

Revised Submission to *Microbes, Infection and Chemotherapy*

Submission category: Original Article

Original Title: **Persistence of first-line antibiotic-resistant typhoid among Pakistani children: a growing concern for regional antimicrobial stewardship**

Revised Title: **Persistence of first-line antibiotic-resistant typhoid **fever** among Pakistani children: a growing concern for regional antimicrobial stewardship**

Thank you for your correspondence of 29th November regarding the suitability of the above titled manuscript for publication. On behalf of both co-authors, I thank the reviewers for their strongly supportive appraisal and greatly appreciate their constructive and insightful comments. In light of these, we have carefully amended the manuscript.

I note that although the comments are exhaustive, there is considerable repetition between reviewers – and so this also applies to our rebuttal. I trust that the revisions indicated on the manuscript (*see marked-up copy*) and explained in full on the following six pages deal with all issues that you have raised and that this manuscript is now acceptable for publication.

I attest that this paper has not been published in whole or in part elsewhere and is prepared following the instructions to authors. The revised manuscript is submitted as a Word .docx, following author guidelines. It contains text only. Both authors have contributed to writing the manuscript, approved its final version and agreed to its submission. There are no conflicts of interest to declare.

On behalf of both co-authors.

A handwritten signature in black ink, appearing to read 'A. Taylor-Robinson', with a horizontal line underneath.

A.W. Taylor-Robinson

Reviewer A:

Recommendation: Revisions Required

1. Relevance of the title to the content of the article

Regular

No specific action required.

Remarks

I understand the author's understanding of the problem presented, however, I believe that the title should be revised to better guide the reader during the appraisal of the manuscript. Considering some inconsistencies about some information, I believe that the title should be modified for a more alarming bias on the importance of investigating the situation of multiresistant.

As this was not recommended by the other reviewers, we have not significantly amended the title. 'Typhoid' is changed to 'typhoid fever', in keeping with its abbreviation to TF' in the text.

2. Summary: Presents the general idea of the topic, objectives, research methods, results and conclusions, written in an objective and concise manner; and are found according to the maximum number of words per section.

Regular

Remarks

No specific action required.

3. Introduction: Presentation of the subject, justification of the problem, objectives, hypotheses and methodological foundation, exposing the subject in an orderly and detailed manner

Regular

Remarks

The text in general is well oriented, except for some inconsistencies about the bibliographical references and the information given by the author.

Inconsistencies are now fixed – refer to marked-up copy.

4. Methodology: Describes the procedure, methods and techniques used in data collection and analysis.

Regular

5. Ethical aspects. Does the manuscript have a paragraph on ethical aspects, where it mentions approval by the ethics committee, informed consent, and strict compliance with research ethics?

No

6. Results: They are presented adequately and it is not redundant with tables or graphs shown.

Regular

Remarks

The author often presents data in the text that are inconsistent with the reported references. I believe that some problem must have occurred without him noticing, since consulting some references I noticed that some information contained in the text was contained in interchanged references.

Inconsistencies are now fixed – refer to marked-up copy.

7. Discussion: They present a level of critical analysis in correspondence with the problem presented. Purposes of the article, scope, support theory and proposed methodological design.

Regular

Remarks

Considering the misunderstandings regarding the information and references, the entire article must be revised so that the author can confirm the information provided concretely about the reported references.

Inconsistencies are now fixed – refer to marked-up copy.

8. Conclusions: Presents the author's inferences and teachings in relation to the investigated topic, it must correspond to the objectives of the study.

Regular

Remarks

There is no direct conclusion presented by the author. The text ends with the information that, although impacting, perhaps does not portray the current scenario, as the referenced base is old.

The last two paragraphs have been rewritten to include a summary. The references have been updated, such that 12 of 15 are from the last 5 years – with 9 published since 2020.

9. References. Quality of bibliographic references and if they are in accordance with the Vancouver format.

Good

Remarks

The references, although it has exceeded the number allowed, are most current. Considering the suggestions given above, I believe that some references will not be part of the final version. However, I suggest that even if it exceeds the allowed limit, this does not impede publication.

Not only is the reference list updated, it is also more appropriate to support each point of discussion.

10. Redaction. Is the manuscript correctly written? Does it contain any spelling or grammar mistakes?

Requires a thorough assessment of grammar and spelling

The corresponding author is a native English speaker with more than 250 peer-reviewed journal publications spanning a 30-year research career. The perceived issue regarding grammar and spelling is a fallacy that lies in the reviewer's preference for US grammar/spelling. In the original submission UK English was used but now this is amended to US.

11. Contributions. What are the main weaknesses of the manuscript and how the author can do to improve it.

The manuscript presents a subject that although it is something we already know, it is important to keep the scenario up to date. The relevance of antibiotic resistance is something that will always have an impact. I suggest that you review the problem with the references and other issues that have been pointed out so that the subject is presented in the best possible way.

We have made great efforts to substantiate the key points of our 'opinion' on this fast-developing, important subject, to update the supporting references and to ensure that each text citation is valid.

Reviewer B:

Recommendation: Revisions Required

1. Relevance of the title to the content of the article

Regular

Remarks

Please see my comments.

We thank the reviewer for providing detailed comments directly on the manuscript. Revisions have been made in accordance with these useful comments.

2. Summary: Presents the general idea of the topic, objectives, research methods, results and conclusions, written in an objective and concise manner; and are found according to the maximum number of words per section.

Regular

Remarks

Please see my comments.

Required action taken – see marked-up copy of revised manuscript.

3. Introduction: Presentation of the subject, justification of the problem, objectives, hypotheses and methodological foundation, exposing the subject in an orderly and detailed manner

Poor

Remarks

Please see my comments.

Required action taken – see marked-up copy of revised manuscript.

4. Methodology: Describes the procedure, methods and techniques used in data collection and analysis.

Good

Remarks

Please see my comments.

No specific action required.

5. Ethical aspects. Does the manuscript have a paragraph on ethical aspects, where it mentions approval by the ethics committee, informed consent, and strict compliance with research ethics?

No

6. Results: They are presented adequately and it is not redundant with tables or graphs shown.

Regular

Remarks

Please see my comments.

Required action taken – see marked-up copy of revised manuscript.

7. Discussion: They present a level of critical analysis in correspondence with the problem presented. Purposes of the article, scope, support theory and proposed methodological design.

Good

Remarks

Please see my comments.

No specific action required.

8. Conclusions: Presents the author's inferences and teachings in relation to the investigated topic, it must correspond to the objectives of the study.

Poor

Remarks

We have made great efforts to substantiate the key points of our 'opinion' on this fast-developing, important subject, to update the supporting references and to ensure that each text citation is valid.

9. References. Quality of bibliographic references and if they are in accordance with the Vancouver format.

Poor

Remarks

Please see my comments.

Not only is the reference list more appropriate to support each point of discussion, it is updated such that 12 of 15 are from the last 5 years – with 9 published since 2020.

10. Redaction. Is the manuscript correctly written? Does it contain any spelling or grammar mistakes?

Needs some language corrections

The corresponding author is a native English speaker with more than 250 peer-reviewed journal publications spanning a 30-year research career. The perceived issue regarding grammar and spelling is a fallacy that lies in the reviewer's preference for US grammar/spelling. In the original submission UK English was used but now this is amended to US.

11. Contributions. What are the main weaknesses of the manuscript and how the author can do to improve it.

Minor comments:

The article is inadequately presented. Furthermore, there are many problems in the different sections as well.

Although the article has scientific rigor, several minor flows need to be improved before publication.

We thank the reviewer for providing detailed comments directly on the manuscript. Revisions have been made in accordance with these useful comments – see marked-up copy of revised manuscript.

The comments listed below have all been addressed, as discussed in previous points made in the reviewer's report.

1. The title is okay.

2. Authors are suggested to use the full form when used for the first time throughout the manuscript.

3. As the dissemination of S. Typhi...section is poorly written. Authors are suggested to develop this section by adding the literature related to Multidrug-resistant.

4. Need to arrange the section logically—very few references are cited in this section. Also, the reference serial is not correct.

5. Delete old references.

6. In recent years there has been an alarming need to be improved by adding significant insights.

7. Many grammatically problematic sentences are in different sections, which must be checked and corrected precisely.

8. The conclusion needs to address future perspectives.

9. Spacing, punctuation marks, grammar, and spelling errors should be reviewed thoroughly. I found so many typos throughout the manuscript.

10. English is modest. Therefore, the authors need to improve their writing style. In addition, the whole manuscript needs to be checked by native English speakers.

Reviewer C:

Recommendation: Revisions Required

1. Relevance of the title to the content of the article

Good

Remarks

It is concise and informative.

No specific action required.

2. Summary: Presents the general idea of the topic, objectives, research methods, results and conclusions, written in an objective and concise manner; and are found according to the maximum number of words per section.

Good

Remarks

No summary, since it is an opinion article

No specific action required.

3. Introduction: Presentation of the subject, justification of the problem, objectives, hypotheses and methodological foundation, exposing the subject in an orderly and detailed manner

Good

Remarks

It is good and presents all the information we need to understand the problem of MDR and XDR in Pakistan, but I think that presenting some numbers about vaccination and why they are so important in avoiding disease but also the occurrence of MDR and XDR would give the introduction a better focus and will make it more interesting.

We have incorporated the requested information in the revised manuscript.

4. Methodology: Describes the procedure, methods and techniques used in data collection and analysis.

Good

Remarks

No comments.

No specific action required.

5. Ethical aspects. Does the manuscript have a paragraph on ethical aspects, where it mentions approval by the ethics committee, informed consent, and strict compliance with research ethics?

No

6. Results: They are presented adequately and it is not redundant with tables or graphs shown.

Good

Remarks

In the sentence "This first report of the emergence of confirmed cases of MDR *S. Typhi* from the only public hospital in its largest neighborhood identifies a grave public health concern. The rise in prevalence of MDR and, in some instances, XDR, *S. Typhi* that has been observed not only in Karachi but also in Hyderabad (9), the second-largest city in Sindh and situated 160 Km to the northeast of Karachi, constitutes a major humanitarian crisis." please correct the bacterium species name.

This is correct in the original version. We agree with the reviewer in their assertion of the Linnean classification of organisms, which we have followed. For this nomenclature, the causative agent of typhoid is *Salmonella enterica* subspecies *enterica* serovar *Typhi*. We surmise that, with all due respect to the reviewer, they are not familiar with the scientific naming system for this enteric pathogen. Otherwise, they would know that the standard, universally accepted abbreviation for this long name - once it is introduced in full - is *S. Typhi* ('*S.*' in italics and '*Typhi*' not italicised). This, admittedly unusual, nomenclature convention is explained very clearly in the first line of the Introduction.

7. Discussion: They present a level of critical analysis in correspondence with the problem presented. Purposes of the article, scope, support theory and proposed methodological design.

Good

Remarks

I think some points should be addressed in this part. In the text when it says "An elementary first step is the implementation of a regular and effective nationwide surveillance mechanism to enable the burden of disease to be determined with a reasonable degree of accuracy" please specify if the surveillance is to detect the occurrence of all cases of typhoid or only the cases caused by MDR/XDR *S. typhi*.

We have incorporated the requested clarification in the revised manuscript.

In the sentence "Moreover, a concerted and consolidated effort should be made to restrict the ready access to non-prescribed antibiotics among the general public in south and southeast Asian countries through unregulated 'over the counter' pharmacy sales and black market trade (10).", please show us some numbers showing why black-market and access to non-prescribed antibiotics are a problem in South and Southeast Asia.

We have incorporated the relevant multidrug resistance data in the revised manuscript.

8. Conclusions: Presents the author's inferences and teachings in relation to the investigated topic, it must correspond to the objectives of the study.

Good

Remarks

No comments.

No specific action required.

9. References. Quality of bibliographic references and if they are in accordance with the Vancouver format.

Good

Remarks

No comments.

No specific action required.

10. Redaction. Is the manuscript correctly written? Does it contain any spelling or grammar mistakes?

Needs some language corrections

The corresponding author is a native English speaker with more than 250 peer-reviewed journal publications spanning a 30-year research career. The perceived issue regarding grammar and spelling is a fallacy that lies in the reviewer's preference for US grammar/spelling. In the original submission UK English was used but now this is amended to US.

11. Contributions. What are the main weaknesses of the manuscript and how the author can do to improve it.

I really liked the manuscript, MDR/XDR are a real problem, especially in low- and middle-income countries. For me, the text missed some aspects on how public policies will help the avoidance of MDR/XDR *S. typhi* in Pakistan and also numbers about the occurrence of it. How many cases are due to XDR/MDR? For what antibiotics are they resistant? Give us more things to think about! Congrats.

We have incorporated population incidence data and multidrug resistance data in the revised manuscript. This indicates the class of antibiotics to which resistance is reported.