line 205-206: *"In malaria-endemic areas, it is often difficult to rule out sepsis in a child with shock or severe illness and decreased alertness, particularly where parasitaemia is common." The term "parasitaemia is common" is confusing and may be read as "asymptomatic parasitaemia" whereas also severe Plasmodium falciparum malaria and invasive bacterial infections (often caused by invasive non-typhoidal Salmonella) can occur together (Church & Maitland, 2014). We propose to clarify the term "parasitaemia" and to place it in the clinical context of frequent co-infections.*

(Tropical Bacteriology, Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp. Dr. Bieke Tack, MD, PhD Candidate and Prof. Dr. Jan Jacobs, MD, PhD)

Response: The text on page 209 of the draft version has been amended as shown:

"In malaria-endemic areas, ***in a child with shock or severe illness and decreased alertness, it is often difficult to differentiate between severe Plasmodium falciparum malaria and invasive bacterial infection (often caused by invasive non-typhoidal Salmonella) and co-infections are also not uncommon.*** *In all such cases, empiric parenteral broad-spectrum antibiotics should be started immediately, together with antimalarial treatment".*

Comment: p 210 – Table 9 & line 217-218 *"In settings with high resistance, particularly for suspected health care-associated infections, a broad-spectrum antibiotic with activity against Gram-negative bacteria should also be considered (e.g. piperacillin+tazobactam)."*

The first-choice regimen (ampicillin + gentamicin) is not effective for invasive non-typhoidal Salmonella because:

- *>85% of non-typhoidal Salmonella are multidrug resistant, which includes ampicillin resistance (Tack et al., 2020).*
- *aminoglycosides are not clinically effective in invasive non-typhoidal Salmonella infections because they do not penetrate intracellularly (Clinical and Laboratory Standards Institute, 2021).*

Therefore, the second-choice antibiotic regimen based on third generation cephalosporins is more appropriate than the first choice in settings where invasive non-typhoidal Salmonella are a major cause of bloodstream infection.

We propose adding this information to this footnote on resistance in Gram negatives or adding it as a separate footnote.

(Tropical Bacteriology, Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp. Dr. Bieke Tack, MD, PhD Candidate and Prof. Dr. Jan Jacobs, MD, PhD)

Comment: "MSF recommends a broad-spectrum 3rd generation cephalosporin, ceftriaxone 80 mg/kg IV or IM as first empiric antibiotic treatment in children with circulatory impairment or shock that are suspected with sepsis as the aetiology or pathogen is not known at this first step of management."

(Médecins Sans Frontières - MSF)

Response: Ceftriaxone and cefotaxime are third-generation cephalosporins listed in the AWaRe Book as second-choice options for the treatment of sepsis in neonates and children and this is aligned with what the WHO Essential Medicines List for children recommends for this indication.

Changes to recommendations in the AWaRe Book would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process). Therefore, these two antibiotics remain a second-choice option in the Book; however, as suggested a note has been added to clarify that in settings where invasive non-typhoidal *Salmonella* are a major cause of bloodstream infection, empiric treatment with ceftriaxone or cefotaxime is preferred because of the high prevalence of isolates resistant to ampicillin.

The relevant footnote to Table 9 ("*Empiric antibiotic treatment for community-acquired sepsis of bacterial origin in neonates and children*", page 210 of the draft version) has therefore been amended as follows:

[b]In settings with high resistance, particularly for suspected health care-associated infections, a broad-spectrum antibiotic with activity against Gram-negative bacteria should also be considered (e.g. piperacillin+tazobactam). Of note, empiric treatment with third-generation cephalosporins (ceftriaxone / cefotaxime) may be more appropriate in settings where invasive non-typhoidal *Salmonella* are a major cause of bloodstream infection. The reason is that 1) >85% of non-typhoidal *Salmonella* are multidrug-resistant, which includes ampicillin resistance and 2) aminoglycosides have reduced clinical effectiveness in invasive non-typhoidal *Salmonella* infections.

5.3 Bacterial meningitis

Meningitis in adults

Comment: P75 *"Needs more clarity around 1st/2nd choice. i.e. which to use for which risk groups, are the second choices to be added in at risk populations or used instead if no access to first choice?"*

(British Society for Antimicrobial Chemotherapy)

Response: This comment refers to Table 4 (pages 219-220 of the draft version). First and second-choice options in the AWaRe Book reflect what is recommended in the WHO Essential Medicines Lists. In general, first choices are those recommended on the basis of the available evidence and are usually narrow-spectrum agents which is not the case for suspected bacterial meningitis where ceftriaxone / cefotaxime have a broader spectrum than second choice options. The reason being that bacterial meningitis is a life-threatening infection where the use of broader spectrum antibiotics such as 3rd generation cephalosporins can be justified. Therefore, second choice options for the treatment of suspected bacterial meningitis should only be considered when first choice options are not available or in specific situations (e.g. adding ampicillin to ceftriaxone / cefotaxime in adults when *Listeria monocytogenes* is suspected).

This has been clarified in additional footnotes to Table 4 (page 220 of the draft version), as shown:

[a]In adults and in children beyond neonatal age, consider second choice options only when first choice options are not available. In neonates consider meropenem (second choice) only where resistant Gram-negative organisms are the suspected causative agents.

[b]Ampicillin (or IV amoxicillin) in adults should be added to ceftriaxone / cefotaxime if risk factors for Listeria monocytogenes are present (e.g. patients ≥50 years, pregnancy).

Comment: "*MSF recommends that chloramphenicol is NOT an option, but where used is only in contexts where there is access to reliable microbiology*"

(Médecins Sans Frontières - MSF)

Response: This comment applies to the treatment of meningitis both in adults and in children.

The AWaRe Book is closely aligned with the WHO Essential Medicines Lists which include chloramphenicol as a second-choice treatment for acute bacterial meningitis. Changes in the Book would first require changes to the Model Lists (which must be requested through the standard submission process). Therefore, no changes to the text were made. However, chloramphenicol should only be used when no other option is available because of toxicity (the most serious adverse event is bone marrow depression) and this is clearly indicated in a footnote (Table 4 pages 219-220 of the draft version). In 2017, the Committee that recommended its inclusion in the WHO Essential Medicines Lists did so "*particularly for epidemic bacterial meningitis*" despite being associated with higher mortality than other antibiotics as the antibiotic is often available in low-and middle-income countries.

Meningitis in children

Comment: *"p 214 – Table 1: Salmonella not listed as a frequent cause of meningitis in children & adolescents. Non-typhoidal Salmonella are an important cause of meningitis in African children (Crump et al., 2015; Gilchrist et al., 2019). Meningitis is also a well-known complication of enteric fever in infants (Crump et al., 2015). We therefore propose adding invasive non-typhoidal Salmonella and Salmonella Typhi to the table"*

(Tropical Bacteriology, Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp. Dr. Bieke Tack, MD, PhD Candidate and Prof. Dr. Jan Jacobs, MD, PhD)

Comment: *"MSF recommends including Salmonella enterica (Africa, immunosuppressed, sickle cell disease)"*

(Médecins Sans Frontières - MSF)

Response: Invasive non-typhoidal *Salmonella* and *Salmonella* Typhi have been added to Table 1 (pages 214-215 of the draft version) as possible cause of bacterial meningitis in children and adolescents, along with a footnote indicating that invasive non-typhoidal Salmonella is mainly in sub-Saharan Africa in children living with HIV and / or sickle cell disease.

Comment: *"MSF would like to request to maintain the option of single doses of Ceftriaxone during Meningococcal meningitis when 5 days standard treatment is not possible. Understanding that 5 days treatment should be a first-line recommendation, we still consider that the possibility of single-dose ceftriaxone should be included to enable decentralized case management in specific cases, like remote areas, weak health infrastructure or high insecurity context, granted the following conditions:*

- *Reliable laboratory confirmation of an epidemic of meningococcal meningitis.*

- *Large scale epidemic which overwhelms management capacity for 5-day treatment*
- *It is essential that all patients are re-examined after 24 hours. In the case of inadequate clinical improvement, change to the 5-day ceftriaxone protocol and/or refer.*
- *Children under 2 years should always receive 5 or 7 days' treatment and should not be treated with the single-dose ceftriaxone protocol"*

(Médecins Sans Frontières - MSF)

Response: The AWaRe book is closely aligned with other WHO guidance documents and for meningitis, the WHO 2015 guidance document "Managing meningitis epidemics in Africa: a quick reference guide for health authorities and health-care workers" states that *"During epidemics in sub-Saharan Africa, ceftriaxone by injection is recommended as first line treatment for a minimum of five days; treatment with single-dose antibiotics is no longer advised due to the lower magnitude of epidemics after the introduction of the serogroup A vaccine and the risk of inadequate treatment of meningitis due to other pathogens"*. The document is referenced in the meningitis chapter (Table 4 page 219 of the draft version).

Comment: "*Meropenem is listed as second choice, while elsewhere in the draft (e.g. unknown origin) the recommendation is to add aminoglycosides to a 3rd generation cephalosporin as a carbapenem-sparing option. This recommendation seems more appropriate for this section too, instead of choosing carbapenems as empiric treatment (piperacillin/ tazobactam could be a better second option)"*

(Médecins Sans Frontières - MSF)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes in the Book would first require changes to the Model Lists (which must be requested through the standard submission process). Therefore, no changes to the text were made. Carbapenem-sparing options should be encouraged and in fact, first choice options for meningitis in neonates are ampicillin/gentamicin or 3rd generation cephalosporin / gentamicin as these combinations provide a good coverage of the most frequently involved pathogens (*Streptococcus pneumoniae*, *Streptococcus agalactiae*, *Listeria monocytogenes* and *Escherichia coli*). However, in 2017, meropenem was added to the WHO Essential Medicines List for children as second-choice *"to treat suspected acute bacterial meningitis where resistant Gram-negative organisms are the common causative agents"*. The recommendation only applies to neonates because Gram-negative bacilli such as *Escherichia coli* rarely cause community-acquired meningitis in other age groups. Of note, piperacillin-tazobactam does not effectively cross the blood brain barrier and should not be a choice for the treatment of bacterial meningitis.

5.4 Severe community-acquired pneumonia

Comment: *"The recommended first line is not manageable by governments in LMIC, gentamicin and benzylpenicillin as first line and ceftriaxone as second line".*

(David Banda, Clinical pharmacy specialist, Senior lecturer, Chreso University, Nursing department, Lusaka, Zambia)

Response: This context-specific comment raises the important issue of how the AWaRe Book may need to be adapted for the treatment of certain infections at the local / national level based on availabilities of antibiotics. The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the Book would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process).

Comment: *"Would the WHO consider offering high-dose amoxicillin + clarithromycin as a first-choice option instead of broad-spectrum cephalosporins? This would provide effective cover for the two most lethal pathogens (S. pneumoniae and L. pneumophila) but with much less selection pressure for Gram-negative resistance compared with 3rd generation cephalosporins. The prevalence of CAP and the over-estimation of severity leads to a massive global selection pressure from the use of 3rd generation cephalosporins – this guidance could offer a unique opportunity to take meaningful action to reduce that selection pressure. To be even more impactful in reducing resistance without compromising outcomes, the guidance could recommend high-dose benzylpenicillin + clarithromycin – the clarithromycin would cover H. influenzae, M. catarrhalis and S. aureus as well as L. pneumophila. Epidemiology data suggest fewer than 5% of patients have a CAP caused by an Enterbacterales and escalation to a 3rd generation cephalosporin could be offered as second choice if patients fail to respond to penicillin + clarithromycin or as first choice for patients with pre-existing lung disease."*

(British Society for Antimicrobial Chemotherapy)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the Book would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process).

However, the idea of replacing ceftriaxone + clarithromycin with less broad-spectrum options such as amoxicillin + clarithromycin or benzylpenicillin + clarithromycin was discussed within the Antimicrobial Working Group. While there was general support for the rationale (i.e. limiting the use of antibiotics with a broader spectrum of activity), the main concern was about the potential impact of this change on patients outcome depending on their severity at presentation (e.g. ICU vs non-ICU patients). While this option could be adequate in non-ICU patients, the evidence for its use in more severe patients requiring ICU admission would need to be reviewed also considering the fact that there are potential pathogens causing severe CAP that would not be adequately covered by the combination penicillin / macrolide. This change may be therefore considered in the future but, as mentioned above, it would first require changes to recommendations in the Model Lists.

A comment to this regard was added to the text (pages 230-231 of the draft version) as shown:

"The primary goal of empiric antibiotic treatment in CAP is to provide effective and timely treatment for Streptococcus pneumoniae infection, because this is the predominant bacterial pathogen and untreated

pneumococcal pneumonia is associated with high mortality (see Table 6 for adults and 7 for children for treatment recommendations – Tables' numbers refer to the draft version). ***While ceftriaxone co-prescribed with clarithromycin is the first-choice recommended option, other less broad-spectrum options (e.g. IV amoxicillin or benzylpenicillin co-prescribed with clarithromycin) could be considered especially in less severe cases not requiring ICU admission".***

Comment: *"MSF recommends considering mentioning anti-staphylococcal specific antibiotics (as in Sepsis) in case of an obvious skin source or radiographic image (pneumatoceles or multiple lung foci suggesting bacteraemia). In these cases, cloxacillin (or cefazolin) could ideally be added"*

(Médecins Sans Frontières - MSF)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the Book would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process).

Comment: *"MSF recommends adding information regarding failure of first line antibiotic regimens, from suspicion to clinical management including change/addition of antibiotics, complications to consider and/or assess antibiotic options for oral step down"*

(Médecins Sans Frontières - MSF)

Response: Failure of first line antibiotic regimens is beyond the scope of the AWaRe Book therefore no changes were made. As stated at the beginning of the Book (page 1) the aim is to include recommendations for empiric antibiotic treatment at the time of first clinical presentation treating the most likely bacterial pathogens causing each infection. However, for pneumonia, some comments to this regard are present in the text. In particular the idea that "*Clinical improvement should be evident within 48–72 hours of starting antibiotic therapy. If there is no response to treatment, a complication (such as empyema) should be considered"* (page 231 of the draft version) or that *"duration of treatment should be guided by measures of clinical improvement (e.g. resolution of fever)"* (page 231 of the draft version).

5.5 Upper urinary tract infection (UTI)

Comment: "*MSF recommends adding a mention to S. aureus also as associated with bacteraemia*"

(Médecins Sans Frontières - MSF)

Response: Table 1 (page 283 of the draft version) has been amended as shown: (Note: only relevant row of table shown).

Table 1 Pathogens commonly causing upper urinary tract infections (in descending order of frequency)

More rarely	*Enterococcus* spp. *Streptococcus agalactiae* (group B *Streptococcus*)

	Staphylococcus aureus (rare in uncomplicated UTIs, often in patients with urinary catheters; can be associated with bacteremia)

Comment: *"MSF recommends a more comprehensive explanation of false positive cultures (asymptomatic bacteriuria), linked with presence of symptoms or not, and highlighting that urine culture should only be done when UTI is clinically suspected"*

(Médecins Sans Frontières - MSF)

Response: It is agreed that urine cultures should only be done when upper UTI is suspected clinically. The text in the section "Patient microbiology tests" (page 283 of the draft version) has been slightly amended as shown to make this more clear:

"If upper UTI is suspected clinically, a urine culture should be done whenever possible, ideally before starting antibiotic treatment. The rationale is to confirm the diagnosis and to adjust empiric treatment based on susceptibility results".

Regarding the explanation of "false positive cultures (asymptomatic bacteriuria)", it is felt that the text (page 284 of the draft version) already addresses the fact that a positive urine culture should not be necessarily interpreted as an active urinary infection. For greater clarity, the following statement been amended as shown:

- *The presence of bacteria in the urine alone is not a sign of infection or an indication for antibiotic treatment. This condition is referred as asymptomatic bacteriuria when no symptoms suggestive of UTI are present.*

Comment: *"MSF notices that duration is over-simplified and recommends duration be made according to disease and host"*

(Médecins Sans Frontières - MSF)

Response: The Book does not provide formal recommendations for treatment duration but rather provides general guidance on what would be considered appropriate empiric treatment choices in most clinical cases. This general guidance seems important since many infections are treated for exceedingly long durations, potentially contributing to the emergence and spread of AMR. It is obvious that treatment decisions need to be individualized as is true with regard to choice of antibiotic (allergy, interactions), dose (renal or hepatic failure) or route (inability to tolerate oral treatments).

For upper UTI, duration is presented according to disease severity (mild / severe) and in both cases, 7 days are suggested even though it is agreed that for severe cases (e.g. cases with sepsis/septic shock) longer durations could be considered based on clinical response. Of note, for severe cases the Book recommends aminoglycosides in combination with a 3rd generation cephalosporin and the use of aminoglycosides can be associated with nephrotoxicity and/or ototoxicity (especially when used for more than 7 days). Therefore, in case of longer treatments, this aspect should be carefully considered.

Comment: "*In uncomplicated pyelonephritis: as a difference among women and men exists, prostatitis with pyelonephritis should be considered in men and antibiotic duration should be longer*"

(Médecins Sans Frontières - MSF)

Response: A footnote to Table 5 (page 289 of the draft version) has been added as shown:

"In men with upper UTI, prostatitis can also be present and longer treatment may therefore be warranted, but not universally as not each UTI episode in a male is associated with prostatitis"

Comment: "*MSF recommends step down to oral treatment may occur after less than 48 hours of IV antibiotics in the case of rapid clinical improvement*"

(Médecins Sans Frontières - MSF)

Response: The Book does not provide formal recommendations for IV to oral switch timing but rather provides general guidance on what would be considered appropriate in most clinical cases. Usually, as stated in the Book, clinical improvement "*should be evident within 48–72 hours of starting treatment*" and oral step down should be considered at this point. Of note, mild cases can be treated with oral antibiotics from the beginning provided the patient is in condition to take oral treatment (e.g. no vomiting).

Comment: *"MSF recommends:*

- For elderly men with catheter and septic: addition of ampicillin for Enterococcus sp.
- Aminoglycoside monotherapy regimens presented as an option for non-septic patients"

(Médecins Sans Frontières - MSF)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the Book would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process). Therefore, no changes to the text were made (i.e. ampicillin was not added).

Regarding the comment on aminoglycoside monotherapy, this option is already listed for severe cases in Table 5 (page 288 of the draft version).

Comment: *"Severe cases – consider piperacillin-tazobactam."*

(British Society for Antimicrobial Chemotherapy)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the Book would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process). Therefore, no changes to the text were made.

Comment: *"Ciprofloxacin for mild UTI cases goes against UK MHRA warnings. Children – consider cefalexin."*

(British Society for Antimicrobial Chemotherapy)

Response: The AWaRe Book recommends ciprofloxacin for mild cases of upper UTI (but not for cystitis). In children an alternative first choice option recommended in the Book is amoxicillin-clavulanic acid. The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the Book would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process). Therefore, no changes to the text were made.

5.6 Intra-abdominal infections

Comment: *"Suggest the use of metronidazole BID (rather than TID) for non-C. difficile related intra-abdominal infection (ie. appendicitis, diverticulitis, abdominal related abscess). This is the typically recommended dose used in Canada. Anaerobes are not typically significant pathogens of concern, and BID dosing has shown to provide adequate drug exposure. Based on the Tokyo guidelines, most uncomplicated biliary related infection would not require anaerobic coverage. Benefits include reduced dosing frequency and adverse effects".*

(Colin Lee, Providence Health care – Antimicrobial stewardship pharmacist, Canada)

Response: The frequency of administration of metronidazole varies among guidelines from 2 to 4 times a day. The reviewer's concern about adherence in the outpatient setting is understood, however, it is difficult to clearly recommend one treatment option over the other as the evidence base for these different dosing strategies is limited. Therefore, it was decided not to make changes to the dosing frequency of metronidazole. Some guidelines for intraabdominal infections even recommend six-hourly administration of metronidazole.

Comment: *"Co-amoxiclav oral dosing not available for all countries. Pip-taz using pseud dose despite not being a frequent causative organism and TDS is the licensed dose for intra-abdominal infections in UK. Why meropenem 2g tds?"*

(British Society for Antimicrobial Chemotherapy)

Response: This comment applies to acute cholecystitis/cholangitis, pyogenic liver abscess, acute appendicitis, and diverticulitis. The AWaRe Book does not provide formal recommendations for dosage but rather provides general guidance on what would be considered appropriate in most clinical cases. Therefore, no changes to the text were made except for meropenem for which the dose has been reduced to 1 g every 8 hours for all intra-abdominal infections, a dose that is appropriate for non-septic patients. However, it is acknowledged that different dosing strategies may be preferred based on local practices (e.g. dosing piperacillin-tazobactam every 8 hours instead of every 6 hours). Providing guidance for alternative dosing strategies is beyond the scope of the AWaRe Book.

Regarding the availability of certain formulations, there may differences from setting to setting, however all formulations mentioned in the AWaRe Book are listed in the WHO Essential Medicines Lists. This context-specific comment raises the important issue of how the Book may need to be adapted for the

treatment of certain infections at the local/national level based on antibiotic and formulation availability.

Comment: Page 265 / Table 5 / first column: *Second choice: Suggest amend to "ciprofloxacin and metronidazole both have excellent oral bioavailability*".

(UK Health Security Agency)

Response: This comment refers to the following sentence: "*Ciprofloxacin has excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function*". As suggested, the same comment has been added for metronidazole.

Acute appendicitis

Comment: "*MSF recommends culture of abscesses are done when drainage is performed and treatment is adapted accordingly*"

(Médecins Sans Frontières - MSF)

Response: This issue is already mentioned for severe cases in the section "Patient microbiology tests" (page 262 of the draft version). The text reads as follows: "*Routine microbiology tests are not usually needed and basing antibiotic treatment on pathogens cultured from the abdominal cavity at the time of operation is not recommended. However, certain microbiology tests could be considered in severely ill patients to adjust empiric antibiotic treatment once the results of antibiotic susceptibility tests are available. In more severe cases blood cultures should be taken and samples from the abdominal cavity may be useful in certain situations such as severely immunocompromised patients or patients known to be colonized with multidrug-resistant organisms or in patients presenting with septic shock".* Additionally, Table 2 (page 262 of the draft version) suggests "*Microscopy and culture of abscess fluid material when this can be drained*" in severely ill patients.

Comment: "*MSF recommends a carbapenem-sparing step with dual GNB coverage including aminoglycoside (especially amikacin) if there is no septic shock before considering meropenem*"

(Médecins Sans Frontières - MSF)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the Book would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process). Therefore, no changes to the text were made. The Book does NOT encourage the routine empiric use of meropenem and clearly indicates that this option should only be considered for severe cases suspected to be caused by extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales.

Acute cholangitis / cholecystitis

Comment: *"MSF recommends that parasites would be better in the "Definition" session as they are not aetiologies per se but rather further causes of biliary obstruction leading to bacterial complications"*

(Médecins Sans Frontières - MSF)

Response: The text has been amended as suggested and parasites have been removed from Table 1 "Pathogens most frequently associated with acute cholecystitis and cholangitis" (pages 243-244 of the draft version). The text (page 243 of the draft version) has been amended as shown:

*"The most common pathogens involved in acute cholecystitis or cholangitis are Gram-negative bacilli and anaerobic bacteria from the intestinal microbiota (Table 1 -of the draft version-). Infections are often caused by more than one pathogen and may include fungal pathogens, especially in patients that have recently received antibiotic treatment. **Certain parasites (e.g. Ascaris lumbricoides, Fasciola hepatica) need to be considered in endemic settings as they may cause biliary obstruction leading to bacterial complications**".*

Comment: *"MSF recommends considering the addition of ampicillin for Enterococcus spp. coverage for severe cases (sepsis, not uncommon) of acute cholangitis using cephalosporins and metronidazole"*

(Médecins Sans Frontières - MSF)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the Book would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process). Therefore, ampicillin was not added as an empiric option for the treatment of severe cases of acute cholecystitis / cholangitis in adults (ampicillin is however listed for children). However, a footnote has been added to Table 4 (page 250 of the draft version) as shown:

"Of note, piperacillin+tazobactam offers anti-Enterococcus coverage (which the other options listed for adults do not). Ampicillin would be another appropriate option, but it was not listed in the Table as it is not currently in the EML for this indication (while it is listed for children)."

Pyogenic liver abscess

Comment: "*MSF recommends considering a shorter duration of antibiotic treatment for milder cases (e.g. small abscess or early source control) from 4 weeks to 2 weeks*"

(Médecins Sans Frontières - MSF)

Response: The Book does not provide formal recommendations for treatment duration but rather provides general guidance on what would be considered appropriate in most clinical cases. For pyogenic liver abscesses, duration of treatment has always been debated but usually, it is between 4 and 6 weeks according to clinical and radiographic evolution. The major concern with shorter treatment (e.g. 2 weeks as suggested) is the risk of recurrence including with small abscesses. This is not a frequent indication for antibiotic treatment, but it is a potentially lethal infection, so antibiotic stewardship considerations (in general preferring shorter durations of treatment where possible) are probably less relevant in this context (costs may be more an issue for patients if longer treatments are required and they need to pay out-of-pocket). No changes have been made in the text.

Comment: "*MSF recommends considering adding a carbapenem-sparing strategy, adding an aminoglycoside (especially amikacin) to the regimens before choosing meropenem, for double GNB coverage (particularly important for ESBL)*"

(Médecins Sans Frontières - MSF)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the Book would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process). Therefore, no changes to the text were made. The Book does not encourage the routine empiric use of meropenem and clearly indicates that this option should only be considered for severe cases suspected to be caused by extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales.

5.7 Hospital-acquired pneumonia

Comment: p80. *"Likely pathogens - distinction between HAP and VAP would be helpful. 7 days duration as standard is excessive"*

(British Society for Antimicrobial Chemotherapy)

Response: The chapter is focussed on HAP (not VAP), therefore the table was not changed in its general structure but, following a discussion within the Antimicrobial Working Group, Enterobacterales and non-fermenters (Acinetobacter and Pseudomonas) were ranked on top of the list (before *S. pneumoniae*). Of note, the text, already mentions that most data on the microbiological etiology of HAP comes from ventilated patients (therefore a clear distinction is difficult to make) additionally, the prevalence of each pathogen may vary depending on the local epidemiology. As for treatment duration, seven days of treatment is recommended by several international guidelines (e.g. ESMID guidelines) and therefore no changes to the text were made.

Comment: *"Distilling the complex evidence and debate around dual pseudomonal cover down into a one line recommendation to consider this does not feel helpful. The discussion in this paper https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5720490/ is much more helpful, although I appreciate does need condensing to fit this guide. They also list pip-taz alone as pseud cover in the recommendations box which is somewhat contradictory."*

(British Society for Antimicrobial Chemotherapy)

Response: The idea of whether to provide more detailed guidance on the issue of *Pseudomonas aeruginosa* empiric coverage in severe cases of hospital-acquired pneumonia was discussed within the Antimicrobial Working Group. In particular the need to empirically give two antibiotics active against *Pseudomonas* to ensure that at least one of them is active against the pathogen was discussed and the group concluded that this remains an area of uncertainty as currently, the evidence available is poor in terms of the clinical benefits of this approach.

This has been clarified in the text (page 240 of the draft version, as shown) but no changes to the treatment recommendations were made. The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the Book would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process).

"There are some areas of uncertainty about empiric treatment for HAP.

.....

- *The need for* ***empiric*** *double coverage against Pseudomonas to improve coverage in severely ill patients (e.g. with septic shock, or in need of ventilatory support) because of the risk of infection caused by Pseudomonas aeruginosa isolates resistant to an antibiotic used for monotherapy. The need for* ***empiric*** *double coverage could therefore be considered in severely ill patients with VAP* ***(or with severe HAP requiring ventilator support)*** *on a case-by-case basis based on local antibiotic resistance data and the personal history of the patient such as known respiratory colonization with multidrug-resistant Pseudomonas aeruginosa, particularly in patients with underlying chronic lung disease.* ***However, specific antibiotic combinations to use in these cases are not covered in the AwaRe book as they are***

currently not included in the EML and EMLc with which this book is closely aligned."

Comment: *"In cases where there is a higher risk of P. aeruginosa infection, Piperacillin/tazobactam should be first line"*

(Médecins Sans Frontières – MSF)

Response: In the AwaRe Book, when more than one antibiotic option is listed for a certain indication, antibiotics are listed alphabetically which, in this case for example, could give the impression that piperacillin-tazobactam is not a first choice while in fact all four options listed are considered adequate alternatives. This has been made clearer and will be further emphasized in the document. Footnotes to Table 4 (pages 240-241 of the draft version) help with specificities of each option. For example, piperacillin-tazobactam is the only option that offers coverage against *Pseudomonas aeruginosa* and could be considered "*in patients with recent antibiotic exposure and especially in patients with known previous respiratory colonization by P. aeruginosa and underlying lung diseases*".

Comment: *"Recommend considering also adding a second GNB antibiotic (aminoglycosides, especially amikacin) for high risk of pseudomonal infection (which are same risk factors for higher MDR GNB risk in general)"*

(Médecins Sans Frontières - MSF)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the Book would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process). Therefore, no changes to the text were made. The rationale for the need of giving two antibiotics to cover for *Pseudomonas aeruginosa* is briefly mentioned in the amended text (page 240 of the draft version) as follows:

"There are some areas of uncertainty about empiric treatment for HAP.

- *The need for* ***empiric*** *double coverage against Pseudomonas to improve coverage in severely ill patients (e.g. with septic shock, or in need of ventilator support) because of the risk of infection caused by Pseudomonas aeruginosa isolates resistant to an antibiotic used for monotherapy. The need for* ***empiric*** *double coverage could therefore be considered in severely ill patients with VAP* ***(or with severe HAP requiring ventilator-support)*** *on a case-by-case basis based on local antibiotic resistance data and the personal history of the patient, such as known respiratory colonization with multidrug-resistant Pseudomonas aeruginosa, particularly in patients with underlying chronic lung disease.* ***However, specific antibiotic combinations to use in these cases are not covered in the AWaRe book as they are currently not included in the EML and EMLc with which this book is closely aligned.***

Comment: *"Recommend mentioning meropenem and vancomycin as a regimen for ICUs with a high prevalence of MRSA (extremely common) and MDR GNB (also far from uncommon)"*

(Médecins Sans Frontières - MSF)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the Book would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process). Therefore, no changes to the text were made. However, the text mentions the need to consider the empiric use of vancomycin if MRSA is suspected (e.g. in settings with a high prevalence of *Staphylococcus aureus* isolates that are methicillin resistant and in patients known to be colonized by MRSA) (page 240 of the draft version). The empiric treatment of infections caused by multidrug-resistant Gram-negative bacteria is not covered in the HAP chapter as options for these indications are not specifically mentioned in the WHO Essential Medicines Lists.

5.8 *Clostridiodes difficile* infection

Comment: p 101. "*Metronidazole should no longer be offered. See NICE guidance for evidence. Vancomycin oral 1st line and Fidaxomicin 2nd line for recurrence with 3 months.* Overview | Clostridioides difficile infection: antimicrobial prescribing | Guidance | NICE "

(British Society for Antimicrobial Chemotherapy)

Comment: *"C diff: See NICE NG199 evaluation*

- *Metronidazole not recommended*
- *Oral vancomycin*
- *Fidaxomicin"*

(The UK Paediatric Antimicrobial Stewardship)

Comment: Page 275: *"We note that the WHO EML recommends metronidazole as the first line choice for the treatment of Clostridioides difficile. We would suggest using oral vancomycin for 10-14 days first line as it had "lower initial cure rates and higher recurrence rates than vancomycin". For either relapse of disease within 12 weeks of first episode, or as a second line antimicrobial, we would suggest the use of fidaxomicin for 10 days if available [1,2]."*

References:

1. Wolf, J., Kalocsai, K., Fortuny, C., Lazar, S., Bosis, S., Korczowski, B., Petit, A., Bradford, D., Croos-Dabrera, R., Incera, E. and Melis, J., 2020. Safety and efficacy of fidaxomicin and vancomycin in children and adolescents with Clostridioides (Clostridium) difficile infection: a phase 3, multicenter, randomized, single-blind clinical trial (SUNSHINE). Clinical Infectious Diseases, 71(10), pp.2581-2588.

2. National Institute for Health and Care Excellence (NICE), 2021. Clostridioides difficile infection: antimicrobial prescribing [NG199]. (https://www.nice.org.uk/guidance/ng199)

(UK Health Security Agency)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the Book would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process). Therefore, no changes to the text were made. Of note, the Book only covers the treatment of first episodes of *Clostridioides difficile* infection (not recurrences) and is focused on mild cases (e.g. the text on page 279 of the draft version clarifies that for severe cases, oral vancomycin would be preferable to oral metronidazole).

Comment: *"Page 279 – starting at line 101: In the section on antibiotic treatment, other medicines such as teicoplanin in recurrent Clostridial infections should be considered. More information about this topic can also be found via* https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(18)30285-8/fulltext*."*

(Stephanie Kohl, Policy and advocacy officer at the European association of hospital pharmacists)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines Lists where teicoplanin is not included, therefore no changes were made in the text. Of note, the Book only covers the treatment of first episodes of *Clostridioides difficile* infection (not recurrences).

Comment: *"Disagree with the statement: "Important: Do not repeat testing during the same episode and do not test to confirm the resolution of the infection at the end of treatment" If initial testing was negative and high index of suspicion then is appropriate to test again."*

(British Society for Antimicrobial Chemotherapy)

Response: The text (page 277 of the draft version) has been amended as shown:

"In patients diagnosed with Clostridioides difficile infection, repeat testing during the same episode and test of cure are not needed and should be avoided".

Comment: *"Severe treatment options need to be detailed where enteral therapy may not be possible."*

(British Society for Antimicrobial Chemotherapy)

Response: The AWaRe Book is focused on the treatment of mild cases of *Clostridioides difficile* infection however severe cases are briefly mentioned in Table 3 (pages 279-280 of the draft version) with suggestions to use high dose oral vancomycin and to consider adding intravenous metronidazole. Adding guidance for more complicated situations (e.g. enteric therapy not feasible) is beyond the scope of the Book, therefore no changes to the text were made.

Comment: *"Where is the statement on prevention of C. difficile?"*

(British Society for Antimicrobial Chemotherapy)

Response: *Clostridioides difficile* infections are usually acquired in hospitals favoured by antibiotic use (often inappropriate) and poor infection control practices. Guidance about hospital infection control practices is beyond the scope of the Book (other WHO documents can be used for this purpose) therefore no changes to the text were made. Of note, appropriate antibiotic use (especially avoiding unnecessary use of broad-spectrum antibiotics) can limit the risk of *Clostridioides difficile* infection and it is hoped that the AWaRe Book, can contribute to this.

5.9 Acute bone and joint infections

Acute bacterial osteomyelitis

Comment: *"MSF recommends the addition of the term 'open fracture-related' to the mention to direct inoculation, as it implicates empiric antibiotic treatment and the need to manage infected fixation hardware"*

(Médecins Sans Frontières - MSF)

Response: The text (page 290 of the draft version) has been amended as shown, to include the possibility of osteomyelitis secondary to inoculation of pathogens from the outside in case of open fractures:

"Osteomyelitis is an infection of the bone characterized by inflammation and bone destruction. Infection can be classified according to how the pathogen spreads in the body (via the bloodstream or by local spread from nearby tissue ***or through direct inoculation, for example in case of open fractures****) or the duration of symptoms (acute or chronic)".*

Comment: *"MSF recommends mentioning open fractures/combat/trauma related relevance of Enterobacterales and A. baumannii"*

(Médecins Sans Frontières - MSF)

Response: The text acknowledges that globally, most cases of acute osteomyelitis develop after a traumatic event especially in adults and this also applies to infections caused by *Staphylococcus* spp. which are the most common. A mention of trauma / combat has been added to the Epidemiology section (page 291 of the draft version) as shown:

"Most cases globally develop after a traumatic event, for example infections in open fractures following road traffic incidents ***or combat****. In addition, in high-income settings, diabetes (which can lead to foot osteomyelitis; not specifically addressed in this chapter) and spinal interventions (which can lead to vertebral osteomyelitis) contribute to the burden of disease".*

Regarding the comment about *Enterobacterales* and *Acinetobacter baumannii,* these are not common causes of acute osteomyelitis but a mention of open fractures has been added to both table 1 (children) and 2 (adults) on pages 291-293 of the draft version. Changes are shown below (Note: only relevant parts of tables shown):

Table 1 Pathogens associated with acute osteomyelitis in children

Pathogen	Most common way of spreading	Patients most at risk
Enterobacterales	Bloodborne **or local spread**	Neonates and immunocompromised children. **Also consider in case of open fractures**
Acinetobacter baumannii	**Bloodborne or local spread**	**Consider in case of open fractures**

Table 2 Pathogens associated with acute osteomyelitis in adults

Pathogen	Most common way of spreading	Patients most at risk
Enterobacterales	Bloodborne or local spread	Patients with decubitus (pressure) ulcers, diabetic foot infections and burn wounds (especially if the wound is close to the perineum) and abdominal surgery
Acinetobacter baumannii	Bloodborne or local spread	Consider in case of open fractures

---

Comment: "*As TB is not only among immunosuppressed, MSF recommends adding a mention as a cause of chronic osteomyelitis (especially vertebral/Pott)*"

(Médecins Sans Frontières - MSF)

Response: The AWaRe Book focuses on acute infections and this also applies to osteomyelitis.

Therefore, Pott disease is not covered and only briefly mentioned in the "Clinical presentation" section (page 293 of the draft version) as follows: "*Consider tuberculous osteomyelitis (mostly vertebral, in that case also known as Pott disease) when the illness is chronic, discharging sinuses are present (i.e. when a passage (sinus) forms from the infected bone to the surface of the skin and pus drains through) or the patient has other signs of tuberculosis*".

Mycobacterium tuberculosis is also mentioned as a less common cause of osteomyelitis in the "Microbiology epidemiology" section (Table 2, page 292-293 of the draft version). A comment has been added in the table to clarify that *Mycobacterium tuberculosis* is often a cause of chronic rather than acute infection.

Comment: "*MSF recommends including Salmonella enterica linked to sickle cell disease or complicating bacteraemia*"

(Médecins Sans Frontières - MSF)

Response: Invasive non-typhoidal *Salmonella* is already listed as a possible cause of acute osteomyelitis in children (Table 1, pages 291-292 of the draft version). The same has been added for adults (Table 2, pages 292-293 of the draft version).

Comment:: "*MSF recommends adding mention to fracture-related, and specifically to suspect osteomyelitis when there is failure in fracture healing/bone fusion and/or loose hardware*"

(Médecins Sans Frontières - MSF)

Response: The text in the "Clinical presentation" section (page 293 of the draft version) has been amended as shown:

"Acute osteomyelitis is characterized by gradual onset of localized pain and/or tenderness with a combination of redness, swelling, pain and warmth of the affected area. Fever (> 38.0 °C) and other signs of systemic infection (e.g. tachycardia, leukocytosis) may be present. In the context of osteomyelitis involving the vertebral spine, hip and pelvis, pain is usually the main symptom. ***Osteomyelitis should also be suspected in case of defective healing of a fractured bone.*** *In children where acute osteomyelitis often involves the femur and tibia, difficulty and/or inability to walk or reluctance to move the limb may be a presenting symptom".*

A reference to loose hardware has not been made because prosthetic joint infections are not covered in the AWaRe Book.

Comment: "*MSF recommends clarifying how a WBC result will change the treatment option in the context of acute osteomyelitis as it is not clear as it is formulated*"

(Médecins Sans Frontières - MSF)

Response: The AWaRe Book does not provide formal recommendations for laboratory tests but rather provides general guidance on what would be considered appropriate in most clinical cases in alignment with tests that are included in the current WHO Essential List of *in-vitro* Diagnostics (EDL). Guidance on the interpretation of laboratory results is beyond the scope of the Book. However, in the "Clinical presentation" section (page 293 of the draft version), it is mentioned that increased white blood cells (i.e. leucocytosis) in a clinical context suggestive of acute osteomyelitis could help confirming the diagnosis.

Comment: "*MSF recommends suspicion of TB is specifically linked to the diagnostic use of GeneXpert*"

(Médecins Sans Frontières - MSF)

Response: Tuberculosis (TB) usually causes chronic rather than acute osteomyelitis and is therefore not covered in the chapter, therefore no changes to the text were made. However, the necessity to think about testing for mycobacteria is mentioned in a footnote to Table 3 (page 294 of the draft version) where laboratory tests to consider are described.

More details on diagnosis of TB can be found in WHO TB guidelines which have been referenced in the chapter.

Comment: "*An anti-staphylococcal penicillin (Cloxacillin) or 1st generation cephalosporin (Cefazolin) should always be part of empiric initial regimen, unless clinical presentation is very suggestive of Salmonella enterica (such as in sickle cell disease)*"

(Médecins Sans Frontières - MSF)

Response: This is in line with what is recommended in the AWaRe Book for the empiric treatment of acute osteomyelitis.

Comment: "*Cloxacillin dose should be higher (12 g per day) given issues with bone penetration and concentration*"

(Médecins Sans Frontières - MSF)

Response: Users of the AWaRe Book should be aware of the limited evidence underlying many antibiotic prescribing strategies and particularly the very poor evidence for dosing guidance, which may explain some of the variation in international recommendations. The Book therefore does not provide formal recommendations for dosage but rather provides general guidance on what would be considered appropriate in most clinical cases. For simplicity and to help prescribers, the Book also tries to harmonize doses across different infections, therefore the dose of cloxacillin (8 g per day divided every 6 hours) has not been changed. However footnotes have been added to Table 5, page 297 of the draft version (osteomyelitis) and Table 6, page 306 of the draft version (septic arthritis) to acknowledge that a higher dose (e.g. 12 g per day) could be considered in adults given the concerns with bone penetration. The current dose is also suggested in the Book for other infections in which cloxacillin is the recommended antibiotic (e.g. septic arthritis, periorbital cellulitis, pyomyositis).

Comment: *"If surgery related, consider MRSA as well"*

(Médecins Sans Frontières - MSF)

Response: Empiric coverage of MRSA (methicillin-resistant *Staphylococcus aureus*) is not recommended in the AWaRe Book because vancomycin (the antibiotic that would preferentially be used in this case) is not listed in the WHO Essential Medicines Lists for this indication. Changes in the Book would first require changes to the Model Lists (which must be requested through the standard submission process). Therefore, no changes to the text were made. However, the need to cover for MRSA in certain situations is mentioned in the "Antibiotic treatment" section (pages 295-296 of the draft version).

Comment: *"Consider oral therapy after 7 days for the remainder of course based on OVIVA study"* Oral versus Intravenous Antibiotics for Bone and Joint Infection | NEJM

(British Society for Antimicrobial Chemotherapy)

Response: The OVIVA study is referenced in the text. Even though the AWaRe Book does not provide formal recommendations for when intravenous to oral switch should occur, in this case the text (page 296 of the draft version) clearly states that "Step down to oral antibiotics at home is increasingly being used early in the treatment course (e.g. in the first week) when the disease is uncomplicated". Since this is already addressed in the text, no further changes were made.

Comment: *"States guidance doesn't cover PJI then discusses PJI in clinical considerations."*

(British Society for Antimicrobial Chemotherapy)

Response: The comment refers to the following text (page 295 of the draft version):

> For prosthetic joint infections, treatment usually requires the surgical removal of the device. This can be done in one stage (the new prosthesis is immediately inserted) or two stages (the infected prosthesis is removed, the area is debrided, antibiotic treatment is given for several weeks and finally the new prosthesis is inserted). The choice of one stage or two stages depends on the location of the

prosthesis (e.g. hip, knee), characteristics of the patient (e.g. advanced age, comorbidities) and local practices.

A detailed discussion of prosthetic-joint infections is beyond the scope of the AWaRe book.

While treatment and management of prosthetic joint infections (PJI) is not covered, general statements like those mentioned above could be helpful from an educational point of view. The reader will then be able to seek further guidance in other documents, if interested. Therefore, no changes to the text were made.

Comment: Pages 290 – 306 / *"Oral step down: We would suggest the following regimen for the treatment of osteomyelitis and septic arthritis, if available [1,2]:*

For children <3 months of age:

- *IV ceftriaxone (or cefotaxime if contraindications)*
- *Switch to oral co-amoxiclav or cefalexin after 14-21 days*

For children >3 months to ≤5 years:

- *IV cefuroxime*
- *Switch to oral co-amoxiclav or cefalexin after 72 hours"*

≥6years:

- *flucloxacillin IV. Oral after 72 hours:*

6-8 years:

- *flucloxacillin OR co-amoxiclav*

8-19 years:

- *flucloxacillin OR clindamycin"*

(UK Health Security Agency and The UK Paediatric Antimicrobial Stewardship)

Response: This comment applies to both acute osteomyelitis and septic arthritis in children. Ceftriaxone and cefotaxime are both listed as second choice options for the empiric treatment of both infections in children and neonates with a note to favour these options in case *Salmonella* spp. and Enterobacterales are suspected. The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the Book (including for example "upgrading" ceftriaxone / cefotaxime to first choice options or adding cefuroxime) would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process). Therefore, no changes to the text were made.

Oral options to use for intravenous to oral step-down are not specifically mentioned in the AWaRe Book (this level of detail is beyond the scope of the Book which is mainly focused on the choice of the initial empiric antibiotic), however for example amoxicillin-clavulanic acid is one of the second-choice options recommended in the Book and could therefore be used for this purpose in line with what has

been suggested.

Comment: *"For unifocal disease:*

- *2-3 weeks total in septic arthritis, 3-4 weeks total in osteomyelitis*
- *IV to PO switch if afebrile, pain free >24 hours, CRP <20 or reduced by two-thirds of its total value*

For complex disease:

- *May require treatment course >6 weeks*
- *IV to PO switch after 14 days"*

References:

1. McMullan, B.J., Andresen, D., Blyth, C.C., Avent, M.L., Bowen, A.C., Britton, P.N., Clark, J.E., Cooper, C.M., Curtis, N., Goeman, E. and Hazelton, B., 2016. Antibiotic duration and timing of the switch from intravenous to oral route for bacterial infections in children: systematic review and guidelines. The Lancet Infectious Diseases, 16(8), pp.e139-e152.
2. Saavedra-Lozano, J., Falup-Pecurariu, O., Faust, S.N., Girschick, H., Hartwig, N., Kaplan, S., Lorrot, M., Mantadakis, E., Peltola, H., Rojo, P. and Zaoutis, T., 2017. Bone and joint infections. The Pediatric infectious disease journal, 36(8), pp.788-799.

(UK Health Security Agency and The UK Paediatric Antimicrobial Stewardship)

Response: It is assumed that this comment only refers to treatment duration of septic arthritis and acute osteomyelitis in children (because of the pediatric references). Reviewers categorize infections in unifocal and complex, and suggest different durations based on the type of infection (shorter for septic arthritis / longer for osteomyelitis) while the AWaRe Book, suggests 3 weeks for both infections and does not cover complex cases. There are therefore no substantial differences with what is already suggested in the Book (except that complex cases are not covered) as the range of durations suggested by reviewers overlaps with what is suggested in the Book. Therefore, no changes to the text were made. Of note, the Book does not provide formal recommendations for treatment duration but rather provides general guidance on what would be considered appropriate in most clinical cases.

Comment: *(line 33, page 292). Add – 'Acute suppurative and non-suppurative osteomyelitis of the jaws may also result from oral and dental infections'*

(World Dental Federation)

Response: This comment refers to the following sentence in the Epidemiology section (page 291 of the draft version) which has been amended as shown:

"Risk factors for osteomyelitis are those associated with bacteraemia (e.g. presence of indwelling vascular catheters, injection drug use, haemodialysis) and those making the bone vulnerable to infection (e.g. bone surgery, open bone fracture, presence of foreign material such as prosthetic joint implants, sickle-cell disease, diabetes, impaired bone vascularization). Acute suppurative and non-suppurative osteomyelitis of the jaw may also result from oral and dental infections".

Septic arthritis

Comment: "*MSF recommends mentioning the relevance of Enterobacterales and A. baumannii in relation to open fractures/combat/trauma. The risk only applies to trauma with joint penetration, and not closed trauma. Enterobacterales can be associated with dirty open trauma and surgery*"

(Médecins Sans Frontières - MSF)

Response: Enterobacterales and *Acinetobacter baumannii* are not a common cause of septic arthritis and the first-choice antibiotic option recommended in the Book (cloxacillin) does not provide coverage for these pathogens (Ceftriaxone or cefotaxime which are listed as second choice would be adequate). However, in certain situations these pathogens should be considered (common risk factors are listed in Table 2 on page 301 of the draft version). Table 2 has been amended to include dirty open wounds with exposed joints as another risk factor to consider as follows (only relevant parts of table are shown):

Table 2 Pathogens associated with acute septic arthritis in adults

Enterobacterales	Bloodborne or by local spread	Patients with decubitus or pressure ulcers, diabetic foot infections, burn wounds (especially if the wound is close to the perineum) and those having undergone recent abdominal surgery. Consider also in case of open skin wounds with exposed joint.
Acinetobacter baumannii	Bloodborne or by local spread	Consider in case of open skin wounds with exposed joint.

Comment: Clinical: "*MSF recommends a stronger mention of TB as an important aetiology for sub-acute arthritis*"

(Médecins Sans Frontières - MSF)

Response: Diagnosis and management of septic arthritis secondary to TB (*Mycobacterium tuberculosis* infection) is beyond the scope of the AWaRe Book. However, in the "Microbiology epidemiology" section (Table 2, page 301 of the draft version) *Mycobacterium tuberculosis* is mentioned as a possible cause of septic arthritis especially in immunocompromised patients and testing synovial fluid for this pathogen is also mentioned in the Laboratory tests section (Page 302-303 of the draft version).

Comment: Lab: "*for TB, MSF recommends inclusion of a specific mention of GeneXpert and gram stain in the work up of septic arthritis, and to mention the use of molecular tests/NAAT (as GeneXpert itself) for gonococcal arthritis*"

(Médecins Sans Frontières - MSF)

Response: Tests for *Neisseria gonorrhoeae* and *Mycobacterium tuberculosis* have been added to Table 3 (page 302 of the draft version) as these tests are also included in the WHO Essential List of *in-vitro* Diagnostics (only relevant parts of table shown below). Commercial names are not mentioned.

Table 3 Microbiology tests to consider when septic arthritis is suspected, as indicated in the WHO EDL

Diagnostic test	*Purpose of the test*	*Settings where the test should be available*
Nucleic acid amplification test of urogenital specimens and urine for Neisseria gonorrhoeae infection[b]	*To diagnose gonorrhoeal urogenital disease and extragenital infection*	*Healthcare facilities with clinical laboratories*
Synovial fluid for Mycobacterium tuberculosis DNA	*To diagnose active tuberculosis and detect rifampicin resistance*	*Health care facilities with clinical laboratories*

[b]*This test is not validated on the synovial fluid but is used in some settings.*

Comment: p113. *"Consider anaerobic cover if caused by penetrating injury.*

"(British Society for Antimicrobial Chemotherapy)

Response: Table 2 (page 301 of the draft version) already mentions that bite wounds (a penetrating injury) is a risk factor for septic arthritis caused by anaerobic bacteria. The text has been slightly amended to make this clearer (only relevant part of the table shown below).

Table 2 Pathogens most frequently associated with acute septic arthritis in adults

Pathogen	*Main dissemination mechanism*	*Patients most at risk*
Anaerobes	*By local spread*	*Patients with* ***penetrating injuries (e.g****. bite wounds)*

Comment: *"Includes some details about PJI - is this included in this definition? Would recommend covered separately."*

(British Society for Antimicrobial Chemotherapy)

Response: Treatment and management of prosthetic joint infections is not covered in the AWaRe Book but it may be considered in the future.

5.10 Severe skin and soft tissue infections

Necrotizing fasciitis

Comment: *"I would add in other pathogens that cause that like GAS and C. perfringes etc. Also other pathogens such as aeromonas, pseudomads in the right host".*

(Dr Devika Dixit, Pediatric infectious disease physician, University of Calgary, Canada)

Response: These pathogens are already mentioned in Table 1 (page 308 of the draft version) in the chapter on necrotizing fasciitis.

Comment: *"MSF recommends some additions. Fast progression of erythema, ecchymosis/bullae are also suggestive of necrotizing fasciitis"*

(Médecins Sans Frontières - MSF)

Response: The text in the Clinical presentation section (page 309 of the draft version) has been amended as shown:

"Necrotizing fasciitis is usually characterized by acute onset of pain out of proportion to physical findings in the affected area and rapid onset of systemic signs - for example, fever ≥ 38.0 °C, tachycardia and increased biomarker levels – leukocytosis, C-reactive protein and procalcitonin*. Signs and symptoms of skin and soft tissue infections* (i.e. redness, skin discolouration, swelling, induration (hardening of soft tissue) and warmth of the affected area) *are usually present when pathogen entry is through the skin. However, at least initially, the overlying skin often appears only minimally affected, and skin changes – typically bullae and necrosis – only become apparent as the infection progresses. Rapid progression of redness, ecchymosis and bullae is also suggestive of this infection".*

Comment: *"MSF recommends some additions. Absence of WBC suggests C. prefringens"*

(Médecins Sans Frontières - MSF)

Response: Guidance on the interpretation of laboratory results is not the focus of the AWaRe Book. This level of detail for a specific pathogen is beyond the scope of the Book. Therefore no changes to the text were made.

Comment: *"consider meropenem and clindamycin 1st line."*

(British Society for Antimicrobial Chemotherapy)

Response: Clindamycin co-prescribed with piperacillin-tazobactam is the first choice recommended in the Book for the empiric treatment of all cases of necrotizing fasciitis. The other option (ceftriaxone co-prescribed with metronidazole) is only adequate if *Streptococcus pyogenes* has been excluded. The AWaRe Book is closely aligned with the WHO Essential Medicines. Changes to recommendations in the Book would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process).

Comment: *"Addition of Clindamycin for all cases"*

(Médecins Sans Frontières - MSF)

Response: Clindamycin co-prescribed with piperacillin-tazobactam is the first choice for the empiric treatment of all cases of necrotizing fasciitis. The other option (ceftriaxone co-prescribed with metronidazole) is only adequate if *Streptococcus pyogenes* has been excluded.

Comment: *"Using ceftazidime instead of ceftriaxone if a cephalosporin is chosen"*

(Médecins Sans Frontières - MSF)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines. Changes to recommendations in the Book would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process). Therefore, no changes to the text were made.

Pyomyositis

Comment: *"It might be useful to add in case of recurrent disease (and especially in sub-Saharan African countries), the possibility of PVL+ S. aureus (Panton-Valentin) as the cause. Looking for it (if possible) and proposing decolonization (if positive or empirically?) might be part of the management".*

(Dr Gilles Eperon, Tropical and humanitarian division, Geneva university hospitals, Switzerland)

Response: The following footnote has been added to *Staphylococcus aureus* (including MRSA) in Table 1 (page 314 of the draft version):

"Some strains can produce the Panton-Valentine leukocidin, a toxin associated with a higher pathogenic potential (i.e. the risk of causing a more severe disease). The possibility of Staphylococcus aureus positive for Panton-Valentine leukocidin should be considered especially in case of recurrent skin infections. In these cases, topical decolonization measures might be considered to prevent recurrence and transmission to others."

Details on specific decolonization protocols are not given as this is beyond the scope of the AWaRe Book.

Comment: p120. *"As Staph aureus mainly, then 1st line cloxacillin / flucloxacillin. Penicillin allergy alternative: Glycopeptide IV."*

(British Society for Antimicrobial Chemotherapy)

"MSF recommends adding cefazolin as an option"

(Médecins Sans Frontières - MSF)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines Lists and treatment options for pyomyositis are extrapolated from those for mild skin infections. Changes to recommendations in the Book would first require changes to recommendations in the Model Lists

(which must be requested through the standard submission process). Therefore no changes to the text were made.

In the AWaRe Book, when more than one antibiotic option is listed for a certain indication (as is the case for pyomyositis), antibiotics are listed alphabetically which, in this case for example, could give the impression that amoxicillin-clavulanic acid is first choice while in fact all three options are considered adequate alternatives. This has been made clearer and has been further emphasized in the Book.

5.11 Febrile neutropenia

Comment: p124. *"Try to exclude penicillin allergy before starting treatment as per local protocol."*

(British Society for Antimicrobial Chemotherapy)

Response: Guidance for management and alternatvies to offer in case of penicillin allergy is beyond the scope of the AWaRe Book and not mentioned in any of the Infections chapters. However, general principles about this topic are given in a separate section of the Book titled "Allergy to antibiotics" (page 13 of the draft version).

5.12 Surgical prophylaxis

Bowel surgery

Comment: "*Cefuroxime where cefazolin not available. For children, cefazolin not always available so cefuroxime as an option."*

(British Society for Antimicrobial Chemotherapy)

Response: Cefuroxime is already listed as a second-choice option if cefazolin cannot be used both for clean and clean-contaminated procedures. However, cefuroxime (a second-generation cephalosporin) has no activity against anaerobic bacteria therefore it is not listed for the prophylaxis of bowel surgery where anaerobic coverage is needed.

Comment: *"Consider treatment rather than prophylaxis where not just bowel content spillage that cannot be irrigated."*

(British Society for Antimicrobial Chemotherapy)

Response: Treatment of surgical site infections (in this case infections of the surrounding tissue that was involved in the surgery) is not covered in the AWaRe Book but may be considered in the future.

Comment: *"Penicillin allergy = glycopeptide, ciprofloxacin and metronidazole."*

(British Society for Antimicrobial Chemotherapy)

Response: The recommendations for antibiotics in the Book are based on antibiotics listed in the WHO Essential Medicines Lists for each indication. Therefore, alternative options (that are not specifically mentioned in the WHO Essential Medicines Lists) are not reported. This may, however, be considered for future updates of the Book. There is a certain risk that these alternatives could be overused which

may have negative consequences e.g. if the alternatives are less effective, less safe and have a higher potential for resistance (e.g. alternatives may often be non beta-lactam Watch group antibiotics). Real-world experience shows for example that prescribers tend to overdiagnose presumed allergic contraindications to beta-lactams.

Comment: *"Redosing of agents required after 2 half-lives."*

(British Society for Antimicrobial Chemotherapy)

Response: The need to re-dose the antibiotic in certain situations (e.g. for long surgeries after two half-lives" is mentioned on page 333 of the draft version. Therefore, no changes to the text were made.

Urological surgery

Comment: *"Urological procedures have high resistance rates in many countries (ESBLs) so pre-op screening often useful."*

(British Society for Antimicrobial Chemotherapy)

Response: Microbiology screening (e.g. rectal and nasal swabs) to detect colonization by multidrug-resistant pathogens prior to surgical procedures is not covered in the AWaRe Book. The text (page 332 of the draft version) mentions the limited evidence available on the implications for antibiotic prophylaxis especially if multidrug-resistant Gram-negative bacteria are detected.

This is different from urinalysis screening to detect asymptomatic bacteriuria (or urinary infection if the patient is symptomatic) which is usually done in patients undergoing urological surgery and requires treatment if the test comes back positive.

Comment: *"Debate whether gentamicin alone enough so another anti Staph agent eg (flu)cloxacillin needed."*

(British Society for Antimicrobial Chemotherapy)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the Book would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process).

Gentamicin alone is only recommended as prophylaxis of urologic procedures (second choice) but not for example for clean or clean-contaminated surgery. For bowel surgery it could be used but in combination with metronidazole because if used alone it does not provide adequate coverage of anaerobic bacteria.

Comment: "*MSF recommends further details and clarification on the selection of antibiotics by conditions and duration*"

(Médecins Sans Frontières - MSF)

Response: Regarding the selection of antibiotics for surgical prophylaxis more details can be found in the report of the Expert Committee on the 2019 WHO Model Lists update, in particular in the section about Surgical prophylaxis (page 27 of the report).

Regarding duration, the text in the Book (page 333 of the draft version) clearly states that one dose of antibiotic within two hours of starting surgery is adequate in most cases and that giving additional doses does not offer additional benefit in reducing the incidence of surgical site infections. The only exceptions would be long surgical procedures or major blood losses during surgery where a second dose of antibiotic could be considered.

Dental procedures

Comment: *"In some parts of the world, dentists commonly prescribe antibiotics for surgical prophylaxis and so the chapters should be cross referenced"*

(World Dental Federation)

Response: Antibiotic prophylaxis prior to dental procedures is not covered in the Book and local/ national guidance should be consulted for this purpose.

Comment: *"Key messages (page 329). FDI agrees that not all surgical procedures require prophylaxis and addressing this is an important aspect of antimicrobial stewardship"*

(World Dental Federation)

Response: This comment refers to one of the Key messages (page 328 of the draft version). In particular "*The indication and choice of antibiotic prophylaxis depends on the type of surgical procedure (not all surgical procedures require prophylaxis)*".

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6 Reserve antibiotics

Comment: *"Imipenem-resistant Pseudomonas" is not the correct definition of "IMP", which should be "imipenemase" (this abbreviation has also been used on page 344 / line 25).*

(UK Health Security Agency)

Response: This has been corrected as suggested (i.e. IMP: imipenemase).

Comment:

Page 336 / line 40-41 refers to "metallo-proteinases"; correct terminology is "metallo-carbapenemases" or "metallo-beta-lactamases".

Please clarify lines 38-41 – does this mean that reserve antibiotics that target carbapenem-resistant pathogens should also have activity against the carbapenemase variants in low and middle-income countries (LMICs)?

(UK Health Security Agency)

Response: Both comments refer to the following sentence in the introduction of the Reserve antibiotics section (page 336 of the draft version): *"This focus on public health emphasizes the importance for Reserve antibiotics to have phenotypic and genotypic activity that is globally relevant. For example, Reserve antibiotics that are active against carbapenem-resistant pathogens should ideally also have activity against the most common genetic types identified in low- and middle-income countries (e.g. metallo-proteinases)".*

The above paragraph follows a general description of what are the characteristics that antibiotics need to have to be classified in the AWaRe Reserve category from a public health perspective and what Reserve antibiotics should be prioritized for addition in the next updates of the WHO Essential Medicines Lists. It does not mean that all Reserve antibiotics should be active against pathogens with patterns of resistance that are most prevalent in low-and middle-income countries but that this could be a criterion to consider when deciding what new Reserve antibiotics to add to the Lists in the next updates.

As suggested, the term metallo-proteinases has been changed for metallo-beta-lactamases.

Comment: Page 338 / Table 1: *"Have recommendations in Table 1 been compared to those in guidance issued by ESCMID [1] and the USDA [2, 3]?"*

- *For example, neither the ESCMID nor USDA guidelines list carbapenem-resistant Acinetobacter baumannii (CRAB) as a target organism for ceftazidime/avibactam, yet in this table it is marked as '?' suggesting that activity may be possible.*
- *We understand A. baumannii to be intrinsically resistant to fosfomycin [4]. However, in this table fosfomycin is marked as '?' suggesting activity may be possible. Should this be marked as '-' for A. baumannii?*
- *Page 349 / line 7: As per comment on Reserve Antibiotics, Overview above, we understand from the literature than A. baumannii was intrinsically resistant to fosfomycin. This seems to be later*

contradicted on page 352, lines 98-99, where it is stated that "fosfomycin does not reliably treat Acinetobacter spp."

- *We also understand fosfomycin to be used in combination therapy for P. aeruginosa [5]. Would suggest adding a comment regarding use in combination therapy for P. aeruginosa.*

References:
1. European Society of clinical microbiology and infectious diseases (ESCMID) guidelines for the treatment of infections caused by Multidrug-resistant Gram-negative bacilli (endorsed by ESICM –European Society of intensive care Medicine), 2021: https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(21)00679-0/fulltext
2. Tamma PD et al. Infectious Diseases Society of America Guidance on the Treatment of AmpC β-lactamase-Producing Enterobacterales, Carbapenem-Resistant Acinetobacter baumannii, and Stenotrophomonas maltophilia Infections. Clin Infect Dis. 2021 Dec 5:ciab1013. doi: 10.1093/cid/ciab1013. Epub ahead of print. PMID: 34864936.
3. Pranita D. Tamma et al. Infectious Diseases Society of America Antimicrobial Resistant Treatment Guidance: Gram-Negative Bacterial Infections: https://www.idsociety.org/globalassets/idsa/practice-guidelines/amr-guidance/idsa-amr-guidance.pdf
4. Paul, Mical et al.Clinical Microbiology and Infection, Volume 0, Issue 0 María Luisa Gil-Marqués et al, Peptidoglycan recycling contributes to intrinsic resistance to fosfomycin in Acinetobacter baumannii, Journal of Antimicrobial Chemotherapy, Volume 73, Issue 11, November 2018, Pages 2960–2968, https://doi.org/10.1093/jac/dky289
5. EUCAST clinical breakdown tables: https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/Dosages_v_12.0_Breakpoint_Tables.pdf

(UK Health Security Agency)

Response: The indications for the use of ceftazidime-avibactam and intravenous (IV) fosfomycin are based on indications in the WHO Essential Medicines Lists with which the AWaRe Book is closely aligned. In the 2019 TRS the indication of ceftazidime-avibactam and fosfomycin (IV) is defined as "treatment of infections caused by carbapenem-resistant organisms which are pathogens classified as 'critical priority' in the WHO Priority Pathogen List" which includes carbapenem-resistant *Acinetobacter* but does not go into further detail.

However, the implications for clinical practice and stewardship principles were discussed within the WHO EML Antimicrobial Working Group and the decision was to change the table as suggested.

Therefore, activity of ceftazidime-avibactam and fosfomycin (IV) against *Acinetobacter baumannii* was changed in Table 1 (page 338 of the draft version) from "?" (possibly active) to "-" (not or insufficiently active) to limit inappropriate use. These changes have been reflected also in the text to clarify that these antibiotics should not be used to treat *Acinetobacter baumannii* infections. Additionally, the activity of fosfomycin (IV) against carbapenemase-producing *Enterobacterales* has been updated to +/- (variable activity).

A comment has also been added that intravenous fosfomycin should preferably be used in combination with other antibiotics "*Consider using only in combination therapy*".

Cefiderocol

Comment: Page 340 / lines 33 and 36: *"cefiderocol does not inhibit the activity of these enzymes, rather it is not degraded by them."*

(UK Health Security Agency)

Response: This comment refers to the sentence on page 340 (of the draft version) that has been amended as shown:

"In vitro, cefiderocol ***is not degraded by*** *ESBL* ***and by*** *certain types of carbapenemase".*

Ceftazidime+avibactam

Comment: *"MSF recommends adding the important association with aztreonam, which provides additional MBL coverage (aztreonam is not included in EML: consider adding in the next EML revision)"*

(Médecins Sans Frontières - MSF)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines Lists. Changes to recommendations in the Book would first require changes to recommendations in the Model Lists (which must be requested through the standard submission process). However, a footnote has been added to Table 1 on page 345 (of the draft version) stating:

"Ceftazidime+avibactam co-prescribed with aztreonam retains activity against MBL-producing bacteria, however aztreonam is not currently listed the WHO EML and EMLc."

Fosfomycin

Comment: *"Would strengthen recommendation not to give as monotherapy"*

(British Society for Antimicrobial Chemotherapy)

Response: It is already clear in the text both in the section about "Clinical efficacy" (page 350 of the draft version) *"Fosfomcyin (IV) is usually used as part of combination treatments, mostly because of concerns about the emergence of resistance when used alone"*; and where indications for targeted and empiric use are reported (pages 351-352 of the draft version) *"usually used as part of combination therapy to reduce the risk of the development of resistance"1.* Therefore, no further changes to the text were made.

Comment: *"MSF recommends considering removing all bacteria from under "Active against" and include them under "Variable action against", reflecting their limited role and to allow for better comparison with superior beta lactam (+/- beta lactamase) reserve options"*

(Médecins Sans Frontières - MSF)

Response: When activity of a certain Reserve antibiotic is reported against carbapenem-resistant bacteria this ultimately depends on the type of carbapenemase produced and the resistance

mechanism therefore use should be limited to the treatment of infections caused by bacteria that have been shown *in-vitro* to be susceptible to the antibiotic. Additionally, prescribers need to recognise the very limited data available on the clinical efficacy of most Reserve antibiotics (including intravenous fosfomycin) in treating multidrug-resistant infections and this is mentioned in the introduction to the reserve antibiotics section (page 335-337 of the draft version). While it is acknowledged that at the time of writing, there is no evidence for the use of intravenous fosfomycin monotherapy for CRE infections, some evidence of its benefit when co-prescribed with other antibiotics exists from *in-vitro* studies and case series and this is acknowledged in other guidance documents (e.g. ESCMID MDRO guidelines https://pubmed.ncbi.nlm.nih.gov/34923128/). Therefore, no changes to the text were made (except for those mentioned in another comment (see Reserve antibiotics section) about the activity of fosfomycin against *Acinetobacter baumannii* and *Pseudomonas aeruginosa*). However, as mentioned before and in the chapter, use of intravenous fosfomycin should be reserved to very selected cases and targeted against susceptible pathogens.

Meropenem+vaborbactam

Comment: Page 361 / line 63: *"For the treatment of infections caused by bacteria resistant to ceftazidime+avibactam (CAZ/AVI), unless CAZ/AVI resistance is due to MBL production."*

(UK Health Security Agency)

Response: This comment refers to the Targeted treatment section of the meropenem+vaborbactam chapter. The text on page 361 (of the draft version) has been amended as shown (only the part of the paragraph relevant to this comment is reported).

"Meropenem+vaborbactam could be considered in the following situations:

- *In the treatment of infections caused by bacteria resistant to ceftazidime+avibactam, **unless resistance to** ceftazidime+avibactam **is due to the production of metallo-beta-lactamases.***
- *Based on the results of available trials, meropenem+vaborbactam could be considered in cases of severe complicated urinary tract and intra-abdominal infections and for hospital-acquired pneumonia when other antibiotics cannot be used or are not effective.*

Comment: *"MSF recommends adding into "Important consideration" on beta-lactamases, another way to guide use (beyond local epidemiology) is to test isolates with molecular tests for beta-lactamases/carbapenemases identification (e.g. GeneXpert)"*

(Médecins Sans Frontières - MSF)

Response: This comment refers to the infographic on meropenem+vaborbactam and in particular to the following statement: *"Since it is not active against metallo-ß-lactamases (Ambler class B) or class D carbapenemases (such as OXA-48), it is important to know the local epidemiology of the most prevalent genotypic variants for aerobic Gram-negative bacteria"*. This statement applies to other Reserve antibiotics and while it is acknowledged that molecular detection is the gold standard to detect carbapenemase production, this test is not listed in the WHO Essential List of *in-vitro* Diagnostics (with which the AWaRe Book is closely aligned) and not available in many low-resource settings therefore no

changes to the text were made. Antimicrobial susceptibility testing (which in this context would allow the detection of carbapenem-resistance but not carbapenemase production) is however listed in the WHO essential list of *in-vitro* diagnostics and has been added throughout the Book where appropriate.

Plazomicin

Comment: *"Plazomicin may be reasonably expected to have activity against MBL producers that lack a gene encoding for an NDM, therefore suggest this should be '?' instead of '-'."*

Page 363 / *"Key messages: Plazomicin can potentially be used to treat MBL producers that produce MBLs other than NDM. Plazomicin resistance is usually due to production of a 16S rRNA methyltransferase - these are most commonly associated with NDM producers and much less so VIM and IMP producers [1, 2]."*

Page 364 / Table 1: *"Expected activity against MBL producers and non-fermenters marked as '?' here, yet as '-' in the table on page 338."*

Page 366 / Line 104: *"For other agents a suggested duration of therapy has been given but not here."*

References:

1. Livermore DM et al. Activity of aminoglycosides, including ACHN-490, against carbapenem-resistant Enterobacteriaceae isolates. J Antimicrob Chemother. 2011 Jan;66(1):48-53. doi: 10.1093/jac/dkq408. Epub 2010 Nov 14. PMID: 21078604.

2. Taylor E, et al. High prevalence of 16S rRNA methyltransferases among carbapenemase-producing Enterobacteriaceae in the UK and Ireland. Int J Antimicrob Agents. 2018 Aug;52(2):278-282. doi: 10.1016/j.ijantimicag.2018.03.016. Epub 2018 Mar 27. PMID: 29596903.

(UK Health Security Agency)

Response: Reviewers suggest mentioning the possible use of plazomicin for non-NDM metallo-beta-lactamase-producing carbapenem resistant bacteria. This has been discussed within the WHO EML Antimicrobial Working Group and the decision was to report plazomicin as "+ / –" (possibly active) for now because of limited clinical data (in addition, determining the genotype of carbapenemase is not feasible in many settings). The spectrum of activity of plazomicin is now presented in both Table 1 (page 338 of the draft version) and Table 1 (pages 363-64 of the draft version) as "+ / –" possibly active against MBL-producing bacteria.

A suggested duration of treatment has been added for plazomicin to align with what is done in other Reserve antibiotics chapters.

Linezolid

Comment: *"Where does 400mg BD dose come from?"*

(British Society for Antimicrobial Chemotherapy)

Response: Linezolid is available either in 400 mg or 600 mg oral tablets and both formulations are included in the WHO Essential Medicines List. The AWaRe Book does not provide formal

recommendations for the dosage of Reserve antibiotics but gives general guidance on what would be considered appropriate in most cases. For linezolid, it is acknowledged that the most commonly used dose in adults is 600 mg given every 12 hours therefore Table 1 (page 356 of the draft version) has been amended accordingly.

Comment: *"As Reserve antibiotic, appropriateness of use of linezolid should be monitored by antibiotic stewardship programs" Surely this applies to all reserve antibiotics and not just to linezolid."*

(British Society for Antimicrobial Chemotherapy)

Response: This is mentioned in the Introduction to Reserve antibiotics (page 337 of the draft version).*"Therefore, all efforts should be made to ensure careful use of Reserve antibiotics within local and national stewardship strategies which should include routine local and/or national monitoring and reporting of their use"*. To avoid confusion, and because as suggested this would apply to all Reserve antibiotics, this sentence has been removed from the Linezolid chapter.

Comment: *"If need to put something here I would discuss MAOI interactions and how to manage (evidence suggests not an absolute contraindication - can give with caution)."*

(British Society for Antimicrobial Chemotherapy)

Response: Interactions between linezolid and other medicines are not covered in the AWaRe Book and this is already mentioned in the chapter (page 356 of the draft version): *"interactions with other medicines should be checked before prescribing linezolid; this topic is, however, not addressed in the AWaRe book"*. Therefore, no changes to the text were made.

Comment: *"Need to include excellent oral bioavailability somewhere in this monograph."*

(British Society for Antimicrobial Chemotherapy)

Response: The following statement has been added to the administration section (page 355 of the draft version):

"The high oral bioavailability of linezolid allows initiation with oral treatment as an alternative to intravenous treatment".

Ceftolozane-tazobactam

Comment: *"Ceftolozane-tazobactam should be added to the reserve list and kept back for the treatment of MDR Pseudomonas infections."*

(British Society for Antimicrobial Chemotherapy)

Response: The AWaRe Book is closely aligned with the WHO Essential Medicines Lists and ceftolozane-tazobactam is currently not included in the Model Lists. Changes in the Book would first require changes to the Model Lists (which must be requested through the standard submission process).

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7 Glossary

Comment: Page 385: *"Definition of "carbapenemase" is incorrect; not all carbapenemases confer resistance to cephalosporins, aztreonam or to carbapenems (at least based on clinical breakpoints). For example, aztreonam may still be effective against MBL producers, and extended-spectrum cephalosporins are effective against OXA-48 producers if ESBL activity is lacking."*

(UK Health Security Agency)

Response: The glossary has been amended as follows:

Carbapenemases	*Carbapenemases are beta-lactamases, enzymes that can break the beta-lactam ring (an essential component of beta-lactam antibiotics) and make* ***most*** *penicillins, cephalosporins, monobactams and carbapenems ineffective.*

Comment: Page 388: *"MRSA may also be due to the presence of mecC."*

(UK Health Security Agency)

Response: The glossary has been amended as follows:

Methicillin-resistant Staphylococcus aureus *(MRSA)*	*MRSA are strains of Staphylococcus aureus that are resistant to methicillin and other beta-lactam antibiotics due to the presence of the mecA* ***(or sometimes mecC)*** *gene which produces a different penicillin-binding protein with lower affinity for beta-lactam antibiotics.*

Comment: *"Ensure antiseptics are defined"*

(Prof J. Conly, Department of Medicine (Infectious Diseases), Cumming School of Medicine, University of Calgary and Alberta Health Services)

Response: The glossary has been amended as follows:

Antiseptics	*Antiseptics are antimicrobial products used to slow or stop the growth of microorganisms. They are usually used on the skin or mucous membranes, for example, the mouth. These include, for example, chlorhexidine. These products can be used as hand rubs, hand or mouth washes and skin preparations.*
