PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Determinants of inappropriate antibiotic prescription in primary care in developed countries with general practitioners as gatekeeper: a systematic review and construction of a framework.
AUTHORS	Sijbom, Martijn; Büchner, Frederike L.; Saadah, Nicholas H.; Numans, Mattijs; de Boer, Mark

VERSION 1 – REVIEW

REVIEWER	Barlam, Tamar Boston University School of Medicine, Department of Medicine
REVIEW RETURNED	25-Feb-2021

GENERAL COMMENTS	Thank you for allowing me to review this paper. The paper has much very interesting content. I am concerned however that the paper is overly ambitious. I would say there are three major sections – inventory of inappropriate prescribing, framework for determinants of inappropriate prescribing, and antibiotic use by country and relationship to antibacterial resistance (ABR). I believe focus on the impact of GP gatekeepers on antibiotic use and resistance is by far the most compelling. The other sections might be appropriate for another paper, but the inventory of inappropriate prescribing is the least interesting, and does not appear to add much new information to the existing literature. Item #1: I do believe the research questions/objectives were clearly defined but I have the most question re: inventory of inappropriate antibiotic prescribing, specifically as it appears to compare one country to another (although does not overtly do so). #3: There is such disparity between number of studies, number of patients and number of diagnoses, that it is unclear to me if the conclusions and discussion really make sense to be reported by country. The number of UTIs is in particular quite small and limited to only studies from 2 nations. The RTI data is not particularly novel, and while the literature search was interesting it seems to add little new information to what is known. The determinants of inappropriate prescribing is appealing because I found it useful how the authors applied it to a particular framework. Again, however, it seems like it belongs in a different paper. The most compelling aspects are the views of GPs and what influences their inappropriate prescribing since this serves as the foundation for the study. In the discussion, lines 395-400 really should be the crux of the paper. The GPs do not feel their antibiotic prescribing is responsible for antibiotic resistance. Then the authors analysis of national prescribing and resistance tell a very different story. Much of the impact is lost because there is too much in the paper and too much of the discussion is about how useful the ASI is, rather than what the data is telling us. In addition, the antibiotic spectrum index should be explained more. While I agree, the results are very interesting and more useful than the DDD, there should have been discussion about the limitations of the ASI. For examples, a small group of pediatric ID physicians/pharmacist created it, there are some strange decisions such as ranking ampicillin-sulbactam as a higher ASI number than ceftriaxone by having several categories for

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	gram positives and anaerobes but indicating ceftriaxone does not cover organisms such as Serratia. They indeed cover those organisms, promote hyperproduction of b-lactamase, and troubling resistance. The ASI has been used in a limited number of studies and there are other indices out there. It is unclear if it as useful to look at gram-positive resistance as gram-negative. #9: the results address the research question but I think if the question was framed as impact of antibiotic use in GP practices on ABR, I would have liked to see more granularity of comparing the GP use of abs vs hospital use. There is one figure that shows the proportion of GP vs hospital antibiotic volume, but there is no detail about which antibiotics are in fact used by GPs. I'd like to see the correlation of the GP prescribing with MDRO, and the hospital prescribing with MDRO. Would we expect that S. pneumoniae might be better correlated with GP practices and E coli with hospital use? I would find that interesting. #12: As noted, while I totally agree that ASI is better for the examination of relationship of resistance with antibiotic use, I think more discussion of the limitations is indicated. Overall, I think this paper has some very interesting information. I would suggest focusing on the antibiotic use by country, primary care and hospital care use, and resistance. I think you can tell a more in-depth story about the most interesting factors. I can see that a second paper might be possibly of interest, focused on the other objectives of the study, but it would be less novel.

REVIEWER	Kurotschka, Peter University of Cagliari, Department of Medical Science and Public Health
REVIEW RETURNED	27-Feb-2021

GENERAL COMMENTS	The article is dealing with a hugely important topic and you tried to answer some important research questions. Unfortunately, the review question is too broad, it is unclear if you are dealing with proportions of antibiotic overuse, determinants or metrics that correlates with multi drug resistance (ASI vs. DD). The setting is also unclear, as you you declare, at the one hand, that you study in the primary care sector, and, at the other hand, you include hospital prescriptions data. I suggest you to focus on one single research question (e.g. determinants of antibiotic overuse): a systematic review, as you did, seems appropriate: bearing in mind this question, select the proper inclusion and exclusion criteria of the studies (quantitative? qualitative? both? years? languages? why this choices?) and move on. The idea of the framework is good. After this (you can build on the work you already did) I encourage you to resubmit your report.

REVIEWER	Salzberger, Bernd University Hospital Regensburg, Infection Control and Inf. Diseases
REVIEW RETURNED	28-Jun-2021

GENERAL COMMENTS	In the invitation there are two statements which I do not find correct: Why inappropriate use of antibiotic should be more a driver of antibiotic resistance than appropriate I cannot accept - the latter should and could be avoided, but that is a different point The second point is whether antibiotics in outpatient settings is more important for antibiotic resistance than inpatient. There is a big difference in quantity, but the "crowding" of patients in hospitals might be a more important factor than the number of prescriptions. In the results and discussion I am not convinced that the cultural

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	categories used to ascribe differences between countries have been shown to be the same for the medical profession. Thus, this should be commented on.

VERSION 2 – REVIEW

REVIEWER	Kurotschka, Peter University of Cagliari, Department of Medical Science and Public Health
REVIEW RETURNED	15-Jul-2022

GENERAL COMMENTS	Thank you for asking me to review the manuscript “Determinants of inappropriate antibiotic prescription in primary care” dealing with a hugely important and relevant topic. General consideration. Comparing the resubmitted work by Sijbom and colleagues with their previous version, the overall quality of the manuscript, the research question, and the design, improved substantially. The authors basically preformed a new study. The research aim is clear, the method of a systematic review seems appropriate to answer the research question. The idea of putting identified factors in a framework highlighting factors deemed to influence negatively, positively or in a conflicting way the appropriateness of antibiotic use is of immediate practical utility for the reader. Nevertheless, there are some major points authors need to address before considering the manuscript for publication. MAJOR POINTS: - Prospero registration is outdated, it was not changed according to the new, more focused, research question, nor was the progress of the study and the expected 8and actual) completion date updated anyhow. The prospero update should be done regularly to meet the objective of a “prospective” registration platform. Conceptually it makes little sense now but I would consider it acceptable if authors perform their update now, the current protocol is not suitable to be included as supplement or mentioned in the manuscript. - The editor needs to decide if authors must update their literature search. My opinion is that it is not likely that the framework would change much, so for me this is a major point but not strictly necessary. - Choice to include qualitative and quantitative studies (and which designs specifically) needs to be stated explicitly in the methods section and needs justification and discussion in the discussion section. - Line 110: “appropriateness of antibiotic prescription at a population level”. Unclear what is meant and why subgroups or diagnoses were excluded. Please explain the reasons for exclusion more clearly, at this point it is unclear which the inclusion and exclusion criteria were. - Unclear why the following a priori decision “Determinants were eligible…if found in at least one quantitative study or repeatedly in two or more qualitative studies”. This choice has to be discussed thoroughly in the discussion section. - Who added the identified factors in the framework, and how were conflicts resolved? - The title does not describe the study thoroughly: it is too vague and broad (keywords: framework, developed countries, GPs as

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	gatekeepers). - The results section, in my view, should be extensively reviewed. o First, you found numerous factors, but only a small selection of them was presented in the results section, a much smaller selection in the abstract I suppose as “examples” or was there another reason? I understand that the difficulty to report and summarize the results could be due to the fact that factors identified were many. A possible solution could be to review your framework grouping the factors you identified in broader categories, or to have 6 paragraphs, one for each group of factors. o The results need to be (simply) described, which need to be discussed in the discussion section. Now, the results section contains also some discussion on why (discussion) and how (methods) factors were included or not in the framework. Thism should be avoided. Examples of what I mean are lines 170-174, 176-177, 181-182. Likewise, factors you did not include in the models could be also part of the discussion and discussed in light of the literature but they are not appropriate for the results. o An example of the inconsistency of the results section is that the abstract and the discussion mention “comorbidity” as one of the most important factor related to inappropriateness, but it is not mentioned in the results section. - Limitation should be reflected more in depth, e.g. no objective measure of the effect (size) was used, it was not possible in your design but this is a limitation, so that in fact you are not able to tell which factor is more relevant. Another limitation is that you searched only for studies published in English. Did this affect your results? How? MINOR POINTS - Editing is needed, some spelling, punctuation and grammar mistakes throughout the manuscript and in the tables and the supplements would need revision - Reference 21 should be referred also to the previous sentence (line 105-108) - Language restrictions need to be explicit - Line 109: qualitative studies (you included also qualitative studies) have no endpoints by definition. Please rephrase. - Regarding “analysis”, authors may consider to rename the paragraph, perhaps unifying it with the previous one (“framework”). - Line 168: delete last sentence - Line 176: unclear what is intended with “medical education outside Canada or the US”, consider rephrasing

REVIEWER	Avent, Minyon University of Queensland, UQCCR
REVIEW RETURNED	30-Jan-2023

GENERAL COMMENTS	Thank you for allowing me to review the publication entitled 'determinants of inappropriate antibiotic prescription in primary care'. Overall, the manuscript has been well written. This paper will assist in the development and implementation of interventions to facilitate the appropriate prescribing of antibiotics in the primary care setting. The literature has supported the following determinants for inappropriate antibiotic prescribing namely the time of day of the patient consultation and the length of the consultation. It would be worthwhile addressing why these determinants were not considered in the paper.

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	In the discussion section lines 244 to 246 relating to a career longer than 10 years was associated with inappropriate antibiotic prescriptions. Another factor to consider would be that the prescribing of antibiotics has been influenced by seniors and clinical experts who were less familiar with guidelines, instead demonstrating a preference for autonomous prescribing. This would also be worthwhile discussing.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Dr. Peter Kurotschka, University of Cagliari, Istituto Superiore di Sanita

Comments to the Author:
Thank you for asking me to review the manuscript "Determinants of inappropriate antibiotic prescription in primary care" dealing with a hugely important and relevant topic.

General consideration.
Comparing the resubmitted work by Sijbom and colleagues with their previous version, the overall quality of the manuscript, the research question, and the design, improved substantially. The authors basically preformed a new study. The research aim is clear, the method of a systematic review seems appropriate to answer the research question. The idea of putting identified factors in a framework highlighting factors deemed to influence negatively, positively or in a conflicting way the appropriateness of antibiotic use is of immediate practical utility for the reader.
Nevertheless, there are some major points authors need to address before considering the manuscript for publication.
Thank you very much for the appreciative comments. We are very grateful for the thorough review and detailed comments that allowed us to make additional improvements.

MAJOR POINTS:
- Prospero registration is outdated, it was not changed according to the new, more focused, research question, nor was the progress of the study and the expected 8and actual) completion date updated anyhow. The prospero update should be done regularly to meet the objective of a "prospective" registration platform. Conceptually it makes little sense now but I would consider it acceptable if authors perform their update now, the current protocol is not suitable to be included as supplement or mentioned in the manuscript.
We had to make a new entry in prospero. As the website does not allow us to make changes to the protocol. The prospero registration has been added as supplement 1.

- The editor needs to decide if authors must update their literature search. My opinion is that it is not likely that the framework would change much, so for me this is a major point but not strictly necessary.
We are of course willing to do an additional literature search, but we do not expect that this will lead to significant changes or additions. The previous update of the search also yielded virtually no new determinants.

- Choice to include qualitative and quantitative studies (and which designs specifically) needs to be stated explicitly in the methods section and needs justification and discussion in the discussion section.

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There were no restrictions for the design of the study, this sentence has been added to the method section (line 104)."*Studies were, regardless of their design, selected for reviewing."*
We explain our choice in the discussion section, (line 177): *"There were no restrictions on the design of the study for the inclusion as our aim was to include as many determinants as possible."*

- Line 110: "appropriateness of antibiotic prescription at a population level". Unclear what is meant and why subgroups or diagnoses were excluded. Please explain the reasons for exclusion more clearly, at this point it is unclear which the inclusion and exclusion criteria were.
We agree and rephrased the sentence (line 112): "*Studies on specific subgroups of patients (for example those with specific co-morbidities) or specific diseases (such as asthma or COPD) were excluded as reasons for appropriate or inappropriate antibiotic prescriptions for these groups differ, while our aim was to develop an framework for the whole popultion*."

- Unclear why the following a priori decision "Determinants were eligible…if found in at least one quantitative study or repeatedly in two or more qualitative studies". This choice has to be discussed thoroughly in the discussion section.
This sentence was not supposed to be in the manuscript as this exclusion criteria was not used for the selection of determinants. The sentence was not noticed at the final check before submission. We removed the sentence. Sorry for the inconvenience.

- Who added the identified factors in the framework, and how were conflicts resolved?
This has been added to the manuscript (line 127). "*One reviewer (MS) added determinants to the framework. Morgan et. al. describe in their manuscript how they chose in which domain each determinant has to be placed."*

- The title does not describe the study thoroughly: it is too vague and broad (keywords: framework, developed countries, GPs as gatekeepers).
The title has been changed to: "*Determinants of inappropriate antibiotic prescription in primary care in developed countries with general practitioners as gatekeeper: a systematic review and construction of a framework."*

- The results section, in my view, should be extensively reviewed.

- **First, you found numerous factors, but only a small selection of them was presented in the results section, a much smaller selection in the abstract I suppose as "examples" or was there another reason? I understand that the difficulty to report and summarize the results could be due to the fact that factors identified were many. A possible solution could be to review your framework grouping the factors you identified in broader categories, or to have 6 paragraphs, one for each group of factors.**

All determinants are already presented in the framework. We did not state all determinants in our results section to prevent repetition with the framework and to improve readability. We choice to describe only results which needed some kind explanation.

- **The results need to be (simply) described, which need to be discussed in the discussion section. Now, the results section contains also some discussion on why (discussion) and how (methods) factors were included or not in the framework. This should be avoided. Examples of what I mean are lines 170-174, 176-177, 181-182. Likewise, factors you did not include in the models could be also part of the discussion and discussed in light of the literature but they are not appropriate for the results.**

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We agree with the reviewer and moved these parts to the discussion section. There is now a stricter distinction between results and discussion. In the result section, relevant results are summarized and the most important results are discussed in the discussion section.

- **An example of the inconsistency of the results section is that the abstract and the discussion mention "comorbidity" as one of the most important factors related to inappropriateness, but it is not mentioned in the results section.**

Please take also notice of our previous response. We did not add co-morbidity to the result section, but discuss this in detail in the discussion. We consider the result section in the abstract to be a combined summary and highlights of the result and discussion section from the manuscript.

- Limitation should be reflected more in depth, e.g. no objective measure of the effect (size) was used, it was not possible in your design but this is a limitation, so that in fact you are not able to tell which factor is more relevant. Another limitation is that you searched only for studies published in English. Did this affect your results? How?
We added a discussion on the lack of objective measures for the effect (line 274): " *Another limitation was the lack of objective measure of the effect size due to the inclusion of qualitive studies. This makes it not possible to determine which determinants is more relevant."* There were no restrictions on the languages for the included studies, this has been added to the manuscript (line 100): *"There were no language restrictions in the search."*

MINOR POINTS
- Editing is needed, some spelling, punctuation and grammar mistakes throughout the manuscript and in the tables and the supplements would need revision
We edited the manuscript as suggested by the reviewer.

- Reference 21 should be referred also to the previous sentence (line 105-108)
This has been added.

- Language restrictions need to be explicit.
This has been added. There were no restrictions for language (line 100)." There were no language restrictions in the search.*"*

- Line 109: qualitative studies (you included also qualitative studies) have no endpoints by definition. Please rephrase.
We rephrased endpoint to outcome (line 110).

- Regarding "analysis", authors may consider to rename the paragraph, perhaps unifying it with the previous one ("framework").
We added this paragraph to framework and remove the title analysis

- Line 168: delete last sentence
We deleted the last sentence.

- Line 176: unclear what is intended with "medical education outside Canada or the US", consider rephrasing
We elaborate on this determinant in the discussion session (line 236): *"As our aim was to construct a comprehensive a framework as possible. The determinants practice location (rural verus urban), hospital affiliation and medical education outside the United States and Canada were put in the framework despite being specific to a country or setting (29, 31, 34, 35). Rural locations in Canada*

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have a different context than rural locations in Europe and this determinant should be used in that context (29). One study found that physicians trained outside Canada or United States prescribed more inappropriate antibiotics while working in Canada (31)."

Reviewer: 2
Dr. Minyon Avent, University of Queensland

Comments to the Author:
Dear Authors,

Thank you for allowing me to review the publication entitled 'determinants of inappropriate antibiotic prescription in primary care'. Overall, the manuscript has been well written. This paper will assist in the development and implementation of interventions to facilitate the appropriate prescribing of antibiotics in the primary care setting.

The literature has supported the following determinants for inappropriate antibiotic prescribing namely the time of day of the patient consultation and the length of the consultation. It would be worthwhile addressing why these determinants were not considered in the paper.
We did not find the determinant the time of day in our literature search. The determinant limited time for a consultation (time pressure) is in our framework (figure 2).

In the discussion section lines 244 to 246 relating to a career longer than 10 years was associated with inappropriate antibiotic prescriptions. Another factor to consider would be that the prescribing of antibiotics has been influenced by seniors and clinical experts who were less familiar with guidelines, instead demonstrating a preference for autonomous prescribing. This would also be worthwhile discussing.
We thank the reviewer for the suggestion. Our framework also has the determinant non-comprehensive guideline, we added the suggestion in our discussion when discussing this framework (line 245): *"A career longer than 10 years was associated with more inappropriate antibiotic prescription (29, 31, 34), with a possible cause being that they are less familiar with guidelines and rely more on their clinical experience."*

VERSION 3 – REVIEW

REVIEWER	Kurotschka, Peter University of Cagliari, Department of Medical Science and Public Health
REVIEW RETURNED	22-Mar-2023

GENERAL COMMENTS	This should get published now.

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