Comments received on the WHO MIA List 7th revision February – 2023

Governmental and intergovernmental Institutions

- Office of Pandemic and Emerging Threats, Office of Global Affairs | U.S. Department of Health and Human Services-USA
- EC Directorate General for Health and Food Safety-BE
- Health Service Executive Antimicrobial Resistance and Infection Control Team, Ireland
- Health Product Regulatory Authority- Ireland
- Antimicrobial Resistance Team at the Veterinary Medicines Directorate, UK
- Department of veterinary affairs and food safety in the Austrian Ministry of Social Affairs, Health, Care and Consumer Protection-Austria
- Department of Agriculture, Food and the Marine in Ireland
- The Swedish Medical Product Agency, the Swedish Board of Agriculture, the National Board of Health and Welfare and the Public Health Agency- Sweden

Academic Institutions

- University of Missouri-USA
- Department of International Health Johns Hopkins Bloomberg School of Public Health-USA
- Antibiotic Resistance Action Center-USA
- Federal Chamber of Veterinary Surgeons-Germany
- Faculty of Veterinary and Agricultural Sciences, University of Melbourne-AU

Veterinary Medical Associations

- American Veterinary Medical Association (AVMA)-IL USA
- German Association of Veterinary Practitioners and one of Europe’s biggest veterinary associations- Germany
- Federation of Veterinarians of Europe (FVE)-BE

CSOs & NGOs

- Keep Antibiotics Working Coalition, Food Animal Concerns Trust, and PIRG-USA
- Natural Resources Defense Council- USA
- Responsible use of Medicines in Agriculture Alliance RUMA-UK
- Centre for Science and Environment-India

Private

- Elanco Animal Health-UK
- Food Innovation Research Science Technology Management FIRST-AU

Other: South Centre-CH
Governmental and intergovernmental Institutions
1. Is the purpose of the document clear?

- The scope of the document is unclear. It specifically mentions that non-human’ use refers to food animal use only. However conflicting statements about companion animals and mentions of the lists helping to guide veterinarians, and mentions for crop production, are listed throughout the document. Additionally, it is not clear how food animals (e.g., ‘non-human sources’) are defined. Different countries may use different species for food. Also, several of the antimicrobials listed on the table as ‘for human use only’ are routinely used for treating companion animal infections, in some countries.

- The introduction appears inconsistent defining “non-human sources” exclusively as “food animals only” on line 61, then:
  i. Discussion of how classification depends on the “type of animal treated such as terrestrial and aquatic, food animals, companion animals, fibre and fur bearing animals, laboratory animals, conservation animals, and working animals” on lines 68-70
  ii. Reference to crops (line 73)
  iii. Reference to plant/crop professionals (line 90).

- If “..medical importance for treatment of serious disease in humans and the potential transmission of AMR from bacterial microorganisms to humans due to the use of these agents in non-human sectors” (Line 57-60) is one of two main criteria for evaluation, it appears inconsistent to say there is only concern regarding antimicrobial uses in food animals. Perhaps one solution is to provide this list of antimicrobials as important for human therapeutic use and should not be aimed at one sector, just as the World Organization for Animal Health provides a list of antimicrobials important for animal therapeutics. The list should be viewed as one source of information to inform risk analysis.

2. Is the new approach of basing the groups of antimicrobials on the authorization status appropriate and clearly explained?

- Limiting or prohibiting the use of antimicrobials approved by regulators in member states, without data demonstrating a risk for the development of AMR, does not meet the stated purpose of the WHO MIA List to “categorize
antimicrobial classes…while considering the potential risk of the development and spread of resistance”.

- The current, 6th edition of the WHO CIA list includes an important statement missing from this document: “The experts recognized that the implementation of the concept at national levels required that national considerations would be taken into account, and consequently lists may vary from country to country, and that the lists should be made publicly available and could be used for the following purposes…” Some countries develop their own lists based on a rigorous scientific approach, and such lists that are appropriate for national circumstances can also be taken into account. The WHO CIA list is useful for those countries that may not have the resources to develop their own list, but it is not the only list. Neither is the AWaRe list. A statement such as that made in the 6th edition of the WHO CIA document should be made in this document.

3. **Are the new and revised prioritization factors clearly understood?**

- Consider improving the clarity of Prioritization Factor 1 by adding brief descriptions of the Access, Watch, and Research criteria early in the document as suggested above and by adding a brief description of the general criteria/purpose of the Essential Medicines List to the explanation in Lines 303-308.

4. **Are the proposed implementation activities providing guidance to countries to improve the responsible and prudent use of antimicrobials in the different sectors?**

- Yes and no. Strongly advise reviewing and considering inclusion of companion animals and antifungals.

- A principle of the AWaRe framework is “minimizing unnecessary costs to patients and health care systems” (AWaRe book page 2), though costs are not mentioned in the implementation activities.

- Consider including some guidance regarding how or whether this list may be helpful in assessing the benefits and costs associated with the regulation of antimicrobial use (Activity example 1.4, p. 21) and/or different risk management strategies (Activity example 3.1, p. 22).

- For example, regulators and policy makers who have limited resources may be interested in information pertaining to the costs and benefits of using or avoiding the use of various antimicrobials when developing policies “to support the responsible and prudent use of medically important antimicrobials” (p. 21) and when considering different strategies for surveillance, monitoring, and risk management (p. 22). The list could potentially help guide the direction of research studies such as benefit-cost analyses or cost-efficacy analyses, which (like risk assessments) can be useful to consider when making regulatory decisions.

- The list may also be helpful in identifying where data gaps exist in valuing the costs and benefits of various antimicrobials or of strategies for surveillance, monitoring, and risk management, especially for antimicrobials in the group authorized for use in both humans and animals.

5. **Do you have any additional comments to enhance the utility of the MIA List?**
• We recommend including a reference to One Health as a citation or in a glossary such as that used by Codex CXC 61-2005 since the term is not defined within the document, and some stakeholders may not be familiar with the approach.
• Since it is stated that the term “antimicrobial” refers to antibacterials in this document, we recommend harmonizing the use of the term antimicrobials to encompass antifungals, antivirals, and antiparasitics, and not only refer to antibacterials throughout the document. Additionally, the antifungals list was already developed and recently released so the note in line 27 and 28 should be updated to reflect that.
• **Line 13:** “…the contribution of non-human use to the risk of transmission of AMR to humans.” Quantification of the contribution of non-human AMU to the risk of transmission to humans is a data gap and unknown. Therefore, the statement would more accurately read, “…the inferred contribution of non-human use…”
• Section 4 seems out of place as it relies on content not discussed until Section 5. Consider re-organizing so that the reader is first primed on the definitions of classes and prioritization factors before describing changes since the previous version of the list.
• **Line 108:** There may be concern that the recategorization may be misinterpreted--some may think that this means that classes in this group, which includes carbapenems, aren’t CIA, when they clearly are--for example, could take away that carbapenems are less important than say fluoroquinolones.
• **Lines 113-116 & Lines 349-351:** Recommendations from the WHO should be science-based rather than automatically pre-determined by default. Use in humans as the factor for classification is not science-based, where the risk of AMR development has been evaluated. Automatically determining the classification does not leave room for innovation in the future, for areas we cannot foresee. For example, if an antimicrobial is discovered for human use that does not result in AMR development, it is not clear why it would automatically be determined that it cannot be used in other sectors.
• **Lines 124-128:** While there is concern about not categorizing by default regarding “Not medically important for humans” in lines 113-116, there does not seem to be the same concern about categorizing by default, “Medically important for humans”. The approach is inconsistent nor is it science-based.
• **Line 132:** second should be “third”
• **Lines 148-152:** References to PF1 and PF2 in this section are not clear because these abbreviations are not defined until later. Should P3 be PF3? It is not clear what P3/PF3 represents since only two prioritization factors are described in the document. Consider including a brief description of how PF3 was defined in previous approaches, if applicable.
• **4.4. Macrolides, lines 182-189:**
  o Macrolides are considered first-line recommended treatment for community-acquired pneumonia in many countries, one of the deadliest
infections worldwide. This should be considered in any decision. It is also one of few oral options for treatment of pneumonia. There are few effective drugs for treatment of specific infections, such as legionellosis. It is also one of the commonly misused medications in human medicine.

- One additional factor to consider might be the newfound importance of azithromycin in managing XDR typhoid fever in regions of the world where carbapenems may not be highly accessible. Macrolides are increasingly being used to treat typhoidal and severe nontyphoidal Salmonella infections in humans (and to treat salmonellosis in people at risk for severe infections) due to resistance to other agents, including cephalosporins and fluoroquinolones. Resistance to macrolides is also emerging in Salmonella from food animals, products from food animals, and humans. Macrolide resistance genes are also emerging among E. coli in food animals.

- **Line 220:** “see section 3.2” should be “see section 5.2”

- **5.2.1 The criteria, lines 250-251:** Consider referencing Figure 1 here and summarizing how these 3 categories are determined. This is a bit confusing since according to the text below, an antimicrobial isn’t classified as CIA unless you are also able to complete prioritization so it can be classified as CIA vs. HPCIA. It might be helpful to simplify this and classify as CIA, HI, or I based on the criteria and to do the prioritization separately, as in previous editions of this document.

- **5.3.1 Antimicrobials “Authorized for use in humans only”, lines 328-329:**
  - **Lines 328-329:** It seems like information is being lost by requiring prioritization before categorizing an antimicrobial as CIA vs. HI or I. If prioritization was separate, this would not be an issue.
  - **Lines 332-335:** Why wait until a drug is approved in food animals to classify it as CIA? See comments above about doing the prioritization separately.
  - **Lines 332-335:** Are there other exceptions or scenarios in which drugs “authorized for use in humans only” should be classified differently or selective monitored, esp. if resistance (to said drug) has been found in food-producing animals? Note linezolid-resistant isolates have been found in food-producing animals. See J Antimicrob Chemother. 2021 24;77(1):49-57

- **5.3.3 Antimicrobials “Not authorized for use in humans”, line 371:** Revise Line 371. If referring to C1 and C2, they are listed above in section 5.2.1.

- **5.4. Decision tree, line 378:** As written, the tree is based on Authorization, which is not the same as Use. Extralabel use may legally occur in humans and in some places and situations, also in food animals.

- **Page 19, Figure 1:** Consider referencing the figure in the text (5.2) and including the criteria and prioritization factors someplace on the page with the figure.

- **6. Implementation activities, lines 398-399:** the EML (Essential Medicines List) Antibiotic book reference does not match.
Page 27, Table 2\(^1\). Antimicrobials “Authorized only for use in humans”, “Drugs used solely to treat tuberculosis or other mycobacterial diseases”: Please note - Although bedaquiline, delamanid and pretomanid are not marketed for use in animals, these agents are increasingly being used in regimens to treat subsets of MDR-TB (i.e., pulmonary XDR TB and TI/NR MDR TB). They are critical because they have safely and effectively reduced treatment duration from 18-24 mos. to 6 mos. Presently, none of the agents is on the AWaRe classification list. Also, of concern are reports of the rapid emergence of acquired resistance to these agents appearing in the literature (e.g., European Resp J 2022 59: 2100621; DOI: 10.1183/13993003.00621-2022022; Clin Infect Dis 2020 71(12): 3252-3259).

Page 28, Table 3. Categorization of “Antimicrobials authorized for use in both humans and animals”, Cephalosporins (3rd, 4th generation), Comments: For “(C1)”, consider mentioning N. gonorrhoeae here – ceftriaxone is the last antimicrobial that works broadly to treat it.

Page 31, Table 3. Categorization of “Antimicrobials authorized for use in both humans and animals”, Ansamycins, Antimicrobial agent, “rifamycin”: 1. Note: rifamycins are a subclass of Ansamycins, which include rifampicin, rifabutin, rifapentine, rifaximin, etc. Not an agent. Consider removing. 2. According to AWaRe, several rifamycins are classified as Watch, however, they are not on the 2021 EML or EMLc. This does not meet the standard set for PF1. Clarify.

Page 32, Table 3. Categorization of “Antimicrobials authorized for use in both humans and animals”, Macrolides (14, 15, 16 membered-ring), Comments, (PF2): Macrolide resistance is emerging in Salmonella in food animals and humans, and salmonellosis can be severe and life-threatening in humans.

Page 33, Table 3. Categorization of “Antimicrobials authorized for use in both humans and animals”, Nitroimidazoles, Comments, (C1): Nitroimidazole class is the only effective class for treating trichomonas vaginalis - Trichomonas is not generally severe but it is the most common, curable STI in the world and is associated with risk for HIV acquisition and adverse birth outcomes.

Page 36, Table 3. Categorization of “Antimicrobials authorized for use in both humans and animals”, Tetracyclines, Antimicrobial Agent, “doxycycline”: doxycycline is the second line therapy for syphilis.

Line 711 & 731: Recommend harmonizing with definition from Codex CXC 61-2005 as the definition was developed through a Member State, consensus-driven process. If WHO uses a different definition, it provides contrary advice and is confusing.
2. EU

European Commission Directorate-General for Health and Food Safety and European Medicines Agency comments on draft WHO MIA List 7th edition

Is the purpose of the document clear?

There are inconsistencies in the terminology throughout the text, which is confusing for the reader. For example, lines 61-62 read; ‘For the purposes of this document, ‘non-human’ use refers to food animal use only’, while in the glossary of terms in lines 734- 741 it is specified that ‘While non-human use encompasses use of antimicrobials in animals and plants, for the purposes of this document, non-human use refers to antimicrobial use in food animals, companion animals and/or working animals. …Unless specifically noted, in this document, ‘animals’ refers to the broad population of non-human animal species’.

Is the new approach of basing the groups of antimicrobials on the authorization status appropriate and clearly explained?

Some revision could be still done with respect to the authorization status. In chapter 5.3 it is written “Antimicrobials were considered authorized for human and/or non-human use if authorized for use in any country.”

Please note that furazolidone and furaltadone (nitrofuran derivates) are authorized in the EU for non-food animals but these substances are currently listed in Table 2 as ‘Authorized for use in humans only’.

Regarding nitrofuran derivatives currently listed in Table 2 as ‘Authorized for use in humans only’, we consider the most important to be nitrofurantoin, furazolidone and nitrofurazone. The last one is not on the list, but there are others with very limited use to our knowledge.

Moreover, concerning Table 2, according to the work conducted in establishing the list of antimicrobials or groups of antimicrobials designated as reserved for treatment of certain infections in humans adopted in 2022, carumonam is not used in humans.

Clofocotol is not used anymore as far we are aware. This was not included in the previous list but is now included in category “only approved in humans” and this is not understood.

We are not clear what is meant by this group: Cephalosporins (3rd, 4th and 5th generation cephalosporins with β-lactamase inhibitors). The description could be revised as “combinations of cephalosporins (gens 3, 4 and 5) with BLI”.

Some of the listed substances are no longer approved in the EU, e.g. doripenem.

We are not sure that ALL quinolones listed (in particular the non-fluorinated ones) merit inclusions in the HPCIA class. Same is true for some CIA included macrolides (e.g. erythromycin).
Are the new and revised prioritization factors clearly understood?

In chapter 5.2.2 it is written: “Prioritization factor 1 (PF1): The class contains at least one antimicrobial that is BOTH on the Essential Medicines List and is classified as Watch or Reserve on the AWaRe classification list”.

In the draft document it is not specified which antimicrobial agents fulfil this criterion (i.e. included in the EML and AWaRe list as Watch or Reserve). This specification would be appreciated in Table 3.

Are the proposed implementation activities providing guidance to countries to improve the responsible and prudent use of antimicrobials in the different sectors?

No comment

Do you have any additional comments to enhance the utility of the MIA List?

There are no additional comments.

Please see editorial comments:

Line 98 and line 108: the headings of 4.1 and 4.1.1 are the same

Line 220: current text: see section 3.2, should be: see section 5.2

Line 224, etc: the term ‘5th-generation cephalosporins’ are not always recognised, consider including the substance names instead (i.e.: ceftobiprole, ceftaroline)

Line 371: current text: below, should be: above

Line 380: current text: summarize, should be: summarizes

Table 1 and Table 3: current text:amidinopenicillins, should be: amdinopenicillins (or include amdinopenicillins as an alternative name in bracket, see WOAH and AMEG list)

Table 3: current text: Fuzadine, should be: Fuzadines

Line 429: The footnote on page 25 is inconsistent with lines 333-335, which makes unclear the categorisation (HPCIA or CIA) of a medicine currently approved only for humans and approved for use in food animals in the future

Line 503: This Annex 1 is not referred in the document; it should be explained in the main text

Line 697: the definition of ‘class’ could be deleted because we have a definition of ‘antimicrobial class’ in line 674. OR ‘see Antimicrobial class’

Line 733, 747 and 768: references should be listed on pages 38-39

Line 754: Glossary should be harmonised: Klebsiella is missing from here but is mentioned in line 299.
3. Health Service Executive Antimicrobial Resistance and Infection Control Team, Ireland

HSE AMRIC team feedback 23.02.2023

Feedback on WHO Medically Important Antimicrobial List (MIA) List 7th revision

Response

Is the purpose of the document clear?
  - Yes clear and concise

Is the new approach of basing the groups of antimicrobial on the authorization status appropriate and clearly explained?
  - Yes clearly explained. Visual on page 19 useful in practice.
  - Approach aligns with iNAP 2 vision for antimicrobial use animal health.
  - Aligns with approach human health AWaRe categorization

Are the new and revised prioritization factors clearly understood?
  - Yes, Comments in Table 3 helpful and clearly explain rationale.

Are the proposed implementation activities providing guidance to countries to improve the responsible and prudent use of antimicrobials in different sectors?
  - Mostly relates to non-human health. Strategic approach used and further support to the country development of implementation approach would be helpful.

Do you have any additional comments to enhance the utility of the MIA List?
  - It would be useful to have more details on individual Antimicrobials rather that Antimicrobial’s classes
  - Tables could be clearer and user friendly e.g. font size
  - Decision tree very useful – suggest that this is brought forward in the document.
  - Overall a very welcomed and useful document to support One Health Approach in countries. This approach would need to be supported from a policy perspective i.e. resources.
4. Health Product Regulatory Authority- Ireland

To whom it concerns

On behalf of the Health Products Regulatory Authority (HPRA) in Ireland have reviewed the WHO Medically Important Antimicrobial List, 7th Revision. The list highlights the ‘at-risk’ antibiotics that are critical for the treatment of humans that can be “tainted” with AMR by use in non-humans. This list could be useful in helping to reducing the use of these antimicrobials in non-humans. From the human side, this list could be helpful to target/prioritise AMR monitoring.

Our comments are outlined below.

As a general point we found Section 1. Background difficult to read. We had to read annex 2 in conjunction with it to be useful. This is an important section as it sets the context for the rest of the document. This section be shortened and rationalised. It would also be difficult for a non-expert reader. There is heavy use of very similar acronyms which could be confusing for a lay reader. A simple glossary at the start of the document could be helpful here. Inclusion of Human and Vet ATC codes in tables 1-4 if possible and if appropriate could be useful if managed carefully. National Regulators are part of the target audience for this document. ATC codes are useful from a regulatory perspective for searching and cross referring to data from other MSs and other agencies. We have included brief responses to the 5 questions included in the WHO document below.

1. Is the purpose of the document clear? No. section 2 line 81-82 is not clear. It does not fully represent the aims which are more clearly outlined on line 49-53 and line 384-385; “minimising the impact of AMU in animals on AMR in humans”. Inclusion of a glossary for the acronyms at the start would be helpful. The glossary provided in annex 3 is confusing and not easy to use as a quick reference document.

2. Is the new approach of basing the groups of antimicrobials on the authorization status appropriate and clearly explained? Yes, Section 5 explains the classification and categorisation.

3. Are the new and revised prioritization factors clearly understood? Yes, Table 3 comments are particularly useful in demonstrating the considered factors for prioritisation.

4. Are the proposed implementation activities providing guidance to countries to improve the responsible and prudent use of antimicrobials in the different sectors? The proposed implementation activities are broad. More specific expected outcomes could be provided, e.g. a specific target for the use of HPCIA in non-human sectors by a given date. However, this may be too prescriptive.

5. Do you have any additional comments to enhance the utility of the MIA List?
   - Further information could be provided on how the MIA list complements the WHO EML antibiotic book and AWaRe classification.
   - The introduction section is not clear. This could be supplemented by annex 2 and the layout of the section improved. Suggest: line 15-22 moved to before 9-14 with wording edits. Line 33 – 49 relates to human use and should be separated from line 49 and previous paragraphs, suggest move to after line 73.
   - Inclusion of Human and Vet ATC codes in tables 1-4 if possible and if appropriate could be useful if managed carefully. National Regulators are part of the target audience for this document. ATC codes are useful from a regulatory perspective for searching and cross referring to data from other MSs and other agencies.
5 Antimicrobial Resistance Team at the Veterinary Medicines Directorate, UK

Hi,

My name is Fraser Broadfoot and I represent the Antimicrobial Resistance Team at the Veterinary Medicines Directorate, UK.

We think the new draft document looks good. We did wonder if WHO considered putting aminopenicillins alongside beta-lactamase inhibitors as a higher risk category (e.g. CIA) than aminopenicillins alone given that the combination of amoxicillin with a beta lactamase inhibitor results in a wider spectrum of activity and thereby a higher selection pressure for multidrug resistant organisms. This is the approach that was taken by the AMEG group in Europe (although we appreciate there are differences in the methodologies between these two documents). We also wanted to note that in the table (p34) under “aminopenicillins with beta-lactamase inhibitors” there is a “*” next to “No” but, unlike with the other actives, there is no corresponding text relating to C1 in the table (see below).
Dear Colleagues,

on behalf of the department of veterinary affairs and food safety in the Austrian Ministry of Social Affairs, Health, Care and Consumer Protection

I would like thank you for the possibility to provide feedback to the 7th revision of the WHO MIA List.

Kind regards,

Fraser

Dr Fraser Broadfoot MRCVS | Head of AMU Surveillance and Stewardship | Antimicrobial resistance, policy and surveillance team Alternative email: amr@vmd.gov.uk | Phone: 01932 338391 |

Say my name: Fray-zer Braw-d-foot

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6. Department of veterinary affairs and food safety in the Austrian Ministry of Social Affairs, Health, Care and Consumer Protection-Austria

Penicillins (aminopenicillins with beta-lactamase inhibitors)  amoxicillin-clavulanic acid ampicillin-subactam  No*  Yes  ((C2) May result from transmission of Enterococcus spp., Enterobacteriales, including E. coli from non-human sources

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After reviewing the MIA List draft, with the purpose of improving and promoting a responsible and prudent use of antimicrobials in all sectors to preserve the public health,

must be mentioned that the purpose of the document is clear, as well as the approach of basing the groups of antimicrobials on the authorization status are clearly explained.

The proposed implementation activities do provide guidance to improve the responsible and prudent use of antimicrobials.

However, I think it should be taken in consideration the availability as well as the purchasing power of the antimicrobials at the time of prescribing them.

It is necessary, to focus future work towards a ban on growth promoters and a limitation of prophylactic use.

Kind regards,

Florian Fellinger

Federal Ministry of Social Affairs, Health, Care and Consumer Protection

Section III - Consumer Policy and Consumer Health

Group B - Consumer Health and Veterinary Affairs

Division 15 - Zoonoses, Veterinary Medicines and Coord. of Internat.

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7 Department of Agriculture, Food and the Marine in Ireland

Good evening,

I wish to provide feedback on behalf of the Department of Agriculture, Food and the Marine in Ireland. Our feedback is as follows:
The Department of Agriculture, Food and the Marine in Ireland welcomes the public consultation on the 7th revision of the WHO Medically Important Antimicrobials list which broadly aligns with the recently published European Medicines Agency’s Antimicrobial Advice ad hoc Expert Group’s Categorisation of Antimicrobials for use in veterinary medicine which promotes responsible use to protect public and animal health.

The purpose of the document is clear and the groupings clearly explained. The revised prioritization factors are clearly understood. This revised list will continue to support antimicrobial stewardship actions across the animal health sector. The definition of antimicrobial in annex 3 however is not aligned with the definition in the recent European Veterinary Medicines and Medicated Feed legislation, Regulation (EU) 2019/6 and Regulation 2019/4 respectively. In the European legislation an antimicrobial refers to an antiprotozoal only, and not all parasiticides, such as for example anthelmintic classes of antiparasitic medicines.

It is noted that on Line 183 “Macrolides were reclassified from HPCIA to CIA after a thorough review. 184 Macrolides were not deemed to have fulfilled the frequent causes of 185 invasive and life-threatening infections” component of PF2. While 186 macrolides are important for treatment of campylobacteriosis, most cases 187 are self-limiting and antibiotic therapy is not advised and Campylobacter 188 rarely causes invasive and life-threatening diseases” and subsequent classification as CIAs rather than HPCIAs as was previously the case in the 2018 published 6th revision of the WHO Critically Important Antimicrobials for Human Medicine list.

It is also noted that 3rd/4th generation cephalosporins, polymixins and quinolones have been classified as HPCIAs which aligns with the AMEG categorisation document which places these actives into category B-Restrict (should be considered only when there are no antibiotics in Categories C or D that could be clinically effective; use should be based on antimicrobial susceptibility testing, wherever possible). Finally there doesn’t appear to be any products containing the HPCIA Fosfomycin currently authorised for use in animals within the EU.

If you require any further clarification on the feedback above please do not hesitate to contact me.

Best wishes,

Caroline Garvan

Caroline Garvan

Senior Superintending Veterinary Inspector

Veterinary Medicines, Antimicrobial Resistance, Animal By-Products and TSEs (VMAAT) Division

An Roinn Talmhaíochta, Bia agus Mara

Department of Agriculture, Food and the Marine

Campas Bhacastúin, Ascaill Steach Cuimne, Cill Droichid,
8. The Swedish Medical Product Agency, the Swedish Board of Agriculture, the National Board of Health and Welfare and the Public Health Agency- Sweden

Dear Sir/Madame,

We wanted to share the feedback provided by the following Swedish government agencies on the WHO Medically Important Antimicrobials List 7th revision: The Swedish Medical Product Agency, the Swedish Board of Agriculture, the National Board of Health and Welfare and the Public Health Agency.

Sweden welcomes the WHO Medically Important Antimicrobial List update and appreciate the renaming from Critically Important to Medically Important. The report is well structured, thoroughly worked through and scientifically sound.

The revision has highlighted the list as another step in the right direction so that it now largely reflects EMA's list of critically important antibiotics for human use. We find that the purpose of the list and the prioritizations made are comprehensible and transparent. Sweden considers the document to be a useful tool to WHO member states for handling antimicrobial use and antimicrobial resistance.

Is the purpose of the document clear?

Yes,
However, the reason why non-human use refers to food-animal production only for the purpose of this report, is unclear and could warrant a further explanation for the sake of clarity (line 61, page 7).

Is the new approach of basing the groups of antimicrobials on the authorization status appropriate and clearly explained?

- It should be made clear if all classes approved for use in humans are considered in this list, or if not, which or which groups that are excluded. Comment on lines 76-77: “Categorize antimicrobial classes that are authorized for human use, in both humans and animals, and not authorized in humans.” This description is unclear. The readers need to know if all antimicrobial classes that are authorized for use in humans, irrespective of authorization for other uses, will be included in this categorization, or if not, which ones are excluded?

At least theoretically, with the current categorisation there may be categories approved for human use that are not included in the evaluation behind the adoption of the list, we find this unfortunate. However, the lists found further down with antibiotics/classes look complete.

- The headings in sections 4.1 and 4.1.1 on page 8 are unclear.
- The separation of fidaxomicin from macrolides is an important improvement.

Are the proposed implementation activities providing guidance to countries to improve the responsible and prudent use of antimicrobials in the different sectors?

Yes,
The list corresponds well with other AMR recommendations and guidelines and provide useful support to member states in their overall AMR work including development and implementation of National AMR Action Plans.

Are the new and revised prioritization factors clearly understood?

Yes.
Sweden supports the change of the previous prioritization factor 3 to the modified new PF2, which reflects a further emphasised one health approach.

Do you have any additional comments to enhance the utility of the MIA List?

- Readers would benefit from a List of abbreviations.
- Why non-human use refers to food-animal production only for the purpose of this report, is unclear and could warrant a further explanation for the sake of clarity (line 61, page 7).
- Sweden supports the change from the previous prioritization factor 3 to the modified new PF2, which reflect a further emphasised one health approach.
- The separation of fidaxomicin from macrolides is important.
- In table 3, page 34, there is a (C1*) missing in the comment column for Penicillins (aminopenicillins with beta-lactamase inhibitors)
- The list corresponds well with other AMR recommendations and guidelines and provide useful support to AMR member states in their overall AMR work including development and implementation of National AMR Action Plans.
• Consider removing “in the future” (line 113, page 8).
• On page 22, line 410 we recommend considering a reference to OIE Standards, Guidelines and Resolutions on Antimicrobial Resistance and the use of antimicrobial agents”, chapter 6.8 “HARMONISATION OF NATIONAL ANTIMICROBIAL RESISTANCE SURVEILLANCE AND MONITORING PROGRAMMES”

Best wishes,

Jessika Yin

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Academic Institutions
1. University of Missouri-USA

Hi, my name is Michael Barchilon, I'm a vet at University of Missouri. Totally support this document! I wanted to make a comment about nitrofurantoin, which is listed under "Human use only." According to the ISCAID guidelines (https://www.vdl.ndsu.edu/wp-content/uploads/2022/02/ISCAID-Urinary-Guidelines-2019.pdf), nitrofurantoin can be considered for sporadic bacterial cystitis in dogs/cats. I'm totally fine not using it based on these recommendations, but just wanted to point out a bit of...inconsistency? that our current urinary guidelines support the use of it.

Thanks so much for putting this together,

Michael

2. Department of International Health Johns Hopkins Bloomberg School of Public Health-USA

Dear Colleagues,

Thank you for the opportunity to provide feedback on the draft WHO Medically Important Antimicrobial List, 7th Revision. Please find our submission attached. We look forward to seeing the submissions posted on the website, along with response by WHO or the WHO AG-CIA. This would help address any concerns and strengthen support by the global community to embrace the important guidance this document provides.

All the best,

Anthony

Anthony D. So, MD, MPA
Professor of the Practice
Director, IDEA Initiative
Innovation + Design Enabling Access
Department of International Health
Johns Hopkins Bloomberg School of Public Health
Feedback on WHO Medically Important Antimicrobial List, 7th Revision 2023

Submitted by Professor Anthony So, IDEA Initiative

Johns Hopkins Bloomberg School of Public Health

We appreciate the opportunity to provide feedback on the draft WHO Medically Important Antimicrobial List. By the time we became aware of the request for input, the timeframe precluded closer organizational review and sign-ons, which may yet be forthcoming here, by members of the Antibiotic Resistance Coalition (ARC) and its partner organizations. Nonetheless, the importance of this work still warranted our sharing preliminary analysis from these discussions, at least within the 1000-word limit, by the deadline. We recognize that much of the detailed evidence and careful work of the WHO AG-CIA developing this guidance document cannot be fully captured in its pages. So, it is even more important that submitted comments, their sources and WHO’s response that might give reason for adoption of this guidance be made transparent and posted publicly.

Equitable consideration of LMIC settings. The 7th Revision proposes significant changes in the prioritization factors, but the labels applied to antibiotic classes remain the same. Macrolides are deprioritized from HPCIA to CIA, and aminopenicillins from CIA to HIA. The rationale for changing the ranking of macrolides rests entirely on not having met the higher requirement in the redefined Prioritization Factor 2: the antimicrobial class treats infections for which there is already extensive evidence of resistance transmission AND these infections are “frequent cause of invasive and life-threatening infections.” Under PF2, macrolides clearly met the first criterion, and in fact, a recent PNAS study identified a novel macrolide esterase that inactivates drugs from this antibiotic class from a western Canadian feedlot, one that had been overlooked for decades “despite a pattern of proximity to known and readily identified ARGs.” However, the WHO MIA analysis focus on Campylobacter infections rather than the value of azithromycin, a low-cost, oral macrolide antibiotic that is WHO’s first choice treatment for yaws, cholera, trachoma, paratyphoid fever, typhoid fever, and gonorrhea. Typhoid fever treatment is increasingly complicated by the emergence and spread of strains resistant to azithromycin. With MDR non-typhoidal Salmonella in sub-Saharan Africa as well as Latin America and Asia, azithromycin may also be an alternative. The justification for deprioritizing aminopenicillins was that other treatment options for enterococci exist in many regions, and while important for treating listeriosis, “there are other treatment options.” In both cases, questions must be answered over whether the deprioritization of these antibiotic classes poses greater burden upon low- and middle-income country settings, where reliance on these antibiotics might be greater, even if not for invasive and life-threatening infections, and where access to alternatives more limited.

Co-resistance and cross-resistance. In categories like macrolides and aminoglycosides, specific drugs with different resistant mechanisms, such as fidaxomicin and plazomicin, were removed and evaluated individually. So if a different resistance mechanism can work to elevate the priority ranking of a drug out of its antibiotic class, should not patterns of co-resistance, cross-resistance and collateral sensitivity factor into lifting priority for certain classes of antibiotics as well? Not Authorized in Humans does not equate
to Not Medically Important, as the last column in Table 1 might suggest (line 418). Importantly, growing evidence indicates that polyether ionophores do not belong in the category of “not medically important.” Removing the use of the ionophore, narasin, from Norwegian broiler production contributed substantially to reducing vancomycin-resistant enterococci. Subsequent research suggests that narAB conferring resistance to several ionophores in enterococci relates to VRE’s persistence in poultry production. Adding to this evidence, Dutch scientists found resistance to the ionophore, salinomycin, was tied to the narAB operon, and correlated with higher levels of enterococci resistance to various medically important antibiotics, including erythromycin, tetracyclines and ampicillin.

Reference to antimicrobials used for plants and crop production. The WHO MIA List suggests its target audience includes plant/crop health professionals (lines 90 and 409). However, the draft document limits its analysis of non-human use to “food animal use only” (line 61), because of “the current limitations of data regarding AMU on plants, and any potential impact of AMR on human health” (line 71-72). Particularly in light of the Joint FAO/WHO expert meeting on foodborne AMR: role of the environment, crops and biocides, more might be done to note that streptomycin, triazoles and tetracyclines among other antimicrobials are used in plant production and a third of recommendations offered by crop advisors from 32 countries called for antibiotic use for crop protection. The use of aminopenicillins has been documented in treating citrus greening in Thailand, and in a CABI study, antibiotics were found to be recommended for treating fungal diseases in all four study regions, against insects and mites in Southeast Asia, and in nearly one out of 10 management recommendations for rice in one region. As the UNEP spotlight report on environmental dimensions of AMR notes (page 34), “widespread use of fungicides in agriculture is linked to a growing number of azole-resistant lung infections in humans.” The WHO MIA List should do more to signal these findings, what data and surveillance are needed, and what is clearly inappropriate use. Failing to do so leaves a policy vacuum that invites inaction.

Related normative guidance. While the WHO MIA List makes important connection to the Essential Medicines and AWaRe classification lists, the omission of mention of the 2017 WHO Guidelines on Use of Medically Important Antimicrobials in Food-Producing Animals is notable. These expert guidelines should be put forward as guidance to the target audience of the WHO MIA List. If there remain reservations that have prevented FAO and WOAH from supporting WHO’s 2017 guidelines, these should be surfaced and discussed openly. This is one of the reasons why ARC supported the creation of the Independent Panel on Evidence for Action Against Antimicrobial Evidence, but with necessary independence. The WHO MIA List can provide needed clarity to the Muscat Ministerial Manifesto target: “Zero use of medically important antimicrobials for human medicine in animals for non-veterinary medical purposes or in crop production and agri-food systems for non-phytosanitary purposes.

3. Antibiotic Resistance Action Center-USA

28 February 2023
WHO MIA expert committee

To the committee,
I appreciate the detailed work that you have put into this revised document. I have two suggestions:
1. Over the past several years major restaurant chains and other food companies have begun using the MIA list to develop policies regarding antibiotic use in their supply chain. From a public health perspective, this is a highly desirable outcome. In recognition of this trend and the important role that food companies play in antimicrobial stewardship, the following entities should be added to the list of target audiences: Food-animal producers; institutional food purchasers; food companies, including restaurants and catering companies; grocery stores; and other purveyors of meat, poultry, and dairy products.

2. Automatically categorize any drugs authorized for human use as HP-CIAs. The decision tree should be modified to reflect this automatic classification. If the day should come that any of these drugs are approved for use in animals, then they can be formally assessed using the C1, C2, and prioritization criteria.

Thank you for your consideration.

Lance B. Price, PhD
Co-director, Antibiotic Resistance Action Center
Professor, Environmental and Occupational Health
Milken Institute School of Public Health, George Washington University

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Washington, DC 20052

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4 Federal Chamber of Veterinary Surgeons-Germany

Dear Sir or Madam,

The Federal Chamber of Veterinary Surgeons (Bundestierärztekammer) in Germany welcomes the opportunity to provide feedback on the 7th revision of the MIA List and would like to comment as follows:

We welcome the revision of the WHO list of medically important antimicrobials. It reflects the EMA’s AMEG categorization and recognizes the One Health approach. Further, it ensures the availability of treatment options for infections in food-producing animals.

We welcome the need for stronger interventions and measures to address non-veterinary use of medically important antimicrobials, such as growth promotion or illicit trafficking. The accumulated experience since the ban of antimicrobial growth promoters in Germany or Europe has shown that such use of antimicrobials is quite dispensable.

In addition, we propose to consistently limit the purpose of the list to the use of antibiotics in food-producing animals and not to ban regulated off-label use.

Best Regards
5 Faculty of Veterinary and Agricultural Sciences, University of Melbourne-AU

To whom it may concern,

As a researcher in antimicrobial stewardship, working directly with clinicians in trying to change prescribing behaviour, and often referring to classifications of antimicrobials, I have two pieces of feedback on the new list of medically important antimicrobials.

1. Please simplify the names of the categories. They are too wordy and confusing, even for native English speakers. Suggest following the lead of the European Medicines Agency and label them A, B, C, D or some other nomenclature with an obvious order.

2. It is difficult to understand why two of the most commonly used antimicrobials, amoxicillin and amoxicillin-clavulanate are in the same category according to WHO, suggesting there is no real difference in the risk level. In Australia, our ASTAG classifications differentiate between the two, and this is important and helpful when we explain to local clinicians that we want them to avoid adding the additional spectrum of clavulanate when it’s not needed (which is most of the time in Australian veterinary medicine). The EMA also has amoxicillin and amoxicillin-clavulanate in different categories.

Thank you for considering these.

Ri Scarborough
Veterinary Medical Associations
Good Morning,

Please find attached the AVMA’s comments regarding the new WHO MIA list.

Michael Costin, DVM, MBA
Associate Director | Division of Animal & Public Health
American Veterinary Medical Association

February 27, 2023

Advisory Group on Critically Important Antimicrobials for Human Medicine
World Health Organization
Avenue Appia 20
1211 Geneva
Switzerland

RE: Public discussion on the WHO Medically Important Antimicrobial List, 7th Revision (Previously known as the WHO Critically Important Antimicrobial List)

Dear Members of the Advisory Group: The American Veterinary Medical Association (AVMA) appreciates the opportunity to provide comments regarding the WHO Medically Important Antimicrobial List, 7th Revision (previously referenced as the WHO Critically Important Antimicrobial List).

We understand and support the need to preserve the efficacy of antimicrobial agents and minimize the risk of antimicrobial resistance (AMR); however, we have concerns regarding the direction the WHO is taking.

Although the document purports to use a One Health approach to justify its classifications of Medically Important Antimicrobials (MIA), it does not address the foundation of One Health— that the health of humans is dependent on the health of animals and the environment. The Quadripartite One Health High
Level Expert Panel (OHHLEP) defines One Health as “an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals, and ecosystems. It recognizes the health of humans, domestic and wild animals, plants, and the wider environment (including ecosystems) are closely linked and inter-dependent.” The Codex Guidelines on Integrated Monitoring and Surveillance of Foodborne Antimicrobial Resistance defines One Health as “A collaborative, multisectoral and trans-disciplinary approach working with the goal of achieving optimal health outcomes, recognizing the interconnection between humans, animals, plants and their shared environment.” This WHO document does not follow globally accepted definitions of One Health, and its narrow focus on use in food animals is not consistent with a One Health, nor risk-based approach. The WHO appears to have only considered the perceived risk of antimicrobial use in food animals to human health, without balanced consideration for the health and well-being of animals or the environment. The WHO fails to address the consequences of removing antimicrobial drugs as a tool for plant and animal health and the impacts of doing so on other public health sectors, food security, and food safety. It is possible that restricting antimicrobials from food production could result in less efficient agricultural systems that require more natural resources, with the potential for detrimental environmental impacts, reduced animal well-being, and possible emergence of novel human infections. Further, ignoring the companion animal population neglects animals likely to live most proximately to humans, and their associated exposures to human-labeled antimicrobials, pathogens, commensals, and resistance genes developed from exposure to antimicrobials used in humans.

We have additional concern regarding the statement that “antimicrobial classes not currently authorized in food animals should not be used in food animals in the future.” This blanket ban seems to pre-emptively preclude the evolution of technology and science to deliver future solutions for animal health and welfare that do not threaten human health or contribute to the development of resistance to medically important antimicrobial drugs. Limiting or prohibiting the use of antimicrobials approved by regulators in Member States, without data demonstrating risk for the development of AMR, does not meet the stated purpose of the WHO MIA List to “categorize antimicrobial classes ... while considering the potential risk of the development and spread of resistance”.

The AVMA believes the WHO should work to establish a foundational solution to such a complex problem, rather than rushing toward a quick fix. Rather than proposing a holistic One Health approach by addressing the contributions of all stakeholders to antimicrobial stewardship, the WHO introduces a “red herring” by blaming agriculture for the global AMR threat. Without acknowledging the contributions of all sectors to the AMR problem, and providing tenable solutions for risk managers, AMR will never be adequately addressed or resolved.

The AVMA is fully committed to antimicrobial stewardship and the judicious use of antimicrobials. We have actively engaged with WHO, WOAH (formerly OIE), FAO, and Codex. We provide substantive input to United States legislators and regulators as they develop national policies to enhance antimicrobial stewardship. Risk- and science-based decision making is critical for protecting animal health, animal welfare and public health.

We thank the WHO for the opportunity to provide input. For questions regarding the AVMA’s comments, please contact Dr. Michael Costin, Assistant Director, Division of Animal and Public Health, at 847-285-6634 or mcostin@avma.org.

Sincerely,
Janet D. Donlin, DVM, CAE  Executive Vice President and Chief Executive Officer

The AVMA, founded in 1863, is one of the oldest and largest veterinary medical organizations in the world, with more than 101,000 member veterinarians worldwide engaged in a wide variety of professional activities and dedicated to the art and science of veterinary medicine.

2 German Association of Veterinary Practitioners and one of Europe’s biggest veterinary associations- Germany

Dear Sirs and Madams,

Herewith we send you the answers of the Bundesverband Praktizierender Tierärzte e.V. (bpt) to the public consultation. bpt is the German Association of Veterinary Practitioners and one of Europe’s biggest veterinary associations.

Yours Sincerely,

Gabriele Moog

Bundesverband Praktizierender Tierärzte e.V.
Rechtsanwältin
Prokuristin (bpt Akademie GmbH)
Referentin der Geschäftsführung
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Registrierter
Interessenvertreter

bpt-INTENSIV Kleintier 2023 – „Der Notfallpatient“

Präsenztagung mit digitalem Zusatzangebot
Is the purpose of the document clear?

Yes, the document is supposed to be written in a clear and understandable way.

However, the definition of "non-human" use seems inconsistent. It should be harmonised to 'food-producing animals' and define the specific species in all parts of the document.

Is the new approach of basing the groups of antimicrobials on the authorization status appropriate and clearly explained?

The approach chosen is very logical. It is comprehensible and based on the One Health approach.

Nevertheless, some of the antibiotics listed under "authorised for humans only" are also approved for animals in the EU, e.g. the third generation cephalosporin cefoperoxone as well as the nitrofuran furazolidone. If possible, individual active ingredients should be distinguished, if the antibiotic class cannot be categorized as a whole.

Are the new and revised prioritization factors clearly understood?

This represents a clear improvement over the previous prioritization factors. Previously, there were misleading overlaps, especially between the first and second of the old prioritization factors. Now the structure has become much clearer. Also the link to the human medicine side (AWaRe List and EML) is a further way towards a desirable common list for human and veterinary medicine alike. In addition clarification regarding the quantities concerning the definition of 'frequent causes' in PF2 could be useful.

Are the proposed implementation activities providing guidance to countries to improve the responsible and prudent use of antimicrobials in the different sectors?

From our point of view, they are clear and comprehensible. We support these activities. However, we unfortunately see greater challenges to implementation in large parts of the world.

Despite the basic correctness of the "veterinary prescription only" principle one has to take into account questions of availability. A regulatory ban on off-label or extra-label use, jeopardizes animal health and welfare because few approved antimicrobial products are available in limited markets (e.g., small countries or minor species). We suggest a change in the sentence on page 21, line 411: "1. Developing of risk management measures such as restricted use, labelling, limiting unregulated off-label or extra-label use and making antimicrobial agents available by prescription only."
Do you have any additional comments to enhance the utility of the MIA List?

No. The proposal is well done. Hopefully, it will contribute to increased cross-sectoral and interdisciplinary collaboration at all levels, i.e., international, national and subnational.

3. Federation of Veterinarians of Europe (FVE)-BE

Dear Sir, Madame,

The Federation on Veterinarians of Europe (FVE) very much welcomes the opportunity to comment on the content, purpose, criteria, and categorisation of the 7th revision of the WHO MIA List out for public discussion for Member States, partners and experts.

The WHO MIA list carefully puts together pieces of evidence for a categorisation. It reflects the EMA AMEG categorization and acknowledges the value of the One Health approach in addressing the challenge of antimicrobial resistance. FVE applauses the drafting authors for this extensive work and would like to stress that the European veterinary profession is fully committed to keeping up the efforts made to support public health and further reduce the need for antibiotic use. FVE welcomes the introduction of the groups “Authorized for use in humans only” and “Not medically important for humans”.

FVE supports stronger interventions and actions to address the use without veterinary oversight as well as non-veterinary use of antibiotics, such as growth promotion, which are needed on a global scale. FVE would like to underline that antibiotic growth promotion is banned in the EU since 2006.

Additionally, FVE wishes to recall that in the EU, over 70% of the health impact of antibiotic-resistant infections is directly linked to healthcare-associated infections. This burden can only be addressed through adequate infection prevention and control measures, as well as antibiotic stewardship in human healthcare settings. The veterinary use of antibiotics does not contribute to this.

MORE SPECIFICALLY, FVE WOULD LIKE TO COMMENT ON THE FOLLOWING QUESTIONS:

- Is the purpose of the document clear?

Whereas the purpose (l72 ff) is straightforward to purely categorise and assist in risk management, the ‘non-human’ use definition is applied inconsistently in the current document. We would suggest harmonising the text, incl. glossary, table, and flowchart to ‘food-producing animals’ and defining the target species. In addition, we would suggest
deleting, for this 7th version, irrelevant references to plants/crops, e.g. l 87, Table 1, page 20, l 352.

• Is the new approach of basing the groups of antimicrobials on the authorization status appropriate and clearly explained?

The new approach is appropriate and clear. However, we would like to remark that some antibiotics mentioned in ‘authorised for humans only’ are authorised for animals in the EU, e.g. the nitrofuran furazolidone. Where possible, it might be helpful to distinguish single active substances, if the antibiotic class cannot be categorised as a whole.

• Are the new and revised prioritization factors clearly understood?

The prioritisation factors are clear and understandable. However, it might be helpful to provide guidance in quantitative terms on the definition of ‘frequent causes’ in PF2.

• Are the proposed implementation activities providing guidance to countries to improve the responsible and prudent use of antimicrobials in the different sectors?

FVE supports entirely the best practice that antibiotics agents should be available under veterinary prescription only. However, prohibiting ‘off-label’ or ‘extra-label’ use, if legally regulated, is a major risk to animal health and welfare as in limited markets (e.g. small countries or minor species) only limited antimicrobial authorised veterinary medicinal products are available. Please change the sentence on page 21, line 411 to ‘1. Developing of risk management measures such as restricted use, labelling, limiting UNREGULATED off-label or extra-label use and making antimicrobial agents available by prescription only.’

• Do you have any additional comments to enhance the utility of the MIA List?

It could be helpful to harmonise the colour coding of the flow chart and the table.

While we welcome the list as such we would like to take the opportunity to stress that ensuring the availability of treatment options for infections in animals contributes fundamentally to public health and the prevention of zoonotic disease in humans. It is noted in the document that the list should be used in conjunction with other relevant guidance and by considering the national and regional situation. That should be clearly highlighted along with the need for enhanced intersectoral and interdisciplinary collaboration at all levels, i.e. international, national, and subnational.

MINOR REMARKS

L 401 Please change from ‘animal sector’ to ‘veterinary sector’

L 742 The definition of prophylaxis could be improved and remain closer to the initial codex text, which refers to prevention/prophylactic use as use of an antimicrobial(s) in healthy
animals considered to be at risk of infection or prior to the onset of clinical infectious disease. This treatment includes:

- Control of the dissemination of a clinically diagnosed infectious disease identified within a group of animals, and
- Prevention of an infectious disease that has not yet been clinically diagnosed.

Please see as well the document attached (902 words).

Many thanks and kind regards, Wiebke Jansen on behalf of the Federation of Veterinarians of Europe.

____________________
Wiebke Jansen
DVM PhD Dipl. ECVPH
Policy Officer
Federation of Veterinarians of Europe (FVE)
Rue Victor Oudart 7
B-1030 Brussels
Tel. +32 484 38 52 22
www.fve.org

KEY POINTS

- The 7th revision of the WHO MIA list is very welcomed by the European veterinary profession as it reflects the EMA AMEG categorisation and acknowledges the value of the One Health approach. It ensures the availability of treatment options for infections in food-producing animals which contributes fundamentally to public health and the prevention of zoonotic disease in humans.
- Stronger interventions and actions to address the use without veterinary oversight as well as non-veterinary use of antibiotics, such as growth promotion are supported as they are needed on a global scale.
- The purpose of this list should be consistently limited to antibiotic use in food-producing animals.
- It might be helpful to provide guidance in quantitative terms on the definition of ‘frequent causes’ in PF2.
- We agree that unregulated ‘off-label’ or ‘extra-label’ use of antibiotics should be limited.
FVE FEEDBACK ON THE WHO MIA LIST, 7th REVISION

The Federation on Veterinarians of Europe (FVE) very much welcomes the opportunity to comment on the content, purpose, criteria, and categorisation of the 7th revision of the WHO MIA List out for public discussion for Member States, partners and experts.

The WHO MIA list carefully puts together pieces of evidence for a categorisation. It reflects the EMA AMEG categorization and acknowledges the value of the One Health approach in addressing the challenge of antimicrobial resistance. FVE applauds the drafting authors for this extensive work and would like to stress that the European veterinary profession is fully committed to keeping up the efforts made to support public health and further reduce the need for antibiotic use. FVE welcomes the introduction of the groups “Authorized for use in humans only” and “Not medically important for humans”.

FVE supports stronger interventions and actions to address the use without veterinary oversight as well as non-veterinary use of antibiotics, such as growth promotion, which are needed on a global scale. FVE would like to underline that antibiotic growth promotion is banned in the EU since 2006.

Additionally, FVE wishes to recall that in the EU, over 70% of the health impact of antibiotic-resistant infections is directly linked to healthcare-associated infections. This burden can only be addressed through adequate infection prevention and control measures, as well as antibiotic stewardship in human healthcare settings. The veterinary use of antibiotics does not contribute to this.

MORE SPECIFICALLY, FVE WOULD LIKE TO COMMENT ON THE FOLLOWING QUESTIONS:

- Is the purpose of the document clear?

Whereas the purpose (172 ff) is straightforward to purely categorise and assist in risk management, the ‘non-human’ use definition is applied inconsistently in the current document. We would suggest harmonising the text, incl. glossary, table, and flowchart to ‘food-producing animals’ and defining the target species. In addition, we would suggest deleting, for this 7th version, irrelevant references to plants/crops, e.g. 187, Table 1, page 20, l 352.

- Is the new approach of basing the groups of antimicrobials on the authorization status appropriate and clearly explained?

The new approach is appropriate and clear. However, we would like to remark that some antibiotics mentioned in ‘authorised for humans only’ are authorised for animals in the EU, e.g. the nitrofuran furazolidone. Where possible, it might be helpful to distinguish single active substances, if the antibiotic class cannot be categorised as a whole.

- Are the new and revised prioritization factors clearly understood?


The prioritisation factors are clear and understandable. However, it might be helpful to provide guidance in quantitative terms on the definition of ‘frequent causes’ in PF2.

- Are the proposed implementation activities providing guidance to countries to improve the responsible and prudent use of antimicrobials in the different sectors?

FVE supports entirely the best practice that antibiotics agents should be available under veterinary prescription only. However, prohibiting ‘off-label’ or ‘extra-label’ use, if legally regulated, is a major risk to animal health and welfare as in limited markets (e.g. small countries or minor species) only limited antimicrobial authorised veterinary medicinal products are available. Please change the sentence on page 21, line 411 to ‘1. Developing of risk management measures such as restricted use, labelling, limiting UNREGULATED off-label or extra-label use and making antimicrobial agents available by prescription only.’

- Do you have any additional comments to enhance the utility of the MIA List?

It could be helpful to harmonise the colour coding of the flow chart and the table.

While we welcome the list as such we would like to take the opportunity to stress that ensuring the availability of treatment options for infections in animals contributes fundamentally to public health and the prevention of zoonotic disease in humans. It is noted in the document that the list should be used in conjunction with other relevant guidance and by considering the national and regional situation. That should be clearly highlighted along with the need for enhanced intersectoral and interdisciplinary collaboration at all levels, i.e. international, national, and subnational.

MINOR REMARKS

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- Control of the dissemination of a clinically diagnosed infectious disease identified within a group of animals, and
- Prevention of an infectious disease that has not yet been clinically diagnosed³.

³
CSOs & NGOs
1. Keep Antibiotics Working Coalition, Food Animal Concerns Trust, and PIRG-USA

Please find the attached comments of the Keep Antibiotics Working Coalition, Food Animal Concerns Trust, and PIRG on the World Health Organization (WHO) Medically Important Antimicrobial List, 7th Revision. In addition to being attached, the text of our comments is posted below. The supporting information for our comments is limited due to the word limit imposed by the WHO. I would appreciate acknowledgement of receipt of these comments.

Thanks,

Steve

Steven Roach
He/Him/His
Safe and Healthy Food Program Director
Food Animal Concerns Trust (FACT)
(773) 525-4952
www.foodanimalconcernstrust.org
www.keepantibioticsworking.org
Learn more about FACT on Facebook, Twitter, and Instagram.

RE: Comments on the WHO Medically Important Antimicrobial List, 7th Revision.

Submitted by: Keep Antibiotics Working, Food Animal Concerns Trust, and PIRG.

February 27, 2023
Plant use should be included as part of non-human use.

In stating that “‘non-human use’ refers to food animal use only” (line 61) the document contradicts itself, ignores Codex recommendations, and ignores the World Health Assembly's direction to adopt a One Health approach to antimicrobial resistance. At multiple points in the document (lines 90, 355, 409) there is reference to using the list to support risk management of antibiotic use in crops/plants, thus the statement designating non-human use as animal use only is inconsistent. All documents adopted by the Codex Alimentarius Commission related to management of antimicrobial resistance include recommendations related to antimicrobial use in plants. The 2021 update of the Code of Practice (CXC 61-2005) includes specific recommendations about antibiotic use in crops based on the medical importance of drugs (e.g. principles 8 and 13) and explicitly defines medically important antibiotics based on the WHO CIA List. Excluding plants also ignores the findings of the “Joint FAO/WHO expert meeting in collaboration with OIE on foodborne antimicrobial resistance: role of the environment, crops and biocides: meeting report” that found clear evidence of the role of plants in the spread of resistant bacteria. There has also been a recent paper showing widespread use of antibiotics in crop/plant production.

**Antimicrobials used in humans that are not currently used in animals should be reserved for human use.**

The draft MIA list first states (line 112) that, “classes not currently authorized in food animals should not be used in food animals in the future.” This is contradicted in line 331-335, when WHO states that if these drugs were to be approved for use in animals they should be considered critically important. Adding to the confusion, the document also states that they should be classified as HPCIAs (line 354). The final guidance should stick with the WHO recommendation that these antimicrobials should not be authorized for use in food animals.

**Macrolides should remain classified as HPCIA’s.**

In the draft revision, macrolides are no longer ranked as HPCIAs because the new prioritization includes a factor that HPCIAs must be used to treat infections that are frequent causes of invasive and life-threatening infections and Campylobacter the basis for the previous HPCIA does not meet this factor. While that may be true for Campylobacter, macrolides have become important for treating serious non-typhoidal Salmonella infections which frequently are invasive and life threatening. The U.S. Centers for Disease Control and Prevention lists macrolides as essential antibiotics for treating serious Salmonella infections and macrolides are especially important for patients returning from countries where resistance to other treatments is high. Macrolides are also considered an alternative treatment for invasive Salmonella in Sub-Saharan Africa. Staphylococcus aureus is another frequent cause of invasive and life-
threatening infection that has been shown to transfer between food animals and humans that if susceptible can be treated with macrolides.

**Aminopenicillins should remain classified as CIA.**

In the draft revision aminopenicillins are no longer ranked as critically important because the basis for that ranking is their role in treating enterococcal infections and “new antimicrobial options for enterococci are available in many regions”. WHO recommendations should cover all regions not just “many” regions particularly when the regions where these new options are not available may have the greatest need. New options are almost always more expensive, making access difficult.

**The Revised List should include reference to the 2017 WHO Guidelines On Use Of Medically Important Antimicrobials In Food-Producing Animals.**

The Guidelines which were based on an expert consultation following WHO requirements for developing recommendations including two systematic reviews should be referenced in the section 6 Implementation Activities (starting at Line 383).

**The Revised List fails to address or even acknowledge important mechanisms of resistance that are not limited to a specific class and the challenge of co-resistance.**

The current list divides antibiotics within classes based on their mechanisms of resistance such as it does when separating fidaxomicin from other macrolides clearly indicating that the rankings give higher priority to mechanisms of resistance than to broader antimicrobial classes. At the same time, the ranking does not take into consideration mechanisms of resistance that impact more than one class such as MLS resistance genes and cfr genes. This creates an asymmetry where resistance mechanisms can be grounds for separating a specific drug from a class allowing the other drugs in the class to have a lower ranking but never to move in the other directions where shared mechanisms of resistance would raise the ranking of a drug.

With respect to co-resistance there is evidence that use of ionophores “can result in resistance to a medically important antimicrobial.” The Norwegian poultry industry stopped using narasin because evidence showed that narasin use led to VRE resistance, and subsequently no VRE were detected in Norwegian poultry. Other researchers found further evidence that “ionophores can contribute to the persistence of VRE in poultry populations.” A recent Dutch study found a “relationship between the use of (ionophore) coccidiostats and the occurrence of other types of AMR relevant for animal and human health.”

**Additional comments:**
Lines 338 and 339 suggests that 3rd and 4th generation cephalosporins without beta-lactamase inhibitors are not used in animals, which is incorrect. This is only correct for 5th generation cephalosporins.

Line 340 and the tables state glycopeptides are not used in food animals. We believe the glycopeptide avoparcin is still authorized in several countries and was reported as a growth promoter in the latest WOAH report on veterinary antimicrobials.

Line 409 bullet 5 states, "The least risk and impact to human health is associated with agents that are 'Not Medically important for humans.'" The document should clarify that this only applies to antimicrobial resistance risk not the overall risk of veterinary drugs. Codex Alimentarius recommends specific drugs not be used in food animals because of residue risk. Some of these drugs are included in this list.

2. **Natural Resources Defense Council- USA**

Please accept the attached comments made on behalf of the Natural Resources Defense Council, a U.S. based NGO with offices in China and India, and more than 3 million members and advocates. The word count is 997 words.

DAVID WALLINGA, MD (HE/HIM)
Senior Health Officer, People and Communities Program

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Lack of transparency around key omissions to the draft List (“the List), and the rationale for those omissions, lessens the List’s public health utility. Potential public health impacts of changes made to this revision are also not sufficiently transparent. Where omissions or changes may result in a lower degree of public health protection, the List should provide an explicit explanation grounded in public health science. The List’s utility depends on it. More specific recommendations follow:

- Macrolide antibiotics are increasingly important for treating invasive and life-threatening infections caused by non-typhoidal Salmonella bacteria, which are also increasingly antibiotic-resistant. The U.S. Centers for Disease Control and Prevention (CDC) deems macrolides to be an “essential antibiotic” for treating these infections; the CDC website also notes macrolides are especially important treatments for patients returning from countries where resistance to other possible treatments is high. Macrolides can be used to treat S. aureus bacteria, which commonly cause invasive, life-threatening infections—at least where the causal strain is susceptible to macrolides. Like invasive Salmonella, invasive strains of S. aureus are known to transfer from food animals to humans, including via the food supply.

  We urge that downgrading macrolides from designation as Highest-priority Critically Important Antibiotics (HPCIs) appears to be inconsistent with the science, and with clinical practice as described by the CDC. They should remain HPCIs.

- Antibiotic use is widespread in crop/plant production. The report from the Joint FAO/WHO expert meeting in collaboration with OIE on foodborne antimicrobial resistance: role of the environment, crops and biocides (2018) cites “clear scientific evidence” that foods of plant origin may serve as vehicles for human exposure to antibiotic-resistant bacteria and resistance genes. The report therefore calls for national surveillance programs to integrate monitoring data around antimicrobial use and antimicrobial resistance, specifically including data from plant production environments. It also urges these data should be folded into related risk assessment and management efforts – presumably including periodic revisions of this List.

  We recommend: The final List should conform with the World Health Assembly’s direction to the WHO to adopt a One Health approach to antimicrobial resistance which includes consideration of plant uses of antimicrobials and their potential contribution to the spread of antimicrobial resistance.
The report from the Joint FAO/WHO meeting in 2018 also details evidence for why non-medical use of medically important antibiotics (including in plant production) may increase selection for the spread of antibiotic resistance genes and drug-resistant bacteria “through the processes of co-resistance, cross-resistance, and co-regulation with certain metal ions.” The draft List neglects to even mention these processes.

These known mechanisms may increase resistance across two or more antimicrobial classes. Yet the current List ignores this science. Instead, it offers only examples where different resistant mechanisms are the basis for downgrading the priority ranking for some antimicrobials within a particular class, but not others. We agree with Steve Roach’s comment that:

“This creates an asymmetry where resistance mechanisms can be grounds for separating a specific drug from a class allowing the other drugs in the class to have a lower ranking but never to move in the other direction where shared mechanisms of resistance would raise the ranking of a drug.”

We recommend: The final List’s priority rankings of antimicrobials should reflect consideration of evidence for instances of shared resistance mechanisms across antimicrobial classes, in addition to instances where antimicrobials within the same class may have different resistant mechanisms.

Reference to the WHO Guidelines On Use Of Medically Important Antimicrobials In Food-Producing Animals is omitted from the List without explanation or justification. These 2017 Guidelines speak to what should be the List’s grounding in science and public health. The guidelines were based on an expert consultation which followed WHO requirements for the development of recommendations. Their scientific basis includes what likely are the two most comprehensive systematic reviews of the topic published to date.

We recommend: The 2017 Guidelines should be referenced in section 6 of the List, titled “Implementation Activities” (starting at Line 383).

2) Several instances of contradictory language in the List also undercut the List’s clarity and public health utility.

Line 112 states antibiotic “classes not currently authorized in food animals should not be used in food animals in the future”. Lines 331-335 are contradictory, stating that if the same drug classes were to be approved for use in animals they should be considered CIAs. (Even more confusingly, line 354 states they should be categorized as HPCIAs.) Compounding the confusion is the decision to no longer include antimicrobials currently used only in humans in their appropriate categories within the table. Carbapenems, for example, are clearly of critical importance to human medicine and should be listed in the table as such.

We recommend: In the final List, human-use antibiotics not currently authorized for food animal use should remain reserved for human use, as WHO itself recommend. As
some of the most important treatments for people, carbapenems should be listed as such within the table itself.

- At multiple points (lines 90, 355, 409) the uses of the List are described as including support of risk management of antibiotic use in crops/plants, which directly contradicts line 61 which states that “‘non-human use’ refers to animal use only”.

The Codex Alimentarius Commission’s adopted documents relating to management of antimicrobial resistance, starting with the 2011 Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance, include recommendations pertaining to antimicrobial use on plants. Another significant example is the 2021 update of the Codex Code of Practice to Minimize and Contain Foodborne Antimicrobial Resistance. It articulates general principles on the use of antimicrobials determined to be medically important, and this determination is based on the WHO’s current CIA List.

**We recommend:** Contradictory language in line 61 should be removed. The final List should unambiguously state that ‘non-human use’ refers to antimicrobials used in plant as well as food animal production.

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### 3 Responsible use of Medicines in Agriculture Alliance RUMA-UK

RUMA welcomes the chance to view the new 7th Revision of the WHO MIA list.

It broadly welcomes the document, but in particular the re categorisation of the Macrolides group to a CIA. Please see attached our full response to your questions.

Kind regards

Chris Lloyd

RUMA – Secretary General

07973 701 211

**RUMA response to the WHO MIA List, 7th revision**

RUMA welcomes the opportunity to respond to the WHO MIA List, 7th revision.

**Background to RUMA**

RUMA is a UK organisation established in November 1997 to promote the highest standards of food safety, animal health and animal welfare in the British livestock industry. Its promotes the responsible use of medicines across all food producing livestock sectors and has a particular focus on the use of antibiotics.

It is a unique, independent non-profit group based on a membership of organisations that represent all stages of the food chain from *farm to fork*. This membership includes those representing interests in agriculture/ aquaculture, veterinary practice,
animal medicines industry, farm assurance, farmer training, retailers, consumers and animal welfare interests.

In 2016 RUMA established the Targets Task Force, with representatives from every livestock sector in the UK. Its objective was to establish antibiotic reduction targets and activities to deliver them. The first set of targets were published in November 2017 - http://ruma.org.uk/wp-content/uploads/2022/07/RUMA-Targets-Task-Force-Report-2017-.pdf.

Having comprehensively achieved the first targets, a new set of targets were established in 2020 which run to 2024 - http://ruma.org.uk/wp-content/uploads/2022/07/RUMA-REPORT-021220.pdf

Response

- Is the purpose of the document clear?
  - Yes
- Is the new approach of basing the groups of antimicrobials on the authorization status appropriate and clearly explained?
  - Yes
- Are the new and revised prioritization factors clearly understood?
  - Yes
- Are the proposed implementation activities providing guidance to countries to improve the responsible and prudent use of antimicrobials in the different sectors?
  - Yes, these are explained but without great detail.
- Do you have any additional comments to enhance the utility of the MIA List?

RUMA welcomes the recategorisation of Macrolides to a CIA on the basis of their limited threat to human health. This aligns with the EMA classification, which RUMA supports and works within.

Submitted by Chris Lloyd, RUMA Secretary General 28/2/23 – chris@ruma.org.uk

4 Centre for Science and Environment-India

Dear colleague,

Please find attached the feedback on WHO MIA List 7th revision sought as per information on the webpage - https://www.who.int/news-room/articles-detail/public-discussion-on-the-who-medically-important-antimicrobial-list--7th-revision

This is on behalf of the Centre for Science and Environment (CSE), New Delhi.
Feedback by the Centre for Science and Environment (CSE), New Delhi

on the draft WHO Medically Important Antimicrobial List, 7th Revision 2023

(https://www.who.int/news-room/articles-detail/public-discussion-on-the-who-medically-important-antimicrobial-list--7th-revision)

February 28, 2023

The following feedback is based on CSE’s review of the draft and experience of working in India and engaging

with several low-and middle-income countries on food-animal routes of Antimicrobial resistance.

1. The overall positioning of antimicrobials that need attention (to be conserved etc.) has reduced due to changes made in categorization/prioritization. However, there are questions/clarifications that remain unaddressed.

Due to the changes, compared to earlier 2018 WHO list of critically important antimicrobials (CIAs), the number (and class/subclass) of antimicrobials categorised as CIA and HPCIA have reduced/changed. While this may look fine on the face of it (as it is aligned with the new approach), but the following points need clarification/attention.

a) It appears that the problem is now actually related to only a limited set of antibiotics i.e., antibiotic class/subclass authorised for humans and animals and therefore those which are authorised only for humans as well as not authorised for use in humans do not pose any problem and need not be saved/preserved. This may not be entirely true for multiple reasons.

b) It is not clear if this new approach is better than before. A good rationale/case example should be provided to reflect on how the new approach serves the purpose better than before, especially, as it was agreed by expert scientists just a few years ago.

c) Frequent shifts in antimicrobials falling under HPCIA and CIA categories make it look like a less-serious exercise. The policy development and regulatory framework at the national level need to have some consistent basis for enforcement/stewardship.
d) What the stakeholders/nations are expected to interpret w.r.t. antimicrobials authorised only for humans to be made amply clear. Similarly, what is the message w.r.t. antibiotics not authorised for human use must also be clarified. This can be done by clear and consistent language across the document.

Otherwise, it can be misinterpreted or interpreted as per convenience.

2. The basis of using for authorization of antimicrobials is not clear and can potentially mislead. It needs to be addressed and made clear.

There are two reasons for this:

a) Antimicrobial authorisations can vary across countries. For example, the Indian drug regulator (CDSCO) approves furaltadone, a nitrofuran derivative, for use in the poultry sector, but the draft categorises it as authorized only for human use.

b) On-the-ground antimicrobial use practices do not necessarily follow authorisations, especially in parts of the global south. For example, certain anti-tubercular drugs (such ethambutol, isoniazid) are known to be used to treat bovine tuberculosis in India.

Additional concerns:

- It is important to understand/communicate the rationale to use authorisations? What additional value it has brought to the table?
  - It is important to understand/communicate, which national-level/global database were referred to understand authorisations?
  - What a country is expected to do in case a contradiction is observed in authorisations (as highlighted above) remains unclear?

3. There is also contradiction/confusion regarding the future animal use of antimicrobials authorised only for humans currently.

   a. Ideally (and preferably), it should be made clear that these are not to be used ever in future in animals. The question of them being considered CIA or HPCIA does not therefore arise.

   b. In case this is not possible, and they are to be allowed for future use in animals, then they should be categorised as HPCIAs from the point of view of conserving them.

4. Macrolides (as well as certain penicillins) getting off the radar may not be a good idea. They are extensively used in the Indian food-animal sector as well as in human health. They are also becoming ineffective due to growing resistance. Their re-categorisation taking them away from HPCIA/CIA should be reconsidered

Resistance against macrolides is growing in India. Data from the Indian Council for Medical Research's (ICMR) shows decline in susceptibility trends of S. aureus, Staphylococci sp. against erythromycin. Our research also suggests extensive use of erythromycin and azithromycin in the Indian poultry sector. Similarly, the re-categorisation of aminopenicillins like ampicillin and amoxycillin should be reconsidered. Otherwise, a route for greater overuse/misuse of these two sets of antibiotics will get created.
Resistance trends (in case of ionophores) and toxicity angle (carbadox, arsenicals) in antimicrobials

“Not authorized for use in humans” is ignored and can pave the way for their misuse/overuse and therefore needs to be addressed.

There is emerging evidence on possibility of cross resistance in medically important antibiotics due to use of ionophores in poultry sector. The use of narasin, an ionophore has shown to have a role in imparting vancomycin resistance in bacteria. Further, due to the toxicity of arsenicals and carbadox, the messaging related to ‘not authorised in humans’ (so as to avoid their overuse/misuse) should be adequately elaborated and clarified.

While crops are not considered as part of non-human use in this document but all caution must be exercised to avoid under-playing the problem of antibiotic misuse in crops and its connections with AMR.

There is evidence of antibiotic use/overuse in crops from several countries and understanding on linkages is growing. Our own research on streptomycin use in crops in India based on which the government of India owing to its potential connections with tuberculosis treatment has proposed to ban use of streptomycin in crops starting.

7. It is not clear if this draft is WHO draft or the one which is supported by quadripartite. It seems to endorse antimicrobial use for prevention and control as veterinary medical use, which should not be the case and is different also from what WHO 2017 guidance on use of medically important antimicrobials.

Submitted by:

1. Amit Khurana (k_amit@cseindia.org), Director and
2. Rajeshwari Sinha (s_rajeshwari@cseindia.org), Programme Manager

Sustainable Food Systems programme, Centre for Science and Environment, New Delhi

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Private
Dear Prof. Weese

We would like to recognize the efforts of the working group in drafting the 7th edition of the WHO CIA and welcome the opportunity to provide comments on the draft document.

It was noted that Hydroxyquinoline has been introduced to the medically important class of antibiotics. We believe this group needs to be divided with the Nitroquinolines (Nitroxoline) being classed as medically important while the Chloroquinolinols (Halquinol) should be placed under non-medically important in Table 1.

Halquinol and Nitroxoline can be classified in to two different subclasses of drugs under Quinolines in the Medical Subject Headings (MeSH) classification system produced by the National Library of Medicine of National Institutes of Health (NIH).

Halquinol belongs to the Chloroquinolinols subclass (i.e., Hydroxyquinolines-> Oxyquinoline-> Chloroquinolinols), defined as 8-hydroxyquinolinols chlorinated on the number 5 and/or 7 carbon atom(s).

Nitroxoline belongs to the Nitroquinolines subclass, defined as quinolines substituted in any position by one or more nitro groups.

Halquinol and Nitroxoline can be differentiated by their specific names, where Hal- stands for chlorine atoms in Halquinol and Nitro- stands for nitro group in Nitroxoline.

Due to the structural difference between Halquinol and Nitroxoline, Nitroxoline is not a derivative of Halquinol since the former does not contain any chlorine atoms in its molecular structure but has a nitro group bonded to its number 5 carbon atom.

This kind of structural difference related to significance of nitro groups in drugs has been recognized in the other two cases within WHO listing (6th revision, 2019) of critically important antimicrobials for human medicine. One case is the class of Nitrofuran derivatives, which is listed as ‘Important’. But other furan derivatives are not listed in the same listing. Another case is the Nitroimidazoles class, which is also listed as ‘Important’. But other imidazole derivatives are not listed in the same listing.

Additionally, we believe very little if any nitroxoline is sold in the EU and its certainly not a first or second choice drug physicians will be reaching for.
We recommend that:

1. Nitroquinolines be classed as medically important in Table 1
2. Chloroquinolinols be classed as non-medically important in Table 1
3. Nitroxoline be added to Table 2 as ‘authorized only for use in humans’
4. Halquinol be added to table 4 as ‘not authorized for use in humans’

Appreciate the WG group considering this feedback and recommendations.

Regards

Dr Simjee

Shabbir Simjee, Ph.D., FISAC
Chief Medical Officer &
Global Regulatory & Technical Senior Advisor – Microbiology & Antimicrobials

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2Food Innovation Research Science Technology Management FIRST-AU

Please find attached comments on the draft WHO MIA List 7th revision.

Dr Ian Jenson
Director and Principal Consultant
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Burramattigal Country,
Thank you for the opportunity to comment on the draft of *WHO Medically Important Antimicrobial List* 7th revision 2023. FIRST Management Pty Ltd is a private technical and food safety consultancy ([www.firstmanagement.com.au](http://www.firstmanagement.com.au)).

**Is the purpose of the document clear?**

The purpose of the document should be clarified by defining (perhaps by reference) risk terminology, such as that used by the Codex Alimentarius Commission. It is not clear what the second aim: ‘risk management of AMU’ (line 81) means. AMU is not a risk. Management of AMU may reduce the risk of AMR prevalence increasing.

Why is the second aim not applicable to the human health sector? However it is written, it is equally applicable to both human and non-human health sectors.

**Is the new approach of basing the groups of antimicrobials on the authorization status appropriate and clearly explained?**

Clear definition of the status for ‘use in humans only’ and ‘not medically important’ is clear. The use of the term ‘authorized’ is not. This term implies that WHO has authority, which I don’t believe it has. Perhaps ‘reserved for use in humans only’ and ‘not used in humans’ would convey the same meaning?

**Are the new and revised prioritization factors clearly understood?**

Criterion 2 is not clear because risk terminology has not been defined. It is not clear how potential for transfer of certain bacteria or genes from non-human sources to humans can be identified through ‘risk assessment’ (line 287). Application of this criterion needs to be defined so its application is transparent and clear.

The text for Prioritization Factor 2 (lines 296-302) refers to the existence of extensive evidence. A risk assessment approach (at least in the Codex Alimentarius Commission’s understanding) would require some level of transparency and production of the evidence. Are there, for example, systematic reviews, or compilations of evidence, with quality assessments of the evidence for transmission of bacteria or genes? The evidence base for the prioritization should be clear.

**Do you have any additional comments to enhance the utility of the MIA List?**
Sulfaquinoxaline is registered for veterinary use in Australia in meat chickens and is included in the *Importance Ratings and Summary of Antibacterial Uses in Human and Animal Health in Australia*[^4] and should be included in this publication.

Sincerely,

Ian Jenson

Principal Consultant

[^4]: *Importance Ratings and Summary of Antibacterial Uses in Human and Animal Health in Australia* | Antimicrobial resistance (amr.gov.au)