

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	A multicenter point prevalence survey of antibiotic use and healthcare associated infections in Ethiopian hospitals
AUTHORS	Fentie, Atalay; Degefaw, Yidnekachew; Asfaw, Getachew; Shewarega, Wendosen; Woldearegay, Mengistab; Abebe, Ephrem; Gebretekle, Gebremedhin

VERSION 1 – REVIEW

REVIEWER	Wendy Thompson, The University of Manchester Faculty of Medical and Human Sciences, Division of Dentistry
REVIEW RETURNED	09-Aug-2021

GENERAL COMMENTS	<p>Thanks for the opportunity to review this excellent and interesting paper. I have only minor comments which I hope will improve its clarity still further.</p> <p>1) Does your study relate only to in-patients? I did not notice reference to outpatient clinics.</p> <p>2) Use of the word 'most' followed by '43.3%' in the first paragraph look strange. I know what you mean but think there might be a better way of writing it (if in deed this figure is important to include at all in this paragraph).</p> <p>3) Were any of the therapeutic or prophylactic antibiotics prescribed for dental conditions/surgery? In other LMICs, we have found this to be a particularly large proportion of overall antibiotic use in hospitals but no mention is made of it here. I wonder whether this is because the data we have includes outpatients and maybe this study relates only to inpatients?</p> <p>4) Ceftriaxone is on the WHO AWaRE 'Watch' list. In the discussion section, it would be useful to draw the reader's attention to the importance of this in addition to talking about it in more general terms as being broadspectrum.</p> <p>5) Funding statement - did I miss this in the paper? How was the study funded?</p>
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REVIEWER	Irit Nachtigall Helios Klinikum Bad Saarow, Infectious Diseases
REVIEW RETURNED	11-Aug-2021

GENERAL COMMENTS	<p>I would like to thank the authors for their informative article, that deals with an important aspect of current medicine. However, I have a few comments on the article</p> <p>Language editing would be usefull, because some sentences are difficult to understand.</p> <p>You mention that 700.000 people that die due to AMR, but a</p>
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	<p>reference for that is missing. Especially since it is difficult to tell whether someone died from or with the pathogen.</p> <p>Methods: How were the hospitals selected, what were the criteria? Figure 1 is somewhat postponed, I can not understand why some of the screened patients were excluded</p> <p>Table 2 1162 Indications were named but the numbers are 887 infections plus 218 surgical prophylaxis and 71, this counts for 1176, what is the reason for this difference</p> <p>I wonder why no primary hospitals were included, that should be discussed. The limitations section is short, since only 10 out of > 400 hospitals and no primary hospitals were picked, this should be discussed there</p>
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REVIEWER	Michael Loftus Monash University, Infectious Diseases
REVIEW RETURNED	19-Aug-2021

GENERAL COMMENTS	<p>A well conducted study using the newly developed WHO PPS in a LMIC setting, with data that can inform clinicians and policy makers.</p> <p>Major comments:</p> <ul style="list-style-type: none"> - Comment in Abstract "Nearly half (45.8%) of the patients were prescribed ceftriaxone and metronidazole" appears to be incorrect. 30.4% of prescriptions were for CTX, and 15.4% of prescriptions were for MTZ, not 30.4% and 15.4% of PATIENTS. In any case, presumably many patients received both agents concurrently (given over half of the patients received >1 antibiotic), so one could not reliably add these percentages even if the denominator was patients and not prescriptions. - Methods section. Unclear how variables were selected for inclusion in the logistic regression model - forward selection? Were any variables included a priori based on previous research? - 'Indications for Antibiotics' section. You have stated that 461 or 39.6% of indications for antibiotics were HCAI. Your denominator in this section appears to be patients (n = 1162) rather than antibiotic prescriptions (n = 2059). However I imagine some patients were prescribed different antibiotics for different indications (e.g. surgical prophylaxis post-surgery, and concurrent treatment of a pre-existing UTI). Are you able to analyze this data with prescriptions as the denominator? (See as example Table 3 of Cai et al 2017, CID - a PPS from Singapore). If not, could this be included as a Limitation? - No Limitations section at all in the Discussion. Potential limitations of this study include: 1) One time point only as PPS, so may not be generalizable (acknowledged in initial 'strengths and limitations' section). 2) Prolonged surgical prophylaxis - it may be that some of these prescriptions had changed from being surgical prophylaxis to being empiric treatment for suspected infection, without this being clearly documented in the notes. This would inflate the rate of prolonged surgical prophylaxis, but underestimate the true rate of HCAI. 3) The reported microbiology may not be representative of the hospital population as a whole. Is there bias determining which patients do/don't get microbiological testing performed? Is it only those who are failing first-line therapy? (Would overestimate rate of AMR)
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	<p>Minor comments:</p> <ul style="list-style-type: none"> - "Retroviral infection" - any reason cannot say "HIV infection" - "Catheterization and intubation history" - this phrasing in Abstract is slightly unclear, this could be interpreted as a combined exposure variable (requiring just one or the other) - Table 1: could some information be removed - e.g. preterm status, malaria treatment history, malarial status? - Table 4: could proportion of patients on antibiotics be ordered from highest % to lowest % (like you have for 'Types of antibiotic prescribed')
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VERSION 1 – AUTHOR RESPONSE

2.	Reviewer 1- Dr. Wendy Thompson	
2.1.	Does your study relate only to in-patients? I did not notice reference to outpatient clinics.	Thank you. As per the WHO PPS methodology, the study included inpatients only. We have clarified this under the eligibility criteria.
2.2.	Use of the word 'most' followed by '43.3%' in the first paragraph look strange. I know what you mean but think there might be a better way of writing it (if in deed this figure is important to include at all in this paragraph).	Thank you for your suggestion. We have now removed this and clarified in the text.
2.3.	Were any of the therapeutic or prophylactic antibiotics prescribed for dental conditions/surgery? In other LMICs, we have found this to be a particularly large proportion of overall antibiotic use in hospitals but no mention is made of it here. I wonder whether this is because the data we have includes outpatients and maybe this study relates	Thank you for this comment and yes antibiotic use is common in dental practice. Given the WHO PPS methodology and study's scope, outpatient settings were excluded from our study (clarified under eligibility criteria in Methods). Dental surgery services are provided primarily in outpatient clinics and thus were not included in the study.

	only to inpatients?	
2.4.	Ceftriaxone is on the WHO AWaRE 'Watch' list. In the discussion section, it would be useful to draw the reader's attention to the importance of this in addition to talking about it in more general terms as being broadspectrum.	Thank you for raising this issue. We now have included a description in the discussion section of the manuscript as <i>“the most widely prescribed antibiotic in this study was the 3rd-generation cephalosporin, ceftriaxone (30.4%) that falls under the WHO watch category of AWaRe classification of antibiotics.”</i>
2.5.	Funding statement - did I miss this in the paper? How was the study funded?	The study was funded by the WHO and commissioned by the Ethiopian Ministry of Health. We now have included language under funding to clarify this: <i>“This multicenter PPS of antibiotic use and HCAs in selected hospitals was commissioned by the Ethiopian Federal Ministry of Health (EFMOH) with the financial and technical assistance of the WHO.”</i>
3.	Reviewer 2: Dr. Irit Nachtigall,	
3.1.	Language editing would be useful, because some sentences are difficult to understand.	Thank you for your suggestion. All authors have thoroughly reviewed the manuscript and made additional edits to improve flow and readability and address identified grammatical and typographic errors.
3.2	You mention that 700.000 people that die due to AMR, but a reference for that is missing. Especially since it is difficult to tell whether someone died from or with the pathogen.	Thank you. Our reference for AMR attributed death is “Reference 3” i.e. “O’Neill J. Antimicrobial Resistance : Tackling a crisis for the health and wealth of nations. 2016. Reference number 3 is cited as a reference.
3.3.	How were the hospitals selected, what were the criteria?	The hospitals were selected purposively based on their readiness to implement the antimicrobial stewardship program, catchment area of service and the sizes. These were also identified by the Ethiopian Ministry of Health as part of its strategic initiatives to serve as first cohort of facilities to implement and strengthen antimicrobial stewardship

		programs. We have included additional clarification under methods.
3.4	Figure 1 is it some what postponed, I can not understand why some of the screened patients were excluded	<p>As per the WHO PPS methodology; patients were excluded from the study if</p> <ul style="list-style-type: none"> ✓ undergoing treatment or surgery and are discharged or expected to be discharged on the same day, or ✓ patients admitted to the ward after 08:00 AM or discharged before on the survey date, <p>We have now clarified this in the method section under subheading of eligibility criteria.</p>
3.5	Table 2 1162 Indications were named but the numbers are 887 infections plus 218 surgical prophylaxis and 71, this counts for 1176, what is the reason for this difference	<p>Thank you for pointing out this error. It was an oversight on our part that 14 patients treated for neutropenic fever (HCAIs) at the same time who were on prophylactic antibiotics were simply considered, as they were on medical prophylaxis by mistake. This makes the number of patients who were on medical prophylaxis 71 and reduced the number of patients who were both on HCAIs plus medical prophylaxis to only “6”. The correct frequency is HCAI + Medical prophylaxis= 20 instead of “6” and, medical prophylaxis alone= 57 instead of “71”. Table 2 has now been updated.</p>
3.6	I wonder why no primary hospitals were included, that should be discussed.	<p>Yes, you are correct we didn't include primary hospitals. Because of the programmatic priorities for the Ethiopian Ministry of Health, the PPS was undertaken only among those hospitals who already started (or demonstrated readiness for) implementation of antimicrobial stewardship program and all were secondary and tertiary hospitals. We acknowledge this as a limitation of the study. We have included more clarification on hospital selection in study setting and design section of the manuscript.</p>
3.7	The limitations section is short, since only 10 out of > 400 hospitals and no primary hospitals were picked, this should be discussed there	<p>Thank you for this comment. We have added a discussion of our study's limitations.</p>

4.0	Reviewer 3: Dr. Michael Loftus	
4.1.	<p>Comment in Abstract "Nearly half (45.8%) of the patients were prescribed ceftriaxone and metronidazole" appears to be incorrect. 30.4% of prescriptions were for CTX, and 15.4% of prescriptions were for MTZ, not 30.4% and 15.4% of PATIENTS. In any case, presumably many patients received both agents concurrently (given over half of the patients received >1 antibiotic), so one could not reliably add these percentages even if the denominator was patients and not prescriptions.</p>	<p>Thank you for your comment. The narrative in the main text was updated to reflect this comment. We have also updated the abstract.</p>
4.2.	<p>Unclear how variables were selected for inclusion in the logistic regression model - forward selection? Were any variables included a priori based on previous research?</p>	<p>Thank you. We used "Entry method" and all the predictive variables in our study were selected based on a priori research work and their prediction significance on the univariable regression analysis.</p> <p>This is because all stepwise techniques are influenced by random variation in the data and so seldom give replicable results if the model is retested. Moreover, type II error is more likely in such models.</p> <p>As you know, when predictors are all completely uncorrelated the order of variable entry has very little effect on the parameters calculated; however, we rarely have uncorrelated predictors and so the method of predictor selection is crucial and stepwise approaches might create lots of problems and we preferred the entry method as most biostatisticians recommended.</p>

		<p>Moreover, to limit number of predictive variables and subsequently avoid a model over fitting problem that could make poor predictions; we performed univariate analysis and variables with $p < 0.25$ were included for our multivariable logistic regression model.</p> <p>References: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7032893/</p> <p>Hence, per recommendations and best practice in existing literature, clinically relevant variables (e.g. length of hospital stay and within 90 days hospitalization history) and variables with p-value < 0.25 in the univariate regression analysis were included in the final multivariable logistic regression model.</p>
4.3.	<p>- 'Indications for Antibiotics' section. You have stated that 461 or 39.6% of indications for antibiotics were HCAI. Your denominator in this section appears to be patients (n = 1162) rather than antibiotic prescriptions (n = 2059). However I imagine some patients were prescribed different antibiotics for different indications (e.g. surgical prophylaxis post-surgery, and concurrent treatment of a pre-existing UTI). Are you able to analyze this data with prescriptions as the denominator? (See as example Table 3 of Cai et al 2017, CID - a PPS from Singapore). If not, could this be included as a Limitation?</p>	<p>Thank you for the comment. We now used number of indications as denominator and revised abstract, table 4 and its description in the manuscript.</p>
4.4.	<p>No Limitations section at all in the Discussion. Potential</p>	<p>Thank you. We have now provided a discussion on limitations</p>

	<p>limitations of this study include: 1) One time point only as PPS, so may not be generalizable (acknowledged in initial 'strengths and limitations' section). 2) Prolonged surgical prophylaxis - it may be that some of these prescriptions had changed from being surgical prophylaxis to being empiric treatment for suspected infection, without this being clearly documented in the notes. This would inflate the rate of prolonged surgical prophylaxis, but underestimate the true rate of HCAI. 3) The reported microbiology may not be representative of the hospital population as a whole. Is there bias determining which patients do/don't get microbiological testing performed? Is it only those who are failing first-line therapy? (Would overestimate rate of AMR)</p>	<p>of our study.</p>
4.5.	<p>Minor comments: - "Retroviral infection" - any reason cannot say "HIV infection"</p>	<p>This comment is well taken, and we now have changed the phrase retroviral infection to HIV infection.</p>
4.6.	<p>- "Catheterization and intubation history" - this phrasing in Abstract is slightly unclear, this could be interpreted as a combined</p>	<p>Thank you for this comment. We now have clarified this both in the abstract and body of manuscript and indicate these as separate variables.</p>

	exposure variable (requiring just one or the other)	
4.7.	- Table 1: could some information be removed - e.g. preterm status, malaria treatment history, malarial status?	Thank you for your comment. Yes, some of the information has been included in the supplementary file
4.8.	- Table 4: could proportion of patients on antibiotics be ordered from highest % to lowest % (like you have for 'Types of antibiotic prescribed')	Thank you for this suggestion. We have now rearranged the ordering from highest to lowest percentage.

VERSION 2 – REVIEW

REVIEWER	Wendy Thompson The University of Manchester Faculty of Medical and Human Sciences, Division of Dentistry
REVIEW RETURNED	20-Nov-2021

GENERAL COMMENTS	Thanks for the modifications which I believe make the paper stronger.
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REVIEWER	Irit Nachtigall Helios Klinikum Bad Saarow, Infectious Diseases
REVIEW RETURNED	20-Nov-2021

GENERAL COMMENTS	many thanks to the authors, all my suggestions were implemented, so from my point of view the manuscript can be published
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REVIEWER	Michael Loftus Monash University, Infectious Diseases
REVIEW RETURNED	28-Nov-2021

GENERAL COMMENTS	<p>Many thanks for incorporating previous suggestions from reviewers</p> <p>Few small comments:</p> <ul style="list-style-type: none"> - In the 'Antibiotics use prevalence and indication' paragraph, duration of treatment is given as a mean. As this could be skewed by a handful of patients on long-term antibiotics, would median (and IQR) be a more appropriate measurement? - 'Prolonged use' of antibiotics is not defined until the Discussion section, should be defined earlier
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VERSION 2 – AUTHOR RESPONSE

2.	Reviewer 3: Dr. Michael Loftus	
2.1	- In the 'Antibiotics use prevalence and indication' paragraph, duration of treatment is given as a mean. As this could be skewed by a handful of patients on long-term antibiotics, would median (and IQR) be a more appropriate measurement?	Thank you for your comment. As per your suggestion, the median and IQR are now provided to describe the antibiotic duration.
2.2.	- 'Prolonged use' of antibiotics is not defined until the Discussion section, should be defined earlier	Thanks for your comment. We have provided definition for prolonged use of surgical prophylaxis (as >24 hours use) in the result section of the manuscript. Please see paragraph three under antibiotics use prevalence and indication sub-heading.