ARTICLE DETAILS

| TITLE (PROVISIONAL) | Emergency Department Antimicrobial Use in a Low-Resource Setting: Results from a Retrospective Observational Study at a Referral Hospital in Liberia |
|---------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| AUTHORS             | Yi, Sojung; Ramachandran, Anu; Epps, Lane; Mayah, Alex; Burkholder, Taylor; Jaung, Michael; Haider, Ahson; Shakpeh, John; Whesseh, Paul; Enriquez, Kayla; Bills, Corey |

VERSION 1 – REVIEW

| REVIEWER           | Tsuzuki, Shinya |
|--------------------|-----------------|
|                    | National Center for Global Health and Medicine |
| REVIEW RETURNED    | 20-Oct-2021 |

GENERAL COMMENTS

This manuscript deals with an important topic and is basically well-structured. However, there are several major concerns which should be more elaborately discussed. I understand the situation in LMIC such as Liberia, then some of challenges due to data quality cannot be resolved and discussed more.

1. The largest concern of the present study is external validity of the results. As you mentioned, this study includes only one hospital. If data from other hospitals in Liberia are not available, how do you validate your results as the representative ones?

2. Pearson chi-square tests were conducted but the results are not available in the manuscript. these results should be demonstrated in Results section and their interpretation should be discussed in Discussion section. First of all, what is the aim of chi-square tests in this study? Is chi-square test appropriate for your aim?

3. The quality of data might impair the value of the study. You described "Given the inconsistent documentation of medication dose, frequency, route and duration, further details of these medications were not included in this study”. Under such circumstances, the name and class of antibiotics prescribed might also be unreliable. Furthermore, the basic information from medical charts might also be unreliable. These concerns about the quality of data used in the study might be critical flaws. What do you think about this issue and how did you validate your data?

| REVIEWER           | Olaru, Ioana D. |
|--------------------|-----------------|
|                    | LSHTM |
| REVIEW RETURNED    | 29-Dec-2021 |
This is an important study describing antibiotic prescribing practices within the emergency department of one large referral hospital from Liberia. Increasing awareness of the high rates of antimicrobial prescribing and its drivers in LMICs are key to planning and implementing antimicrobial stewardship interventions in these settings.

Comments

Methods

1. Please provide more detail on the patient flow at the hospital ED. Were some of the patients described in this study presenting as outpatients (discharged immediately after consultation). Also detail on how prescriptions are made – was it a one-off record in the patient notes or were prescriptions changed during ED admission and would this influence the number of antimicrobials and medicines prescribed

2. The authors should reconsider (or clarify) the definitions for broad-spectrum. For example, ceftriaxone which is prescribed frequently in hospitals in LMICs as a single agent has a broad spectrum of activity.

Results

1. The authors report that 3% of patients were deceased on presentation. Please clarify if these were excluded from the antimicrobials analysis.

2. The majority of patients with malaria were prescribed antimicrobials. Is this because they were treated with antimalarials or did they receive in addition antibacterials? The authors should check the figures for malaria diagnosis and treatment: in Table 4 there were 99 patients who were treated with antimalarials while in Table 3, 115 patients with malaria received antimicrobials.

3. Discuss if there were differences in prescriptions among patients who were admitted and those who were not.

4. Table 2: please clarify in the disposition of patients why the percentages do not add to 100% (was it because of missing data?). Were the patients in whom the ED disposition was discharged, discharged immediately after consultation (outpatients) or were they discharged after some days of admission.

5. Table 3: please clarify what is meant by abdominal infection – is this diarrheal disease or does it include intraabdominal infections like cholecystitis, appendicitis, etc.

Discussion

1. page 10 line 42: lack of diagnostics in general leads to increased antimicrobial prescriptions due to diagnostic uncertainties, lacking microscopes is a very specific example.

VERSION 1 – AUTHOR RESPONSE

Reviewer One

This manuscript deals with an important topic and is basically well-structured. However, there are several major concerns which should be more elaborately discussed. I understand the situation in LMIC such as Liberia, then some of challenges due to data quality cannot be resolved and discussed more.
1. The largest concern of the present study is external validity of the results. As you mentioned, this study includes only one hospital. If data from other hospitals in Liberia are not available, how do you validate your results as the representative ones?
   - Given the lack of comparative data available from Liberia and the fact that our study was single-site, we opted to compare our results to available data from other Low- and Middle-Income Countries (LMICs). Please see Discussion section paragraph two, where average medicines prescribed per encounter are compared to data from Kenya, Nigeria, and Ghana. The fact that our data fall within the ranges calculated in other LMICs supports its validity. However, as mentioned, our external validity is limited by lack of available data from Liberia, and the Discussion section has been expanded to discuss this limitation more fully.

2. Pearson chi-square tests were conducted but the results are not available in the manuscript. These results should be demonstrated in Results section and their interpretation should be discussed in Discussion section. First of all, what is the aim of chi-square tests in this study? Is chi-square test appropriate for your aim?
   - Chi-squared tests were used in this study to evaluate categorical data, including the number of encounters in which antimicrobials were prescribed differed by patient sex, age category, and disposition. The Methods section has been updated to clarify our statistical approach.
   - The results of the chi-squared tests are provided in the Results section under “Indicator 3. Percentage of encounters with an antibiotic prescribed” (as we structured the Results section to reflect the WHO/INRUD indicators). They are also discussed in paragraph six of the Discussion section.

3. The quality of data might impair the value of the study. You described "Given the inconsistent documentation of medication dose, frequency, route and duration, further details of these medications were not included in this study". Under such circumstances, the name and class of antibiotics prescribed might also be unreliable. Furthermore, the basic information from medical charts might also be unreliable. These concerns about the quality of data used in the study might be critical flaws. What do you think about this issue and how did you validate your data?
   - We have made note of the limitations regarding the reliability of the primary data in the Discussion. All studies that rely on chart review as the primary source of data encounter this limitation, as analysis can only be performed on what is documented. Unfortunately, in many low-resource settings, patient charting is used as the primary source of data and cannot be cross-referenced with other records in the hospital. While significant documentation gaps in patients charts do exist, both the names and classes of antibiotics prescribed appeared to be consistent across demographic variables in the paper charts reviewed in our study, leading us to presume that the names of the antibiotics are reliable. The facility-based formulary and suspected stocks were also reviewed to demonstrate there is consistency with provider prescribing practices of medication dose and routes of administration.
Reviewer Two

This is an important study describing antibiotic prescribing practices within the emergency department of one large referral hospital from Liberia. Increasing awareness of the high rates of antimicrobial prescribing and its drivers in LMICs are key to planning and implementing antimicrobial stewardship interventions in these settings.

Methods

1. Please provide more detail on the patient flow at the hospital ED. Were some of the patients described in this study presenting as outpatients (discharged immediately after consultation). Also detail on how prescriptions are made – was it a one-off record in the patient notes or were prescriptions changed during ED admission and would this influence the number of antimicrobials and medicines prescribed.

   • We have added additional details regarding the patient flow and care in the ED:
     ○ “This study includes adult patients (greater than or equal to 18 years old) presenting to and cared for in a single ED. Patients seeking walk-in care are initially evaluated at the hospital triage and then referred based on complaint to an outpatient clinic, the obstetric unit, the pediatric ED, or the adult ED. Only patients referred to and treated in the adult ED were included in this study. After patients are referred to the adult ED for evaluation, their charts are retrieved from medical records. The patient is then evaluated in the ED. Despite pediatric patients occasionally presenting to the adult ED for various reasons, they were excluded from this study.
     ○ Eventual disposition after initial treatment and stabilization may include either discharge or hospitalization. Low acuity complaints are dealt with immediately and the patient is discharged from the ED with prescriptions for medication if needed. Most complaints, however, require more resources from the ED often leading to a prolonged ED stay. Among those patients necessitating admission, the lack of inpatient beds and providers leads to further ED length of stay and continued care management by ED providers.”
   • We have also included additional detail regarding specific prescriptions:
     ○ “Only antibiotics prescribed by and initiated for use in the ED were included. This study did not attempt to detail or describe in-hospital antibiotic use. The patient chart reflected the patient’s complete hospital course and not a static entry at one time period, therefore antibiotics could be changed including the addition of, or eventual discontinuation of, specific treatments depending on the patient’s clinical course. Some antibiotics were changed during the course of the ED stay and contributed to the number of antibiotics prescribed. Often a patient with a prolonged stay in the ED is often noted to be “admitted” to the ED however with care continually managed by ED staff. This study examines all antibiotic prescribing practices within the ED, whether discharged immediately or a prolonged stay.”
2. The authors should reconsider (or clarify) the definitions for broad-spectrum. For example, ceftriaxone which is prescribed frequently in hospitals in LMICs as a single agent has a broad spectrum of activity.
   ● Thank you for this comment. Definitions of “broad-spectrum” were varied in the literature, so we have clarified our definition of broad spectrum as discussed in paragraph seven of the Methods section, with examples.
     ○ “We defined broad spectrum as any antibiotic that acts against a wide range of disease-causing bacteria. These broad-spectrum antibiotics included combinations of penicillins including beta-lactamase inhibitors, third- and fourth-generation cephalosporins, fluoroquinolones and carbapenems. Narrow-spectrum antibiotics were defined as first-generation penicillins, aminoglycosides, metronidazole, or macrolides.”
     ○ Under this categorization, third-generation cephalosporins such as ceftriaxone would be considered “broad-spectrum” despite the frequency of their use.

Results

1. The authors report that 3% of patients were deceased on presentation. Please clarify if these were excluded from the antimicrobials analysis.
   ● Thank you for this comment. As patients deceased on presentation were considered part of the group of patients who died, they were not excluded from the antimicrobial analysis. We have included a comment on how this may have affected our results within the Discussion section.

2. The majority of patients with malaria were prescribed antimicrobials. Is this because they were treated with antimalarials or did they receive in addition antibacterials? The authors should check the figures for malaria diagnosis and treatment: in Table 4 there were 99 patients who were treated with antimalarials while in Table 3, 115 patients with malaria received antimicrobials.
   ● Thank you for this comment. In Table 3, 115 patients diagnosed with malaria received antimicrobials, which includes both antimalarials and antibiotics. In Table 4, 99 patients in total received antimalarials. This suggests that some patients with a diagnosis of malaria received both antimalarial prescriptions and antibiotic prescriptions. This medication order has been clarified as an interesting observation in the Results section.

3. Discuss if there were differences in prescriptions among patients who were admitted and those who were not.
   ● This study examines all antibiotic prescribing practices within the ED, whether the patient was discharged immediately, had a prolonged ED stay or was admitted to an inpatient service. Antibiotic prescription patterns were not stratified by eventual disposition as the care received in the ED and medications prescribed by ED providers were independent of hospital course for admitted patients.

4. Table 2: please clarify in the disposition of patients why the percentages do not add to 100% (was it because of missing data?). Were the patients in whom the ED disposition was
discharged, discharged immediately after consultation (outpatients) or were they discharged after some days of admission.

- ED disposition data was only available for 862 of the 1083 total patients, which is why the percentages do not add up to 100%. The Results section has been updated to explain this discrepancy more thoroughly:
  - “Disposition information was available for 868 of the 1082 patients (80.2%), of which 53.2% (n=575) were discharged from the ED and 9.8% (n=106) were admitted to the inpatient wards. For patients with an ED disposition of “discharged”, they were discharged directly from the ED after initial evaluation.”

5. Table 3: please clarify what is meant by abdominal infection – is this diarrheal disease or does it include intraabdominal infections like cholecystitis, appendicitis, etc.
   - We have clarified this as an addendum to Table 3:
     - “Abdominal Infection includes diarrheal illnesses (eg. enteritis, colitis) and presumptive acute intra abdominal infections (eg. presumed cholecystitis, appendicitis, or diverticulitis).”

Discussion

1. page 10 line 42: lack of diagnostics in general leads to increased antimicrobial prescriptions due to diagnostic uncertainties, lacking microscopes is a very specific example.
   - Thank you for this comment. Microscopes were one of the examples used in the paper cited, but we have removed it to keep the discussion more general.

**VERSION 2 – REVIEW**

| REVIEWER | Tsuzuki, Shinya  
National Center for Global Health and Medicine |
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| REVIEW RETURNED | 18-Feb-2022 |

| GENERAL COMMENTS | There are many flaws in their methods and the way to describe the results even after revision. I could not understand why the authors defined this study as prospective one. Table 2 was very confusing. What is 4.995.00%? Why the number of “died” patients became larger than the “Total” number of cases? If the authors would like to write p value, they have to explain what kind of statistical analysis derived these p values. According to their results, the rate of antibiotics prescription was different among ED disposition. However, chi-square test reveals only the existence of difference. It would be better to describe which disposition different from any other ones then chi-square test is not sufficient. Multivariable analysis also might be considered in order to what kind of factors influenced the prescription rate. In other words, the authors should include someone who is more familiar with data analysis. |
| REVIEWER | Olaru, Ioana D. |
VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Dr. Shinya Tsuzuki, National Center for Global Health and Medicine, Nagasaki University

Comments to the Author:

There are many flaws in their methods and the way to describe the results even after revision.

- We understand that this dataset indeed includes incomplete data and have communicated these limitations throughout our manuscript. Regarding the methods, we have updated and enhanced our Methods section to include the specifics of our statistical analysis. Please see the subheading Statistical Analysis.
- Given the general nature of the concern, we have attempted to clarify the methodological approach as much as possible in the abstract and text of the manuscript. Specifically, this study was a retrospective review of charts initially gathered prospectively and was done as part of a larger quality improvement project of patients presenting to a low-resource emergency care setting in a low-income country. All data was extracted from chart review, and as such is limited by clinician documentation, though cross referenced with known hospital based antibiotic formularies.

I could not understand why the authors defined this study as prospective one.

- We have clarified our methods to address this confusion. Data were collected prospectively from paper medical charts as part of a larger quality improvement project. However, by strict definition, this study is a retrospective, observational study of antimicrobial prescription patterns among patients presenting to the adult ED at Redemption Hospital, Liberia.

Table 2 was very confusing. What is 4.995.00%? Why the number of "died" patients became larger than the "Total" number of cases?

- When the table was copied over in the last editorial process, the numbers were copied incorrectly, which is why they appear not to add up. We apologize for this oversight and the confusion that it may have caused. The numbers have been checked again and corrected in this final, re-submitted version of the manuscript. Please see Table 2 for more clarification. We have also formatted each of the tables for consistency, though defer to the BMJ Open copyeditors.
To clarify, the total number of patients with a disposition is N= 898. A total of 133 patients died, and not greater than the total number of patients in the sample.

If the authors would like to write p value, they have to explain what kind of statistical analysis derived these p values.

- P-values were calculated from Pearson chi-square tests for discrete, categorical data. The chi-square tests were used to assess whether antimicrobial ordering practices differed by patient sex, age, and disposition. A p-value <0.05 was considered statistically significant. Subsequent multivariable modeling (presented as Odds Ratios and 95% Confidence Intervals), was attempted to explore the association between whether patients received any antibiotic and their demographic and clinical characteristics. This clarification has been included in the Statistical Analysis subsection of the Methods section, as well as noted in the tables.

According to their results, the rate of antibiotics prescription was different among ED disposition. However, chi-square test reveals only the existence of difference. It would be better to describe which disposition different from any other ones then chi-square test is not sufficient.

- We compared the proportion of antibiotics for admitted vs discharged patients, and not all categories of disposition, as was suggested by Reviewer 2 in the first review. A notation in Table 2 was provided specifically indicating this change, which was likely lost in the formatting. The proportion of patients that received antibiotics among the admitted group was 88.7%, and among the discharged group was 71.5%. The difference between these two groups was statistically significant.
- We have provided additional language that underscores that the comparison was only made between these two groups in the manuscript text, as well as what was previously written in the table. We were intentional in excluding AMA and transfers given that their ED care was not completely. We also excluded those that died from this analysis, given the large proportion of dead before arrivals, and the fact that all those dead before arrival received no antibiotics, consistent with their status.

Multivariable analysis also might be considered in order to what kind of factors influenced the prescription rate. In other words, the authors should include someone who is more familiar with data analysis.

- While multivariable analysis is an important tool and was considered in this study, there are two reasons why it was not an appropriate tool in this case. First, it does not fit within the primary aim of the paper, which is to compare antibiotic use to known measures of quality as purported by the WHO. Second, and perhaps more importantly, even if it were an aim of the paper, the data, and the overwhelmingly high rates of antibiotic use across multiple variables, regardless of patient demography and clinical characteristics, make multivariable analysis less useful. Aside from disposition, there were no clear clinical characteristics that were different at the univariable level. We have made note of this in the text.
We appreciate that we may be missing an opportunity for further analysis and have consulted with a biostatistician. In general, they agree with the methodology and use of chi-square analysis for comparisons among discrete (non-linear) data. All other data, as it relates to comparisons with known WHO measures of quality, are presented as numbers and associated percentages.