

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Etiology of ear infection and antimicrobial susceptibility pattern among patients attending otorhinolaryngology clinic at a tertiary hospital in Dar es Salaam, Tanzania: A hospital-based cross-sectional study
AUTHORS	Shangali, Aminiel; Kamori, Doreen; Massawe, Willybroad; Masoud, Salim; Kibwana, Upendo; Mwingwa, Anthony G.; Manisha, Anselmo; Mwandigha, Ambele M.; Mirambo, Mariam M; Mshana, Stephen E.; Manyahi, Joel; Majigo, Mtebe

VERSION 1 – REVIEW

REVIEWER	Taylor, Steven University of South Australia, Infection and Immunity
REVIEW RETURNED	30-Sep-2022

GENERAL COMMENTS	<p>The authors present a cross-sectional analysis of microbiology associated with ear infections in a hospital in Tanzania. They report high levels of antibiotic resistance, which is of interest given the lack of literature in this space for this region. The manuscript overall is well written and the results are presented clearly. There are however, several minor grammatical errors, and a few general questions that I feel would improve this manuscript if addressed.</p> <p>Comments:</p> <ol style="list-style-type: none">1. The main strength noted after the abstract is “the study has revealed the antimicrobial susceptibility patterns that is useful in guiding on the choice of empirical treatment in resource limited settings.” The findings of this analysis cannot be extended to all resource limited settings, as suggested, rather only other settings with similar geographical, demographic, and social characteristics.2. It would be interesting to include in the introduction how often empiric antibiotic therapy doesn't lead to cleared ear infection in Tanzania. If the data doesn't exist, a hint towards this anecdotally may be useful. This would help set the rationale for the study, that improved understanding of AMR in this setting can inform empiric therapy and lead to less treatment failure.3. A brief description of the hospital site would be useful to orientate the readers. For example, is Muhimbili National Hospital the primary hospital of the region/how large is the region that MNH serves?4. One of the more interesting findings was that 22% of isolates were resistant to ciprofloxacin, given it is the primary topical antibiotic. I feel this could be better highlighted earlier in the results and perhaps in the abstract rather than the last sentence of the results. It is also discussed as though 22% is a low rate of resistance and cipro is still effective. However, these data indicate
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	<p>that might become less true if rates are at 22% and will likely climb.</p> <p>Grammatical/spelling errors Strengths and limitations: Change specie to species Strengths and limitations: Change susceptibility to susceptiblity Strengths and limitations: Change “the present has some limitations,” to “the present study has some limitations:” Introduction: Klebsiella species, the species shouldn't be italicised Introduction: “AST” not defined Methods: Change H. influenza to H. influenzae Methods: Capital E for Enterobacteriaceae Methods: MNH is not spelled out Results: Capital E for Enterobacterales Results: “Resistance towards sulfamethoxazole-trimethoprim was higher among ESBL producers (57-100%) than non-ESBL producers (29-100%).” It is unclear what the range of 57-100% and 29-100% represents Results: “At least 14% of the non-ESBL-PE bacteria were resistant to all the third-generation cephalosporins”. Please give exact numbers: “At least” isn't specific</p>
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REVIEWER	Heward, Elliot University Hospital of South Manchester NHS Foundation Trust
REVIEW RETURNED	09-Jan-2023

GENERAL COMMENTS	<p>This is an interesting manuscript investigation the microbiology and resistance patterns of patients presenting with ear infections in Tanzania. It is well written and well structured. It provides up to date evidence to help guide antimicrobial prescribing strategies in Tanzania. It is suitable for publication after minor revisions.</p> <p>Revisions required:</p> <ul style="list-style-type: none"> - Please make it clear in the abstract and the results from which conditions the positive cultures arose (e.g. OE / CSOM / OM). The reader is made to feel that the majority of microbiological samples arose from patients with otitis externa. However, on review of Figure 2 B it is clear that the majority of specimens arose from patients with CSOM which is a different disease process to otitis externa. - Please define the chronicity of otorrhoea which is used to diagnose CSOM in the methods (e.g. >2 weeks). - Patients with otitis media were also included in the study. Please can the authors specify in the methods the specific type of otitis media which was diagnosed in these cases. It is presumed that these patients have acute otitis media with a perforation as collecting a microbiology specimen from the middle ear without a perforation would require an invasive procedure. Please clarify. - There are 2 acronyms not defined in the introduction and methods (AST & NMH). Please add the full word before the first use of the acronym.
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VERSION 1 – AUTHOR RESPONSE

1st Reviewer comments and Responses

1 The main strength noted after the abstract is “the study has revealed the antimicrobial susceptibility patterns that is useful in guiding on the choice of empirical treatment in resource limited settings.” The findings of this analysis cannot be extended to all resource limited settings, as suggested, rather only other settings with similar geographical, demographic, and social characteristics.

Response:

We acknowledge the valid comment of the reviewer. To respond to this comment, the statement has been rephrased to “The present study reports the common bacterial and fungi etiology of ear infection; importantly, the study has revealed the antimicrobial susceptibility patterns that are useful in guiding the choice of empirical treatment in similar settings with limited resources and comparable geographic, demographic, and social characteristics.” See lines (62-66)

2 It would be interesting to include in the introduction how often empiric antibiotic therapy doesn't lead to cleared ear infection in Tanzania. If the data doesn't exist, a hint towards this anecdotally may be useful. This would help set the rationale for the study, that improved understanding of AMR in this setting can inform empiric therapy and lead to less treatment failure.

Response:

We thank the reviewer for this comment. Indeed, there needs to be more data on the effectiveness of empirical treatment in managing ear infections in Tanzania. However, experience based on the clinic's patient return rate after initial treatment for ear infections, it appears that a considerable number of patients return to the clinic with the same problem. This suggests that relying solely on empirical treatment methods may not be effective in treating ear infections. Hence this warrants further research to investigate the antimicrobial susceptibility patterns of bacteria isolated in ear infections to improve the outcome of ear infections following appropriate empirical treatment. See lines 88-95.

3 A brief description of the hospital site would be useful to orientate the readers. For example, is Muhimbili National Hospital the primary hospital of the region/how large is the region that MNH serves?

Response:

This is a good comment by the reviewer. To address this comment, we have modified one paragraph in the methodology section adding more details regarding Muhimbili National hospital setting and capacity. See lines (106-110).

4 One of the more interesting findings was that 22% of isolates were resistant to ciprofloxacin, given it is the primary topical antibiotic. I feel this could be better highlighted earlier in the results and perhaps in the abstract rather than the last sentence of the results. It is also discussed as though 22% is a low rate of resistance and cipro is still effective. However, these data indicate that might become less true if rates are at 22% and will likely climb.

Responses:

We appreciate the reviewer's feedback. We have highlighted the significance of resistance to ciprofloxacin in the abstract, lines (54-56) and results section in lines 236-238.

Grammatical/spelling errors

Responses:

We appreciate the reviewer's feedback on the grammar and spelling mistakes. The comment has been addressed.

5 Strengths and limitations: Change specie to species

Response:

This spelling error was edited to species. See line 68

6 Strengths and limitations: Change susceptibility to susceptibilty

Response:

This spelling error was edited to susceptibility. See line 64

7 Strengths and limitations: Change “the present has some limitations,” to “the present study has some limitations.”

Response:

This grammar error was corrected. See line 67

8 Introduction: *Klebsiella* species, the species shouldn't be italicised

Response:

The comment has been addressed in line 76

9 Introduction: “AST” not defined

Response:

AST was well spelled out in line 83

10 Methods: Change *H. influenza* to *H. influenza*

Response:

The comment was well addressed in line 148

11 Methods: Capital E for Enterobacteriaceae

Response:

The comment was addressed by capitalizing the letter E in line 173

12 Methods: MNH is not spelled out

Response:

MNH was spelled out in line 106

13 Results: Capital E for Enterobacterales

Response:

The comment was addressed in lines 225

14 Results: “Resistance towards sulfamethoxazole-trimethoprim was higher among ESBL producers (57-100%) than non-ESBL producers (29-100%).” It is unclear what the range of 57-100% and 29-100% represents

Response:

The statement has been rephrased accordingly. See lines 230 - 231.

15 Results: “At least 14% of the non-ESBL-PE bacteria were resistant to all the third-generation cephalosporins”. Please give exact numbers: “At least” isn't specific

Response:

The comment has been addressed in lines 231

Second Reviewer's Comments and Responses.

1 Please make it clear in the abstract and the results from which conditions the positive cultures arose (e.g. OE / CSOM / OM). The reader is made to feel that the majority of microbiological samples arose from patients with otitis externa. However, on review of Figure 2 B it is clear that the majority of specimens arose from patients with CSOM which is a different disease process to otitis externa.

Responses:

We thank the reviewer for this comment. We have clearly described the percentage of positive bacterial culture isolated from individuals with CSOM. See lines 48-49

2 Please define the chronicity of otorrhoea which is used to diagnose CSOM in the methods (e.g. >2 weeks).

Response:

- In the present study, CSOM was diagnosed when there is persistent otorrhea from the ear for at least 3-12 weeks despite appropriate medical treatment or when there is a persistent perforation of the eardrum with otorrhea for more than three months.
- This chronicity of otorrhea distinguishes CSOM from acute otitis media, a short-term middle ear infection with acute onset and rapid resolution.
- We have added this information in the methodology section, lines 134-138.

3 Patients with otitis media were also included in the study. Please can the authors specify in the methods the specific type of otitis media which was diagnosed in these cases. It is presumed that

these patients have acute otitis media with a perforation as collecting a microbiology specimen from the middle ear without a perforation would require an invasive procedure. Please clarify.

Responses:

We acknowledge the comment from the reviewer.

- The type of otitis media frequently diagnosed was chronic suppurative Otitis Media (CSOM), characterized by the oozing of pus or fluid from the middle ear.
- Sample collection did not involve invasive procedures since pus was aseptically collected from the external ear canal. See lines 140-142.

4 There are 2 acronyms not defined in the introduction and methods (AST & NMH). Please add the full word before the first use of the acronym.

Responses:

We appreciate the reviewer for the comment. The acronyms of AST and MNH have been spelled out in lines 83 and 106, respectively.

VERSION 2 – REVIEW

REVIEWER	Taylor, Steven University of South Australia, Infection and Immunity
REVIEW RETURNED	06-Mar-2023

GENERAL COMMENTS	All comments addressed. Congratulations on a great manuscript
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REVIEWER	Heward, Elliot University Hospital of South Manchester NHS Foundation Trust
REVIEW RETURNED	10-Mar-2023

GENERAL COMMENTS	Many thanks for making suitable adjustments following the reviewer's comments. Overall I feel this paper is well written and adds sufficient evidence to the current literature. I would recommend adding a section within the methods section e.g. Reporting Guideline and under this heading state that this manuscript has used the STROBE guideline for cross section studies.
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VERSION 2 – AUTHOR RESPONSE

Reviewer 2 Comments and responses

I would recommend adding a section within the methods section e.g. Reporting Guideline and under this heading state that this manuscript has used the STROBE guideline for cross-section studies.

Response: Thank you for your suggestion. We have added a subsection "Reporting Guideline" within the methods section explicitly stating that this manuscript used the STROBE guidelines for cross-sectional studies (see lines 190 - 198).