

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

## ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Antibiotic prescribing practice using WHO Access, Watch, and Reserve classification and its determinants among outpatient prescriptions dispensed to elderly population in six community chain pharmacies in Asmara, Eritrea: a cross-sectional study
<b>AUTHORS</b>	Abdu, Nuru; Idrisnur, Saleh; Tewelde, Tomas; H.Tesfamariam, Eyasu

## VERSION 1 – REVIEW

<b>REVIEWER</b>	Tagashira , Y. Tokyo Medical and Dental University Hospital, Infectious Diseases
<b>REVIEW RETURNED</b>	14-Mar-2024

<b>GENERAL COMMENTS</b>	<p>Summary:</p> <p>This study extracted prescription data for elderly individuals aged 65 and above from six pharmacies in urban areas of Eritrea and analyzed the frequency of antibiotic prescriptions and the types of antibiotics prescribed based on the WHO's AWaRe classification. By revealing the prescription practices in each country, differences at various levels such as national and continental become apparent, potentially leading to strategies for combatting antimicrobial resistance. Elderly individuals, often complicated with multiple underlying conditions, are particularly concerning in terms of infection susceptibility and may have a lower threshold for antibiotic prescription. However, due to the high frequency of adverse effects associated with antibiotics and the increased risk of antimicrobial resistance and CDI, it is crucial to use them appropriately. This study's data could be vital in considering approaches to ensure appropriate antibiotic use. On the other hand, the acquired data are limited, and there are significant deficiencies in the method and results, requiring substantial revisions.</p> <p>Major Comments:</p> <p>Introduction:</p> <p>1, Could you specify how Eritrea's action plan restricted "antibiotic dispensing without a prescription"? Whether it was a complete restriction or conditional limitation, please provide details, either in the Method section or elsewhere.</p> <p>2, I recommend using consistent terminology throughout the paper, such as "outpatient oral antibiotic prescriptions for the elderly population." You may consider using abbreviations for ease of reference.</p> <p>Methods:</p>
-------------------------	--

	<p>1, If the study design is cross-sectional, expressions like "analytical" or "retrospectively" should be removed. Given the examination of one month's prescription data, a cross-sectional study seems appropriate.</p> <p>2, The information on lines 99-101 of page 5 does not seem to relate to this study. Consider either adding clarification or removing it.</p> <p>3, Line 104 on page 5 seems to pertain to information about the study population, referring to individuals rather than prescriptions.</p> <p>4, How was the data collected and from which database?</p> <p>5, Is polypharmacy defined as the simultaneous prescription of five or more drugs? It is commonly understood that polypharmacy involves the concurrent use of five or more medications, for example anti-hypertensive drug, drugs of diabetes. However, to define polypharmacy in this study regarding antibiotic prescriptions, information on medications other than antibiotics is needed. Whether short-term medications for symptom relief are included in polypharmacy is subject to debate.</p> <p>6, Since the collected data are limited, detailed explanations of each variable may be beneficial. For instance, clarification regarding the types and definitions of prescriber qualifications. Knowing the specialization of specialists might provide valuable insights.</p> <p>Results:</p> <p>1, Inquiring about the definition of polypharmacy in the Method section seems unnecessary if it accounts for only 1.6% of the total.</p> <p>2, Please reorganize lines 155-158 on page 8 for clarity. Additionally, specify the number of prescriptions containing multiple antibiotics and the number containing a single antibiotic in each prescription, followed by the total number of prescriptions and antibiotics prescribed.</p> <p>3, Line 160 on page 8 should include actual numbers. Results should be presented with both percentages and actual numbers for accuracy. Please double-check the entire results section.</p> <p>4, What are the numbers of physicians and nurse practitioners mentioned on line 165 of page 8? Providing the denominator would be useful.</p> <p>5, Please include units for the percentages in Table 1. Consistency with Table 2 formatting would enhance readability, for example: 322 (30.3%).</p> <p>6, It is stated that "14.1% of the antibiotics were ungrouped in these three AWaRe classification categories." Could you specify the types of antibiotics included?</p> <p>7, Are you analyzing factors influencing antibiotic prescriptions and those associated with "watch" antibiotics? Please clarify in the Method section.</p> <p>8, Is there data available on the annual experience or years of practice of prescribers? In developed countries, prescriber</p>
--	---

	<p>experience is known to correlate with inappropriate antibiotic prescribing.</p> <p>9, Is there information available on the diagnoses for prescribed antibiotics?</p> <p>Discussion:</p> <p>10, Please aggregate comparisons with other countries regarding prescription practices.</p> <p>11, Line 212-214 on page 12 should specify what needs caution.</p> <p>12, Is ceftriaxone suitable for discussion citation on line 219 of page 13, considering it is intravenous antibiotic?</p> <p>13, The discussion on line 236 of page 13 suggests that while physicians may have knowledge, they may not always prescribe antibiotics appropriately. Variations based on experience and specialty are known. Although there may be differences in patient backgrounds, the lack of data in this study could be a limitation.</p> <p>14, Please summarize limitations appropriately.</p> <p>Minor Comments:</p> <p>1, The last sentence of the Results section in the Abstract appears incomplete. Please either remove it or provide additional information. Additionally, conclusions should be stated in the Conclusion section.</p> <p>2, On page 4, line 74, instead of "elderly," should it be "elderly population"?</p> <p>3, Lines 74-76 on page 4 require re-evaluation and revision for clarity. What does "Immunosenescence" refer to?</p> <p>4, Consistency in terminology regarding the elderly population may improve readability.</p> <p>5, Please include references for lines 84-85 on page 4.</p> <p>6, "To the best of the authors' knowledge" on line 89 of page 4 should be removed.</p> <p>7, On page 5, line 92, consider changing "practices" regarding prescribing practices due to the limited information available.</p> <p>8, On page 5, line 97, change "com-munity" to "community."</p> <p>9, On page 7, line 148, please explain the abbreviation for IQR here.</p> <p>10, On page 8, line 159, replace "ones" with "antibiotics."</p> <p>11, Is "nurse prescriber" on line 197 of page 11 synonymous with "nurse practitioner"?</p> <p>12, Is 35.8 on line 206 of page 12 a percentage?</p>
--	--

	13, On page 12, line 215, should it be "elderly population" instead of "geriatrics"?
--	--

<b>REVIEWER</b>	Kim , Christine Centers for Disease Control and Prevention
<b>REVIEW RETURNED</b>	03-Apr-2024

<b>GENERAL COMMENTS</b>	<p>Thank you for the opportunity to review this important analysis in Ethiopia on antibiotic prescribing and application of the WHO AWaRE classification scheme. My specific comments are below. This is an important manuscript but I hope the authors will consider strengthening their analysis by reconsidering their methodological approach.</p> <p>General comments:</p> <ul style="list-style-type: none"> <li>• I recommend specifying “older adults aged 65 years and above” and consistently using “older adults” as it was defined, rather than descriptive terms such as “elderly” or “geriatric” for “old” people which are not specific by age for research purposes.</li> </ul> <ul style="list-style-type: none"> <li>• Abstract <ul style="list-style-type: none"> <li>o Line 23: Should this be “ambulatory care patients” ?</li> <li>o Line 24: Please clarify the design further.</li> <li>o Line 26: Prescriptions cannot be described as elderly. Please edit to “Outpatient prescriptions dispensed to older adults aged 65 years and above”</li> <li>o Results: Please refrain from describing the prescriptions as elderly.</li> <li>o Line 33: Space needed between 95% and CI – please consider doing an overall copy-edit of the manuscript.</li> </ul> </li> <li>• Background: <ul style="list-style-type: none"> <li>o Line 65: Please edit to “US Centers for Disease Control and Prevention (CDC)”</li> <li>o Line 67: Who are AMR collaborators? Either exclude or describe more appropriately.</li> <li>o Lines 72-79: “Geriatrics”, “Older adults”, and “Elderly” are all used in this paragraph it is unclear what age ranges these people are across these studies. Please define.</li> <li>o Line 89: first person language is preferred.. “To the best of our knowledge...”</li> </ul> </li> <li>• Methods: <ul style="list-style-type: none"> <li>o Line 97: Authors could probably rephrase as “retrospective cross-sectional study”...</li> <li>o Line 104: Prescriptions cannot be described as elderly. Please edit to “Outpatient prescriptions dispensed to older adults aged 65 years and above”</li> <li>o Line 115: Is this encounter with the pharmacy or encounter with their healthcare provider/clinician? “The percentage of encounters with antibiotics prescribed was calculated by dividing the number of encounters with antibiotics by the total number of encounters surveyed, multiplied by 100”.. Is this percentage of encounters with antibiotics prescribed the definition of “prescribing practice”?</li> <li>o Line 120: Is prescribing practice a %? For prescription of a watch antibiotic – compared to no prescription or compared to any other antibiotic prescription?</li> <li>o Line 121: Please specify patient age, patient sex, etc..</li> <li>o Please move the quality assurance paragraph under the data collection section.</li> <li>o Line 136: Please ensure both statistical software programs are properly cited.</li> </ul> </li> </ul>
-------------------------	---

	<p>o It is not recommended practice to base the multivariate model on variables significant in bivariate analyses alone. There are documented issues with this methodology including problems with omitted variable bias, multicollinearity, and p-hacking. It's recommended that the authors consider a conceptual model or theoretical basis of the relationships between their independent variables and dependent variable. The current approach may be omitting an important variable to control for in the model just because it is insignificant in bivariate analyses. For instance, age and sex were both excluded from the first multivariate model, but studies in many countries have shown that even among older adults &gt;65 years of age, oldest age groups around &gt;75 years have higher antibiotic prescribing; studies have also shown prescribing tends to be higher among females possibly due to healthcare seeking behavior or for increased susceptibility to conditions such as UTI, which is acknowledged in the discussion section, but not presented in the model.</p> <ul style="list-style-type: none"> <li>• Results</li> </ul> <p>o What is the purpose of having both Table 1 and Table 3? It would be more informative to combine these tables and have Table 2 as your table 1 and include patient characteristics.</p>
--	--

### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Y. Tagashira, Tokyo Medical and Dental University Hospital

Comments to the Author:

Summary:

This study extracted prescription data for elderly individuals aged 65 and above from six pharmacies in urban areas of Eritrea and analyzed the frequency of antibiotic prescriptions and the types of antibiotics prescribed based on the WHO's AWaRe classification. By revealing the prescription practices in each country, differences at various levels such as national and continental become apparent, potentially leading to strategies for combatting antimicrobial resistance. Elderly individuals, often complicated with multiple underlying conditions, are particularly concerning in terms of infection susceptibility and may have a lower threshold for antibiotic prescription. However, due to the high frequency of adverse effects associated with antibiotics and the increased risk of antimicrobial resistance and CDI, it is crucial to use them appropriately. This study's data could be vital in considering approaches to ensure appropriate antibiotic use. On the other hand, the acquired data are limited, and there are significant deficiencies in the method and results, requiring substantial revisions.

Major Comments:

Introduction:

1, Could you specify how Eritrea's action plan restricted "antibiotic dispensing without a prescription"? Whether it was a complete restriction or conditional limitation, please provide details, either in the Method section or elsewhere.

Response: Thank you for your interesting comment. The national action plan for antimicrobial resistance completely restricted the dispensing of antibiotics without a legal prescription written from a health facility.

2, I recommend using consistent terminology throughout the paper, such as "outpatient oral antibiotic prescriptions for the elderly population." You may consider using abbreviations for ease of reference.

Response: Thank you for the comment. In this study, a total of 2,680 outpatient prescriptions for the elderly population were analyzed. The prescriptions contained antibiotics and/or other medications

apart from an antibiotic. Thus, where applicable I used the terminology “outpatient prescriptions for the elderly population” throughout the paper.

Methods:

1, If the study design is cross-sectional, expressions like "analytical" or "retrospectively" should be removed. Given the examination of one month's prescription data, a cross-sectional study seems appropriate.

Response: Comment well noted. Expressions like "analytical" are removed from the revised manuscript. Besides, to add “retrospective” in the study design is worthwhile given the outpatient prescriptions dispensed to the elderly population were collected retrospectively.

2, The information on lines 99-101 of page 5 does not seem to relate to this study. Consider either adding clarification or removing it.

Response: Thank you for the comment. The information on lines 99-101 of page 5 is removed from the revised manuscript. Moreover, additional information on the community pharmacies (“Moreover, the community chain pharmacies receive and fill prescriptions ordered from a number of health facilities including national referral hospitals”) is added [Page no: 5; line number: 99-101].

3, Line 104 on page 5 seems to pertain to information about the study population, referring to individuals rather than prescriptions.

Response: Thank you for the comment. The information about the study population is modified as “The study population included all elderly outpatient prescriptions for the elderly population (aged 65 and above) dispensed in the study areas during the data collection period” in the revised manuscript.

4, How was the data collected and from which database?

Response: Comment well noted. Data were collected retrospectively from a hand-written outpatient prescriptions for the elderly population. Database was not used for retrieval of data.

5, Is polypharmacy defined as the simultaneous prescription of five or more drugs? It is commonly understood that polypharmacy involves the concurrent use of five or more medications, for example anti-hypertensive drug, drugs of diabetes. However, to define polypharmacy in this study regarding antibiotic prescriptions, information on medications other than antibiotics is needed. Whether short-term medications for symptom relief are included in polypharmacy is subject to debate.

Response: Thank you for the comment. In this study, polypharmacy was defined as the simultaneous prescription of five or more drugs. As the outpatient prescriptions contained an antibiotic and/or other medicines, information on all kinds of prescriptions were incorporated to define polypharmacy.

Moreover, polypharmacy was detected in 1.6% of all the prescriptions. All the prescriptions with polypharmacy did not contain medications for short-term use.

6, Since the collected data are limited, detailed explanations of each variable may be beneficial. For instance, clarification regarding the types and definitions of prescriber qualifications. Knowing the specialization of specialists might provide valuable insights.

Response: Comment well noted. Clarification on the types and definitions of prescriber qualification in the Eritrean healthcare system is provided in the method section [Page no: 6; line number: 118-121].

Moreover, specialization of specialists are provided in the result section [Page no: 8; line number: 157-158].

Results:

1, Inquiring about the definition of polypharmacy in the Method section seems unnecessary if it accounts for only 1.6% of the total.

Response: From the literature reviews that we have obtained, polypharmacy is one of the variables that affect antibiotic prescription and Watch Category Antibiotic prescription. The comment seems sound, however, we also need to be aware of the omitted variable bias which might exist while modeling. Actually, one of the conducive inputs in making analysis is adequate study population or the prescriptions (n=2700), which helps us not to neglect the results in the logistic regression even though the prevalence of polypharmacy is 1.6%.

2, Please reorganize lines 155-158 on page 8 for clarity. Additionally, specify the number of prescriptions containing multiple antibiotics and the number containing a single antibiotic in each prescription, followed by the total number of prescriptions and antibiotics prescribed.



Response: Thank you for the comment. Statements on page 8; Line 155-158 are reorganized in the revised manuscript. Besides, the number of prescriptions containing multiple antibiotics and the number containing a single antibiotic in each prescription, followed by the total number of prescriptions and antibiotics prescribed are specified clearly with the addition of Table 1. Please see the changes in the revised manuscript.

3, Line 160 on page 8 should include actual numbers. Results should be presented with both percentages and actual numbers for accuracy. Please double-check the entire results section.

Response: Comment well noted. Results are presented in both frequencies and percentages as necessary.

4, What are the numbers of physicians and nurse practitioners mentioned on line 165 of page 8? Providing the denominator would be useful.

Response: Thank you for the comment. The numbers of physicians and nurse practitioners are indicated in the revised manuscript.

5, Please include units for the percentages in Table 1. Consistency with Table 2 formatting would enhance readability, for example: 322 (30.3%).

Response: Thank you for the comment. As Table 1 and table 3 are similar, Table 1 is omitted and Table 3 will be table 2 instead.

6, It is stated that "14.1% of the antibiotics were ungrouped in these three AWaRe classification categories." Could you specify the types of antibiotics included?

Response: Thank you for the comment. The type of antibiotics which were uncategorized are provided in the table below. This table is also provided as an online supplemental file in the revised manuscript.

Name of antibiotic	Frequency	Percent
Chloramphenicol eye drop	61	40.7
Mebendazole	17	11.3
Neomycin/Bacitracin Ointment	15	10.0
Chloramphenicol eye ointment	9	6.0
Clotrimazole cream	8	5.3
Griseofulvin	6	4.0
Miconazole cream	6	4.0
Clotrimazole	5	3.3
Tetracycline eye ointment	5	3.3
Ciprofloxacin eye drop	3	2.0
Fluconazole	3	2.0
Silver cream	3	2.0
Benzoic acid/Salicylic acid	2	1.3
Dexamethasone/Chloramphenicol eye drop	2	1.3
Gentamicin eye drop	2	1.3
Chloramphenicol ear drop	1	.7
Clotrimazole ear drop	1	.7
Clotrimazole vaginal suppository1	1	.7
Total	150	100.0

7, Are you analyzing factors influencing antibiotic prescriptions and those associated with "watch" antibiotics? Please clarify in the Method section.

Response: Comment well noted. Associates of antibiotic prescribing prescription and 'watch' antibiotic prescription were assessed primarily using bivariate logistic regression. Furthermore, factors that were significant at bivariate were retained for multivariable logistic regression and adjusted odds ratios (AORs) were computed to assess the determinants. This information is already indicated in the 'statistical analysis' section.

8, Is there data available on the annual experience or years of practice of prescribers? In developed countries, prescriber experience is known to correlate with inappropriate antibiotic prescribing.

Response: Your comment seems sound. However, data regarding year of practice of prescribers were not present in the prescriptions. This was one of the limitation of the current study and indicated as a limitation in the revised manuscript.

9, Is there information available on the diagnoses for prescribed antibiotics?

Response: Information on the diagnosis for prescribed antibiotics cannot be obtained from the outpatient prescriptions. This was indicated as a limitation in the manuscript.

Discussion:

10, Please aggregate comparisons with other countries regarding prescription practices.

Response: Thank you for the comment. The main objective of the study was to assess the antibiotic prescription practices. Findings of our study (antibiotic practice with regard to percentage of prescriptions with antibiotics and the WHO AWaRe classification system and determinants of antibiotic prescription) are compared with findings from developed and developing countries.

11, Line 212-214 on page 12 should specify what needs caution.

Response: Comment well noted. During comparison of our findings with other similar studies (percentage of antibiotic prescription), the study population differs that is, our study included outpatient prescriptions dispensed to elderly population whereas other studies included prescriptions dispensed to all age categories. Thus, caution should be exercised during result comparison of these studies.

12, Is ceftriaxone suitable for discussion citation on line 219 of page 13, considering it is intravenous antibiotic?

Response: Thank you for the comment. The comparison of our findings (most commonly prescribed antibiotic) with ceftriaxone is omitted in the revised manuscript.

13, The discussion on line 236 of page 13 suggests that while physicians may have knowledge, they may not always prescribe antibiotics appropriately. Variations based on experience and specialty are known. Although there may be differences in patient backgrounds, the lack of data in this study could be a limitation.

Response: Your comment seems very sound. One of the limitation of the study was the lack of data obtained from the outpatient prescriptions. Owing to more years of studies, extensive theoretical and practical sessions on a range of infectious diseases, specialists are more knowledgeable in medical area than nurse practitioners thus can contribute to the increased antibiotic prescriptions. However, this finding does not have any relationship with appropriateness of the prescribed antibiotics. Further research is required to address such issue.

14, Please summarize limitations appropriately.

Response: Comment well noted. The possible limitations resulted from the study are rehearsed and included in the revised manuscript.

Minor Comments:

1, The last sentence of the Results section in the Abstract appears incomplete. Please either remove it or provide additional information. Additionally, conclusions should be stated in the Conclusion section.

Response: Thank you for notifying this issue. Amendments are made in the revised manuscript.

2, On page 4, line 74, instead of "elderly," should it be "elderly population"?

Response: Thank you for the comment. Amendments are made in the revised manuscript.

3, Lines 74-76 on page 4 require re-evaluation and revision for clarity. What does "Immunosenescence" refer to?

Response: Comment well noted. "Immunosenescence" refers to weakened immunity. The statement is revised for clarity in the revised manuscript.

4, Consistency in terminology regarding the elderly population may improve readability.

Response: This is an important comment. Consistency in the terminology 'elderly population' is assured throughout the revised manuscript.

5, Please include references for lines 84-85 on page 4.

Response: Comment well noted. For the mentioned statement, citation is added in the revised manuscript.



6, "To the best of the authors' knowledge" on line 89 of page 4 should be removed.

Response: Comment well noted. The phrase is removed in the revised manuscript.

7, On page 5, line 92, consider changing "practices" regarding prescribing practices due to the limited information available.

Response: Thank you for the comment. Amendments are made in the revised manuscript.

8, On page 5, line 97, change "com-munity" to "community."

Response: Thank you for notifying this typos error. Amendment on the correction is made in the revised manuscript.

9, On page 7, line 148, please explain the abbreviation for IQR here.

Response: Comment well noted. Full form for IQR is provided in the revised manuscript.

10, On page 8, line 159, replace "ones" with "antibiotics."

Response: Comment well noted. The term "ones" is replaced with "antibiotics" in the revised manuscript.

11, Is "nurse prescriber" on line 197 of page 11 synonymous with "nurse practitioner"?

Response: Thank you for the comment. "nurse prescriber" and "nurse practitioner" can be used interchangeably.

12, Is 35.8 on line 206 of page 12 a percentage?

Response: Thank you for notifying the issue. 35.8 is a percentage thus a percent symbol is added after it in the revised manuscript.

13, On page 12, line 215, should it be "elderly population" instead of "geriatrics"?

Response: Comment well noted. The term "elderly population" is used instead of "geriatrics" in the revised manuscript.

Reviewer: 2

Dr. Christine Kim, Centers for Disease Control and Prevention

Comments to the Author:

Reviewer notes

Thank you for the opportunity to review this important analysis in Ethiopia on antibiotic prescribing and application of the WHO AWaRE classification scheme. My specific comments are below. This is an important manuscript but I hope the authors will consider strengthening their analysis by reconsidering their methodological approach.

General comments:

- I recommend specifying "older adults aged 65 years and above" and consistently using "older adults" as it was defined, rather than descriptive terms such as "elderly" or "geriatric" for "old" people which are not specific by age for research purposes.

Response: Thank you for an important comment. The target population in the study was indicated clearly so as to avoid confusion on the definition of elderly with respect to age ("The study population included all elderly outpatient prescriptions dispensed to the elderly population (aged 65 and above) dispensed in the study areas during the data collection period"). The consistently used the term "elderly population" throughout the manuscript.

- Abstract

- o Line 23: Should this be "ambulatory care patients" ?

Response: Comment well noted. The term "elderly ambulatory patients" is changed to "outpatient prescriptions dispensed to the elderly population" in the revised manuscript.

- o Line 24: Please clarify the design further.

Response: Comment well noted. The design is clarified further while avoiding details to comply with the length of abstract.

- o Line 26: Prescriptions cannot be described as elderly. Please edit to "Outpatient prescriptions dispensed to older adults aged 65 years and above"

Response: Comment well taken. Amendment is made in the revised manuscript.

- o Results: Please refrain from describing the prescriptions as elderly.

Response: Thank you for the comment. Amendment is made in the revised manuscript.

o Line 33: Space needed between 95% and CI – please consider doing an overall copy-edit of the manuscript.

Response: Thank you for the comment. Amendments are made throughout the revised manuscript.

• Background:

o Line 65: Please edit to “US Centers for Disease Control and Prevention (CDC)”

Response: Thank you for the comment. Amendment is made in the revised manuscript.

o Line 67: Who are AMR collaborators? Either exclude or describe more appropriately.

Response: Thank you for notifying this issue. The term ‘AMR collaborators’ is removed and replaced with ‘Murray et al.’ in the revised manuscript.

o Lines 72-79: “Geriatrics”, “Older adults”, and “Elderly” are all used in this paragraph it is unclear what age ranges these people are across these studies. Please define.

Response: Thank you for the comment. “Elderly population” is consistently used in the revised manuscript. The age ranges across all the studies are 65 years and above (similar with that of our study).

o Line 89: first person language is preferred.. “To the best of our knowledge...”

Response: Comment well noted. “To the best of our knowledge...” is removed in the revised manuscript.

• Methods:

o Line 97: Authors could probably rephrase as “retrospective cross-sectional study”...

Response: Comment well noted. The term “retrospective cross-sectional study” is used in the revised manuscript.

o Line 104: Prescriptions cannot be described as elderly. Please edit to “Outpatient prescriptions dispensed to older adults aged 65 years and above”

Response: Comment well noted. Amendment is made in the revised manuscript.

o Line 115: Is this encounter with the pharmacy or encounter with their healthcare provider/clinician?

“The percentage of encounters with antibiotics prescribed was calculated by dividing the number of encounters with antibiotics by the total number of encounters surveyed, multiplied by 100”.. Is this percentage of encounters with antibiotics prescribed the definition of “prescribing practice”?

Response: Thank you for an important comment. The encounter is with the pharmacy. Moreover, the percentage of encounters with antibiotics prescribed is not the definition of “prescribing practice”.

Antibiotic prescribing practice was evaluated by considering two elements: percentage of encounters with antibiotics and antibiotic prescription with respect to the WHO AWaRe classification system recommendations.

o Line 120: Is prescribing practice a %? For prescription of a watch antibiotic – compared to no prescription or compared to any other antibiotic prescription?

Response: Thank you for an important comment. Prescribing practice is not indicated with %.

Antibiotic prescribing practice was evaluated by considering two elements: percentage of encounters with antibiotics and antibiotic prescription with respect to the WHO AWaRe classification system recommendations.

o Line 121: Please specify patient age, patient sex, etc..

Response: Comment well noted. Patient age and sex are already specified in the result section of the manuscript.

o Please move the quality assurance paragraph under the data collection section.

Response: Comment well noted. The Data collection tool and variable measurement section and the quality assurance sections are indicating different contents thus I prefer to keep the sections as they are with great appreciation on your comments.

o Line 136: Please ensure both statistical software programs are properly cited.

Response: Comment well noted. The statistical software programs are cited in the revised manuscript.

o It is not recommended practice to base the multivariate model on variables significant in bivariate analyses alone. There are documented issues with this methodology including problems with omitted variable bias, multicollinearity, and p-hacking. It’s recommended that the authors consider a

conceptual model or theoretical basis of the relationships between their independent variables and dependent variable. The current approach may be omitting an important variable to control for in the model just because it is insignificant in bivariate analyses. For instance, age and sex were both excluded from the first multivariate model, but studies in many countries have shown that even among older adults >65 years of age, oldest age groups around >75 years have higher antibiotic prescribing; studies have also shown prescribing tends to be higher among females possibly due to healthcare seeking behavior or for increased susceptibility to conditions such as UTI, which is acknowledged in the discussion section, but not presented in the model.

Response: It is good comment in the sense it provides a good insight on the potential biases which might occur as a result of omitted variables, multicollinearity and p-hacking. However, it is also advisable to make the independent variables that might affect the dependent variable as few as possible, so as to stick with the principle of parsimony in modeling. To bring these two issues in balance, we have tried to make two models:

First model: multivariable analysis which incorporates insignificant ones (such as age, sex...)

Second model: multivariable analysis without the insignificant ones

The results in both models that signify significance based on the p-values were the same. Then, we decided to stick with the second model because the model provides less standard errors, as a result of the few independent variables incorporated. By doing so, we have tried to keep the balance between the biases and principle of parsimony while modeling.

• Results

o What is the purpose of having both Table 1 and Table 3? It would be more informative to combine these tables and have Table 2 as your table 1 and include patient characteristics.

Response: Thank you for the important comment. Table 1 is removed in the revised manuscript while keeping Table 3 as it is. Patient characteristics are described in the result section thus no need to repeat such information in table 3 to avoid text versus table content duplication.

**VERSION 2 – REVIEW**

<b>REVIEWER</b>	Tagashira , Y. Tokyo Medical and Dental University Hospital, Infectious Diseases
<b>REVIEW RETURNED</b>	21-Apr-2024

<b>GENERAL COMMENTS</b>	Thank you for revised manuscript. I confirmed your reply to the queries.  There are many parts with inappropriate spacing, so please double check them.
-------------------------	--

<b>REVIEWER</b>	Kim , Christine Centers for Disease Control and Prevention
<b>REVIEW RETURNED</b>	11-May-2024

<b>GENERAL COMMENTS</b>	Thank you for responding to reviewers' comments.
-------------------------	--

**VERSION 2 – AUTHOR RESPONSE**

Reviewer: 1

Dr. Y. Tagashira, Tokyo Medical and Dental University Hospital

Comments to the Author:

Thank you for revised manuscript. I confirmed your reply to the queries.

There are many parts with inappropriate spacing, so please double check them.

Response: Thank you for your comment. All the spacing throughout the revised manuscript are corrected.

Reviewer: 2

Dr. Christine Kim, Centers for Disease Control and Prevention

Comments to the Author:

Thank you for responding to reviewers' comments.

Response: I appreciate all your valuable comments throughout the peer-review process.