Author’s response to reviews

Title: Microbiology Investigation Criteria for Reporting Objectively (MICRO): a framework for the reporting and interpretation of clinical microbiology data

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Author’s response to reviews:

Reviewer #1: Matthew Robinson

The manuscript, "Microbiology Investigation Criteria for Reporting Objectively (MICRO): a framework for the reporting and interpretation of clinical microbiology data," introduces a series of criteria to standardize the reporting of AMR data with a focus on LMICs. Systematic and consistent reporting of clinical AMR data is lacking from many LMICs, and there is a lack of guidance for how to better report such data. The authors describe a methodical process by which they created these criteria which included reviewing a subset of a systematic review and consultation with relevant content experts. Although these criteria are thoughtful and useful, there are some important limitations in how they were derived and a lack of clarity as for whom they are intended.

Response
• We thank Dr Robinson for these comments and have strived to address / explain our reasoning behind the issues he highlights below.

General comments:
It would be helpful to more clearly define the audience for these criteria. It seems that the goal is to provide a framework to report microbiology data from LMICs, but this is not clear from the title or abstract. Additionally, the data used to derive this framework appears to be restricted to studies performed in South and Southeast Asia. Although this region is of critical importance to understanding the global epidemiology of AMR, if the goal is to provide a framework to be used globally, or at least in LMICs, data from other regions would improve confidence in the generalizability of this approach. Additionally, the authors appear to be based exclusively in the UK and Southeast Asia. If this is supposed to be applied more globally, it would be helpful to seek the input of authors outside of these locations.

Response
• This is a key point and we have re-worded various sections to make it clear that accurate reporting of AMR data is a global issue, but problems are likely more common in LMICs where quality management etc may not be so robust. The intention was not to restrict applicability based on geography / country income status.
• We have previously commented in similar issues around AMR / microbiology data reporting from Africa and, given the similarities of issues identified, decided to focus on South and Southeast Asia in the literature review. We have clarified this in the text.
• We acknowledge this as a limitation which was also highlighted by the other reviewers. To avoid compromising the guideline development process we described, we have not included additional authors / opinions at this stage but have clarified that we fully expect to issue revised guidance in due course once feedback has been received from professional organisations and other key stakeholders (see further comments by reviewers #2 and #3).

The global challenge of treating resistant Gram-negative infections seems to be outpacing the challenge of treating resistant Gram-positive infections. This framework I believe places too much emphasis on GP organisms and not enough emphasis on GN organisms.

Response
Background

Table 1 and lines 139 - 141: Of the many inconsistencies in global AMR data reporting, the choice of which beta-lactam drug to classify a Staph aureus isolate as MRSA or not seems to be a minor one. If this is going to be a main emphasis in this article, the authors should provide a reference or justification as to why MRSA rates determined by testing with alternative beta lactams such as cefazolin yield clinically meaningful differences compared to testing with cefoxitin.

Response

• We respectfully disagree with this comment, as we believe it flags potentially major methodologic issues in datasets from laboratories reporting that CLSI or EUCAST guidance was followed. The choice of agent tested is a critical point from which choice of agent for treatment is inferred separately and one which we should have made clearer with unambiguous reference to both CLSI and EUCAST documentation (added in the revised manuscript). Both guidelines specify that cefoxitin (historically oxacillin) is used to infer beta-lactam susceptibility for Staphylococcus aureus isolates: breakpoints for other agents are not available and, thus, accuracy of such results cannot be determined in the absence of cefoxitin (oxacillin) testing. To use the reviewer’s example there are no guidelines for in vitro susceptibility testing with cefazolin and it should not be used for this purpose. The choice to use it as treatment is inferred from testing with cefoxitin. The key sections from CLSI M100 (28th edition, 2018) and EUCAST (V8.1, 2018) are are visible in the coverletter version [could not paste into the text box].

• On re-review of manuscripts reporting MRSA based on non-cefoxitin/oxacillin results were identified only two where appropriate methodology was mentioned in the methods section (i.e. tested oxacillin or cefoxitin but reported methicillin or another penicillinase-stable beta-lactam. The review results have been updated to reflect this.

Table 1: The authors suggest that it is inappropriate for bacteriology labs to avoid vancomycin susceptibility testing for MSSA. I do not think that this is correct. When resources are limited or for reasons of diagnostic stewardship, it can be appropriate to only selectively test for and report resistance to 2nd line agents when 1st line agents are susceptible.

Response

• We agree with the reviewer on this point (i.e. selective testing is appropriate) and apologise that our wording was unclear. We have added the appropriate reference to this section of the table along with another example of when selective testing/reporting might occur.

• The issue we were (clumsily) trying make is that resistance rates can be distorted if the incorrect denominator is chosen when calculating percentages. We have altered the example to be E. coli and meropenem (to provide more Gram negative context) and have added the following example to clarify this: “For example, 100 E. coli isolates are tested against ceftriaxone and 10 (10%) are found to be resistant. These 10 isolates are tested subsequently against meropenem and 1 is resistant. This could be reported as 1/10 (10%) or 1/100 (1%) meropenem resistance. Neither of these percentages may be correct”.

Table 1: The definitions for MDR published 6 years ago by Magiorakos are no longer recent. I think that it is worth referencing them, but not in isolation as others since then have reported ways of standardizing MDR definitions across pathogens.

Response

• We thank the reviewer for highlighting this issue. We screened titles of the 951 articles in Pubmed that had cited Magiorakos and found two relevant references to include. We have amended this example to state: “The definition of MDR often reflect local AST selection and
antibiotic availability and thus rates are difficult to compare meaningfully. MDR definitions for major bacterial pathogens have been proposed recently but there remains no overall consensus for many species.”

Methods
Lines 118 - 124. Although it is helpful that the database is briefly described, the link provided to PROSPERO describes only the initial search strategy. There is no reference to the data itself. I believe that there have been multiple publications already generated by the systematic review, "Mapping the aetiology of non-malarial febrile illness globally in malaria endemic regions." It would be helpful to the readers to provide a reference to this.

Response
• Manuscripts from the “Mapping the aetiology of non-malarial febrile illness globally in malaria endemic regions” are currently in preparation. At the outset, the intention was for the MICRO manuscript to form part of the series of papers from the project. However, we agree that it would be much better to highlight the data directly and, with reference to a comment from reviewer #2, we have added a complete summary of the manuscripts reviewed as a supplementary table.

Line 138: I imagine that there were many deviations in AST reporting practices. How did the authors choose the particular deviations on which to focus their criticism?

Response
• We agree. The problems were selected based on early discussions between the author group: they were things that we had all encountered frequently when reading or reviewing manuscripts. They were also all issues that could be defined unambiguously as deviations from the CLSI / EUCAST guidelines. We have commented that “These four pathogens were selected on the basis of being important AMR organisms globally, covering both Gram negative and positive species, with a range of demonstrable reporting problems resulting from deviations from international guidelines. The intention was to provide examples of problems frequently encountered, with potentially important consequences, rather than identify the entire range.”

Lines 129 - 132: Among the GLASS pathogens, why did the authors choose to include Klebsiella, Salmonella, Staph aureus, and Strep pneumoniae and exclude Acinetobacter, E. coli, Neisseria, and Shigella? In many settings, effective treatment for drug-resistant is already used routinely for Strep pneumoniae, while clinicians struggle to find effective regimens for drug resistant E. coli and Acinetobacter.

Response
• Again, this was based on our experiences as reviewers and also that these organisms are likely to be relevant in the majority of settings. We could have selected other problems (e.g. reporting macrolide susceptibilities for E. coli or ampicillin susceptible A. baumannii) but wanted to highlight a few key issues rather than the entire range of possibilities. We have made this clearer in the revised manuscript as stated above.

Line 153-155: This particular criticism of how Klebsiella AST is reported seems to miss the mark on highlighting the most problematic issues regarding GN AST reporting.

Response
• Whilst we agree that there are many issues from which to choose, we selected ampicillin resistance since it is a clear quality indicator: it is rare to identify an ampicillin susceptible Klebsiella pneumoniae isolate in a quality-assured laboratory and CLSI classifies K. pneumoniae as intrinsically resistant to ampicillin and specifically recommends reporting all
isolates as resistant (without testing). We have added the appropriate CLSI reference to this section for clarity.

Lines 160 - 168 and Table 2: It is unclear to me who was invited for the group discussions that led to the final checklist. Were they all bacteriologist based in Southeast Asia? Were they all affiliated with international research organizations? I think that if these guidelines are to be adopted probably for use in LMICs it would be important to have the input of bacteriologist from a variety of geographic locations and institution types including public health agencies, private hospitals, local medical schools, etc.

Response
• This is an important point and one that has been picked up also by reviewers #2 and #3. The group members were all past or present members of the University of Oxford Tropical Medicine Network, with experience working in Europe and across Asia and Africa. Most group members are currently working at, or are associated with, clinical and/or research institutions in Asia (Cambodia, Indonesia, Laos, Myanmar, Nepal, and Vietnam). The group included infectious diseases doctors (adult and paediatric), clinical microbiologists, laboratory microbiologists and managers, epidemiologists, and mathematical modellers.
• We agree that, in order to promote uptake of these guidelines we need to consult more widely and we have revised the manuscript, clearly stating an aim to promote the MICRO framework to various professional organisations and global health networks (e.g. ReAct (www.reactgroup.org); European Society of Clinical Microbiology and Infectious Disease; American Society for Microbiology; American Society of Tropical Medicine and Hygiene; Royal Society of Tropical Medicine and Hygiene; South African Society for Microbiology). In particular, we will involve the EQUATOR network (https://www.equator-network.org/), who have been made aware of the development of the MICRO framework. We plan a formal feedback exercise to gather responses from early users and would aim to revise the guideline at an appropriate point in the future with broader representation of stakeholders.

Discussion
Lines 195 - 196: What is meant by a "well-functioning clinical microbiology laboratory service?" Do the authors mean that routine microbiology data from a lab with fewer resources should simply not report their data?

Response
• Apologies for this poorly worded sentence. We were implying that the checklist items are not over and above what should be available / recorded in a quality-assured diagnostic clinical laboratory. We strongly agree that fewer resources does not necessarily imply “poorly functioning”. The sentence has been adjusted to “The final checklist contains items that should be available for a quality-assured clinical microbiology laboratory service”.

Lines 196 - 197: There is a typo in the sentence: "It expected"

Response
• Thank you for spotting this: the missing “is” has been added.
Reviewer #2: Michihiko Goto

(General Comment)
Authors described their new proposal to set a standard for the reporting and interpretation of clinical microbiology data, based on their systematic review intended for non-malarial febrile illness in tropical regions. The manuscript is clearly written, concise, and covering essential components of clinical microbiology data reporting. Overall, I believe this is a very important companion to already existing framework, such as CONSORT or STROBE, and the relevance is not limited to low- and middle-income countries.

Authors are correctly pointing out that reporting variability and incomplete presentation of microbiology data are hampering critical review of existing literatures (especially when conducting systematic review), and making systematic and objective data collection to assess the burden of bacterial infectious diseases and antimicrobial resistance. These problems are important and frequently encountered also in outbreak/transmission reports as well.

Response
- We thank Dr Goto for these encouraging comments.

(Specific Comments)
Line 104-105: I completely agree that this reporting standard should be applied not only to observational studies but to any clinical study involving microbiology results, and understand that authors specifically avoided to incorporate the term STROBE. However, it will give some challenge for dissemination plan of this new proposal. Do authors have a plan to submit this to existing dissemination initiatives such as EQUATOR network? Was it considered to approach both STROBE and CONSORT groups to make this "An extension to CONSORT and STROBE"? I think there is no precedence for this approach, but it may be worth considering due to broad relevance of this proposal.

Response
- With reference to a comment from reviewer #1, we have made the EQUATOR team aware of the MICRO framework and will liaise with them closely post-publication to ensure the guideline reaches its target audience. We agree that consideration as a formal extension to CONSORT and STROBE would be ideal and will address this issue via the EQUATOR network.

Line 110-112: It appears authors largely followed toolkit from EQUATOR publication ("Guidance for developers of health research reporting guidelines"), but did not conduct Delphi exercise in pre-meeting phase (Line 192-193). Authors provided brief description of pre-meeting phase in Line 160-168, but there is no detail provided. Which component of Delphi exercise was followed and which was not? (e.g. anonymity or group discussants, staged questionnaires)

Response
- We have summarised the pre-meeting steps in the revised manuscript: “The need for a guideline was mooted during informal network meetings as a result of discussions around the highly variable clarity and quality of clinical microbiology and/or AMR data in manuscripts submitted for peer-review. All pre-meeting steps were open and non-anonymised: discussions occurred by teleconference and documents were iterated and circulated electronically to the group”. This level of description is consistent with that included in the STROME-ID manuscript.
The original systematic review protocol in PROSPERO included Africa, South Asia, China, Southeast Asia, and Latin America as target geographic area, but it appears authors included studies from South and Southeast Asia when evaluating qualities of existing literatures. What is the justification for this limitation?

Response
- As per responses to reviewer #1, we have previously commented on reporting issues for data from Africa, where we found many similar problems. We have highlighted that in the text. Given that our intention was to highlight a few common issues around AMR / microbiology reporting, we felt that expanding the review to other geographic areas would be unlikely to make a stronger case. We used a dataset which, although from one geographical region, was generated following a comprehensive and systematic literature search which we think is a strength and minimises selection bias.

Authors summarized results of their systematic review to assess quality of reporting in existing literature in this section. For the sake of transparency, it is ideal to provide summary table of these 123 studies (presumably authors have list readily available) as online supplemental material, just for relevant quality evaluation of included studies.

Response
- We agree and, with reference to a comment from reviewer #1, this table is now included as supplementary material.

Has pilot implementation been considered for proposed checklist?

Response
- We plan to pilot the checklist in in the Oxford Tropical Network (sites across Asia and Africa) and we will engage with the EQUATOR network and various professional organisations regarding promotion and implementation (see reviewer #1 comment).

Table 3: The list of items is comprehensive and well-summarized for culture-based microbiology results reporting. However, it covers very little for non-culture based microbiology and antimicrobial susceptibility testing, which middle-income countries are rapidly undertaking, not only high-income countries (good example is Xpert MTB/RIF). Since this guidance has wider application to diverse settings, I believe this checklist should incorporate some non-culture based methods to recommendations.

Response
- We thank the reviewer for this important point. The inclusion of completely non-culture-based detection points was not discussed widely by the group. However, we appreciate that this is an area of growth and ought to be recognised in the MICRO checklist. For now, we have agreed to the inclusion of a statement regarding specimen processing for molecular testing (included in Table 3; number 7) and highlighted the use of Xpert MTB/RIF in number 9 (Additional tests performed to identify resistance mechanisms). We have also highlighted in the discussion that we expect the checklist to be expanded to give more guidance on such methods in future versions: “We expect that technological development will result in significant expansion of guidance on reporting of molecular-only organism identification and AST results.”

Table 3: Another item which authors should consider incorporating was strain identification within organism. This is overlapping area between this proposal and already existing STROME-ID. However, strain typing is becoming more accessible to many settings and commonly performed for many microbiology studies with public health relevance. If authors need to avoid overlap with STROME-ID, they can simply state "Strain subtyping methods should be reported according to STROME-ID"
We agree and have added the comment as suggested (Table 3; number 8): “Strain subtyping methods should be reported according to STROME-ID”.

Reviewer #3: Rajeshwari Nair

The study entitled 'Microbiology Investigation Criteria for Reporting Objectively (MICRO): a framework for the reporting and interpretation of clinical microbiology data' was conducted to develop a checklist that will enhance the quality and scientific reporting of clinical microbiology data, increase data utility and comparability to improve surveillance, grade data quality, facilitate meta-analyses and inform policy and interventions from local to global levels. The authors identified an existing study registered in the PROSPERO system and reviewed the datasets published in this system to identify relevant domains for the checklist. These checklist items were reviewed and revised per consensus by involved personnel, which was not conducted per the Delphi system. Based on the final checklist items, the authors present a reasonable checklist that is recommended for use with other standard reporting guidelines such as STROBE. This checklist appears very relevant not only to LMIC's and can be used to improve reporting of microbiological data on a global basis. With that said the checklist should be updated based on feedback from investigators using the checklist to conduct and report studies.

We thank Dr Nair for these helpful comments. We have emphasised the global applicability and need for feedback / revisions in our updated manuscript.

There are few deficiencies in the manuscript that would be relevant for readers. These should be addressed in the best possible manner before publication of the manuscript.

1. Although the authors did not use the Delphi system, it would still be relevant to know how important decisions were made on selection of domains and items for the checklist. Why was the non-malarial study used from the PROPSERO system? Who reviewed the 178 databases to identify data deficiencies or inconsistencies? How were people invited to be part of the decision making team? Were there intermediate processes that may have changed people's response on the importance of the item to be included in the checklist? What do the authors mean by biomedical scientists, were these bench science researchers, did you involve epidemiologists and statisticians? Were these team personnel from LMIC's too?

We hope that we have addressed most of these issues in responses to comments from reviewer #1 and #2. The microbiology data extraction was performed using a standard form by a scientist from the Infectious Diseases Data Observatory (Poojan Shreshta) for the “Mapping the aetiology of non-malarial febrile illness globally in malaria endemic regions” project. Another author (Paul Turner) then double checked data extraction for the papers suspected of including reporting errors for S. aureus, S. pneumoniae, and K. pneumoniae, and Salmonella spp. We have highlighted this process more clearly in the text.

We have clarified the term biomedical scientist (“laboratory microbiologist”: to distinguish from clinical microbiologist).

2. It will be important to include access to a convenience sample in 'sampling strategy' of the checklist. Several times observational microbiology studies use existing sample repository. It is important know if
these samples were readily available or collected from a sample of patients that were intended to be included in the study based on the research question.

Response
• We agree and have added this to checklist item 3.

3. If the intention of the authors is to use this checklist as a potential resource to conduct meta-analyses then it would be beneficial to create a scoring system based on the checklist. For example, a study conducted may get a star if the checklist item was met and none if not. These stars can be added up to identify the quality of the study to be included in a potential meta-analyses.
  • We agree and had devised an example grading scheme, which was removed from the original manuscript to avoid being too prescriptive. We have added Table 4 (“An example of quality grading criteria based on the laboratory components of MICRO”) to the revised manuscript.

Additional author-generated revisions

During manuscript revision, one study from the “Review of published microbiology datasets from LMICs in South and SE Asia” was found to have been included in error, leaving 177 papers in the review. Preparation of the supplementary table, and re-review of key papers, resulted in minor changes to the results in this section (specifically to the AST methodology, QC organism, S. aureus and S. pneumoniae-penicillin sections).