

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Global status of essential medicine selection: a systematic comparison of national essential medicine lists with recommendations by WHO
AUTHORS	Piggott, Thomas; Nowak, Artur; Brignardello-Petersen, Romina; Cooke, Graham; Huttner, Benedikt; Schünemann, Holger J; Persaud, Nav; Magrini, Nicola; MOJA, Lorenzo

VERSION 1 – REVIEW

REVIEWER	Gray, Andy L University of Kwazulu-Natal, Discipline of Pharmaceutical Sciences
REVIEW RETURNED	19-Jul-2021

GENERAL COMMENTS	<p>The authors have presented a clear description of a novel analysis of a database previously described (Persaud et al.). However, understanding of this paper would be improved by briefly describing the fact that the national EMLs included (for 137 countries, representing 70% of all) were obtained from the WHO repository, and not specifically sought out from source for that study. It would also be important to briefly describe how national EMLs that drive procurement are differentiated from those that are relied on for reimbursement by national insurers. In that regard, it would also be important to briefly define, as was done in Persaud et al., how items in the MLEM with a square box symbol were handled.</p> <p>It would also help to expand Table 1 slightly, to show the number of national EMLs per region that were included, and what proportion of Member States that represented in each region. However, is Figure 4 needed, if Table 1 were to be more complete, for example, by adding min and max?</p> <p>In each of the tables, understanding the IQR would be assisted by reporting the range (25th and 75th percentile) rather than a single value.</p> <p>Lastly, references 6 and 10 have been incorrectly captured in the software used. References 1 and 3 are also inconsistent with the style used, in that the WHO is not identified as the author.</p>
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REVIEWER	Xie, Xuefeng Anhui Medical University, college of pharmacy
REVIEW RETURNED	17-Aug-2021

GENERAL COMMENTS	<p>Thanks for the opportunity to review this manuscript. Rational use of essential medicine is a global health issue. However, the actual effect of National Essential Medicines Policy implementation remains unclear. This manuscript tries to examine the availability of essential medicines by comparing the 2017 essential medicine lists of 137 countries to the WHO Model List. In my view, this manuscript could play a role in guiding country's decision-makers to design an evidence-based NEM policy. I have a few suggestions that might strengthen it:</p> <ol style="list-style-type: none"> 1. Not only the medicine list, but also the policy of National Essential Medicines should be introduced and explained in brief in the Introduction section. 2. Evaluating the availability of essential medicines involves many aspects. Is descriptive research on the EM list sufficient for the research question or objective? 3. This study highlights divergence in EML listing in countries. However, we are more concerned with the causes of this differences. It suggested that the authors should supplement the indicators related to the policy of how the medicines on the list are used in priority, for example, whether the national essential medicines are included in the national health insurance scheme, and so on, cause some countries may only have lists of EM but may not have policies to actually utilize them, these kind of EM lists might be ineffective. 4. In the results section, is it appropriate to start with a brief table showing the baseline data such as the distribution of 137 countries and the basic information of those essential medicines lists? 5. Needs some language corrections before being published.
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REVIEWER	Duong, Mai The University of Sydney
REVIEW RETURNED	24-Aug-2021

GENERAL COMMENTS	<p>This is a well conducted study that has applied a contemporary statistical method to give a global overview of the priority of medicines on national EMLs compared to the WHO standard. While the F1 statistical method and sensitivity/specificity analysis are not novel techniques, the authors have demonstrated it can be a useful way to display complex comparisons across countries. While priorities differ between countries, this method may allow policy makers to compare themselves to similar economies or neighbouring countries to improve access to medicines. For example, this could potentially be used to facilitate or negotiate bulk medicine procurement in regions.</p> <p>Please see some my comments and suggestions below:</p> <ol style="list-style-type: none"> 1. Can you please clarify the abbreviation "TPR" on page 10? I assumed it was true positive rate? 2. I found some of the figures hard to read, perhaps due to the proof format (i.e. Fig 3 box plots legend description against the black background and fig 6 heat map were not legible).
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	<p>3. Did the authors observe any differences between acute and chronic or communicable and non-communicable disease treatments listed on the nEMLs?</p> <p>4. Did the authors' analysis include countries where there were no national EMLs, but instead had multiple statewide EMLs or formularies? If so, how was this accounted for?</p> <p>5. Were there any stratification or analysis done for low, middle or high income countries?</p> <p>6. In many instances, listing on the EML unfortunately does not translate to availability of a treatment at the point of care, especially when lists are outdated. How can we apply the authors findings to support individual consumer priorities and procurement variations in clinical settings such as primary care or institutions, to improve access?</p> <p>7. What were the most common or key medicines not included in nEMLs (true negatives), and why? What are the potential clinical and policy impacts of not listing these true negatives, and how can policy makers use this information?</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Mr. Andy L Gray, University of Kwazulu-Natal

Comments to the Author:

The authors have presented a clear description of a novel analysis of a database previously described (Persaud et al.). However, understanding of this paper would be improved by briefly describing the fact that the national EMLs included (for 137 countries, representing 70% of all) were obtained from the WHO repository, and not specifically sought out from source for that study.

- Thank you for this helpful comment. To add clarity on the WHO Global EML database, we have added text in response to this comment. See lines 141-144:

“This database draws on national EMLs that have been included in the WHO repository and does not directly draw from WHO member states for the purposes of this paper. The database consists of 137 country EMLs and the validation and full methods of extraction are described elsewhere.⁵”

It would also be important to briefly describe how national EMLs that drive procurement are differentiated from those that are relied on for reimbursement by national insurers.

- Thank you for this comment. A section to add clarity around this has been incorporated into the background. See lines 105-112:

“Essential medicine lists (EMLs) are critical to prioritizing evidence-based interventions that people around the world should have access to, and governments have to work to fund. The adoption of these priority tools into public policy could generate important savings by concentrating competition on a smaller number of medicines and better negotiating medication prices. In some settings, EMLs may drive medicine procurement decisions and in other settings national insurers will utilize EMLs for reimbursement decisions. Approximately 137 countries out of 194 World Health Organization (WHO) member states have formal national EMLs (70.6%).”

In that regard, it would also be important to briefly define, as was done in Persaud et al., how items in the MLEM with a square box symbol were handled.

- Thank you for this helpful suggestion. We have introduced and addressed how square box medicines were handled. See lines 149-153:
“The MLEM includes medicines with a square box indicator, which denotes therapeutic equivalence with other medications in the same class. For the purpose of this study we have assumed that for square box MLEM medicines any class therapeutic equivalent alternative listed by national EMLs is a matching entry.”

It would also help to expand Table 1 slightly, to show the number of national EMLs per region that were included, and what proportion of Member States that represented in each region.

- Thank you for this suggestion. We have updated table 1 and now include the number of National EMLs in each WHO region included in the analysis. See table 1.

However, is Figure 4 needed, if Table 1 were to be more complete, for example, by adding min and max?

- We have elected to keep Figure 4 at the present time, because we feel it is an important visualization of the variability by WHO region. We intend to reuse the figure during WHO meetings, and it would be important to reference this paper as origin source. We certainly could consider changing if required by the editors. Thank you.

In each of the tables, understanding the IQR would be assisted by reporting the range (25th and 75th percentile) rather than a single value.

- Thank you for this suggestion, we have amended Table 1 and 2 to your recommendation including the 1st and 3rd quartile F1 values for readability. See lines 524-531.

Lastly, references 6 and 10 have been incorrectly captured in the software used. References 1 and 3 are also inconsistent with the style used, in that the WHO is not identified as the author.

- Thank you for noting this. We have corrected these references and reviewed all references for accuracy. See lines 425-476.

Reviewer: 2

Dr. Xuefeng Xie, Anhui Medical University

Comments to the Author:

Thanks for the opportunity to review this manuscript. Rational use of essential medicine is a global health issue. However, the actual effect of National Essential Medicines Policy implementation remains unclear. This manuscript tries to examine the availability of essential medicines by comparing the 2017 essential medicine lists of 137 countries to the WHO Model List. In my view, this manuscript could play a role in guiding country's decision-makers to design an evidence-based NEM policy. I have a few suggestions that might strengthen it:

1. Not only the medicine list, but also the policy of National Essential Medicines should be introduced and explained in brief in the Introduction section.

- Thank you for this comment. We have elaborated on the policy/use of National EMLs in the text. See lines 105-112:

“Essential medicine lists (EMLs) are critical to prioritizing evidence-based interventions that people around the world should have access to, and governments have to work to fund. The adoption of these priority tools into public policy could generate important savings by concentrating competition on a smaller number of medicines and better negotiating medication prices. In some settings, EMLs

may drive medicine procurement decisions and in other settings national insurers will utilize EMLs for reimbursement decisions. Approximately 137 countries out of 194 World Health Organization (WHO) member states have formal national EMLs (70.6%).”

2. Evaluating the availability of essential medicines involves many aspects. Is descriptive research on the EM list sufficient for the research question or objective?

- Thank you for this comment. We have sought to further refine our research question in the background section with this addition, that we hope provides the specificity suggested, see lines 133-134:

“In particular, we explore analysis and visualizations using a single entity, the F1 statistic to assess national essential medicine listings in relation to the MLEM.”

- We have also added your point as a limitation in the discussion, see lines 350-352: “Finally, our evaluation is limited to the availability of essential medicines in official government documents. Results can or cannot translate in availability at patient level.”

3. This study highlights divergence in EML listing in countries. However, we are more concerned with the causes of this differences. It suggested that the authors should supplement the indicators related to the policy of how the medicines on the list are used in priority, for example, whether the national essential medicines are included in the national health insurance scheme, and so on, cause some countries may only have lists of EM but may not have policies to actually utilize them, these kind of EM lists might be ineffective.

- Thank you for this comment. We feel this is an excellent suggestion for future research direction. Accordingly, we have added comment to this in the discussion, see lines 388-392:

“Finally, further research is needed to better understand how listing on an EML translates to access policies and availability of medicines for patients, the ultimate goal. Simply listing medicines is not going to solve the problem of scarce coverage, but it is a necessary first step to enable identification of priority medicines and the subsequent tracking of their availability.”

4. In the results section, is it appropriate to start with a brief table showing the baseline data such as the distribution of 137 countries and the basic information of those essential medicines lists?

- Thank you for this comment. We have sought to limit and focus on the more advanced comparative analyses in this manuscript. However, to address your point, we have added reference that basic descriptive information may be sought from Persaud et. al 2019. See lines 205-206: “Further descriptive analyses on the countries and medicines included are available in Persaud et al.”

5. Needs some language corrections before being published.

- Thank you for this comment. We have sought to edit again from start to finish for corrections throughout as suggested.

Reviewer: 3

Dr. Mai Duong, The University of Sydney

Comments to the Author:

This is a well conducted study that has applied a contemporary statistical method to give a global overview of the priority of medicines on national EMLs compared to the WHO standard. While the F1 statistical method and sensitivity/specificity analysis are not novel techniques, the authors have demonstrated it can be a useful way to display complex comparisons across countries. While priorities differ between countries, this method may allow policy makers to compare themselves to similar economies or neighbouring countries to improve access to medicines. For example, this could potentially be used to facilitate or negotiate bulk medicine procurement in regions.

Please see some my comments and suggestions below:

1. Can you please clarify the abbreviation "TPR" on page 10? I assumed it was true positive rate?

- Thank you for this comment. We have incorporated the definition and acronym of TPR and FPR in their first point of reference for clarity in the text. See line 170-171: "Firstly, we estimate differences between the reference standard and index tests using the true positive rate, TPR, (sensitivity) and false positive rate, FPR, (1-specificity)."

2. I found some of the figures hard to read, perhaps due to the proof format (i.e. Fig 3 box plots legend description against the black background and fig 6 heat map were not legible).

- Thank you for this comment. We have included high quality figures with the submission and in copy-editing and publication these should be very readable and high quality for readers.

3. Did the authors observe any differences between acute and chronic or communicable and non-communicable disease treatments listed on the nEMLs?

- Thank you for this helpful comment. We feel these future analyses are very important, but due to the initial analysis approach taken in this paper, where we use medicine categorization (ATC) not disease categorization we are unable to comment on this. We have added commentary on this and future research priorities accordingly in the discussion, see lines 374-376: "Future research continue to assess medicine listings on NEMs by disease groups and for focused disciplinary as has been done for tobacco addiction, diabetes, and heart disease among other topics. 16-18"

4. Did the authors' analysis include countries where there were no national EMLs, but instead had multiple statewide EMLs or formularies? If so, how was this accounted for?

- Thank you for this comment. As we reference in the background and methods, this paper utilizes the existing repository of national EMLs reported to WHO. Therefore, we are unable to capture sub-national schemes or other formularies not identified as EMLs. It would be worthwhile in future research to explore this question, however, would require a different survey approach for the identification and comparison of these formularies.

5. Were there any stratification or analysis done for low, middle or high income countries?

- This was not completed in this work, however, analysis on income-level was explored in previous work as referenced, see Persaud 2019.

6. In many instances, listing on the EML unfortunately does not translate to availability of a treatment at the point of care, especially when lists are outdated. How can we apply the authors findings to support individual consumer priorities and procurement variations in clinical settings such as primary care or institutions, to improve access?

- Thank you for this comment. We feel this is very important and as we continue work to increase the transparency of national EMLs, and the linkage to availability at the point of care, we believe this work will support an understanding of this and the eventual availability of medicines. We have added commentary on this and future research priorities accordingly in the discussion, see lines 388-392: "Finally, further research is needed to better understand how listing on an EML translates to access policies and availability of medicines for patients, the ultimate goal. Simply listing medicines is not going to solve the problem of scarce coverage, but it is a necessary first step to enable identification of priority medicines and the subsequent tracking of their availability."

7. What were the most common or key medicines not included in nEMLs (true negatives), and why?

- This is an important question and the most honest answer is that we have no idea. True negative medicines, as described in lines 161-162 are medicines not listed on the MLEM and not listed on any NEMs. We can assume that in most countries there are more than 1000s of medicines, which are not listed on either the MLEM or NEM, but which may be relevant, approved and in use.

Among these it is likely that the most important ones are very expensive, but highly priced, medicines, such as checkpoint inhibitors for different cancers, or immunomodulators for chronic diseases such as multiple sclerosis.

What are the potential clinical and policy impacts of not listing these true negatives, and how can policy makers use this information?

- During the last expert committee for the first time, the EML has recommended WHO to form a working group to explore policies for contending with the high prices of medicines that are considered essential, but unaffordable in many low and middle-income countries. These medicines are likely to be important “true negative”. Establishing a working group is not a solution per se, but it can be seen as a first step to focus on potential solutions.

VERSION 2 – REVIEW

REVIEWER	Gray, Andy L University of Kwazulu-Natal, Discipline of Pharmaceutical Sciences
REVIEW RETURNED	24-Oct-2021
GENERAL COMMENTS	The authors have comprehensively addressed each of the concerns raised in the initial review. The changes made are appropriate. The decision to retain the additional Figure is supported.
REVIEWER	Xie, Xuefeng Anhui Medical University, college of pharmacy
REVIEW RETURNED	15-Nov-2021
GENERAL COMMENTS	1. The authors have addressed most of my concerns. 2. Although this study only involved data on medicines, ethical review is recommended.