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Title	Development of a preliminary essential medicines list for Canada
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Reviewer 1	Dr. David G. Bailey
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General comments (author response in bold)	A recent meeting of federal, provincial and territorial health ministers to develop a national pharmaceutical strategy to cut the cost of prescription drugs would involve the development of a national formulary. Thus, this manuscript is very topical and the authors make a strong argument in the introduction for a short essential list of drugs for clinicians. They started with a list created by the World Health Organization, modified it to the Canadian circumstance, sent it to healthcare professionals for comments (additions, deletions) and finally tested the list through chart reviews at two Toronto hospital – based family practice teams. Thus, the design appears to be well thought-out. Unfortunately, an important aspect was the poor response from healthcare professionals. None of the 100 randomly selected and only 8/60 carefully selected clinicians replied. In total, 13 healthcare providers (5 primary care physicians, 5 pharmacists, 2 nurse practitioners, 1 neurologist) provided a total of 43 suggestions. Although there was apparent good acceptance of the list by the two local hospital teams, this reviewer is still concerned about support on a broader scope by colleagues. I would be interested to know whether the two hospitals had the list of essential medications before or after the assessment. Being given the list and then modifying prescribing habits to comply before assessment would likely give better results. Also, clinicians under other circumstances may be resistant to change in prescribing habits, which could reduce acceptance of this list. Methods (page 4): the reasons for removal of a drug from the WHO are provided. I would suggest adding that the medication is not commonly prescribed in Canada. Methods (page 8): 'if the prescribed medication was not on the list, whether there was an equivalent medication on the list. Medications were considered equivalent if they treated the same condition (eg. hypertension) and were from the same class of medications (eg. ACE inhibitors).' I am not clear about what this means. It seems that a drug not on the list but has the same therapeutic use and belongs to the same drug class as one on the list would still mean that there was coverage. In other words, a clinician might prescribe the beta blocker, metoprolol, for hypertension management. This drug is not on the list but there are 2 other infrequently used beta blockers, bisoprolol and labetalol, for the same condition. It would then be concluded that there was coverage. I would not consider this to be case, which would diminish the score for coverage. I compared the 2012 top 100 prescribed drugs in Canada (Pharmacy Practice, Feb/March 2013, see attached), which was the most recent version that I had available, with the authors' table. A little over 40 of the drugs from the former are found in the latter. Although this is encouraging, there were some omissions worth mentioning. Based on higher frequency of use, I submit the following for consideration: beta blockers (#8 metoprolol and # 31 atentolol for bisoprolol and labetalol); HMG Co-A reductase inhibitors (#3 rosuvastatin or #48 simvastatin for pravastatin); diuretics (#12 hydrochlorothiazide for chlorthalidone); antidepressant (#43 amitriptyline for nortriptyline); ADHD (#63 methylphenidate for atomoxetine). Subsequent to this, I viewed Table 1S that outlined the responses to the 43 suggestions from the healthcare providers. Of note, all alterations suggested by this reviewer were found in "considered changes" but the outcomes were opposite to mine. The specific reasons for the "final decision" were not provided which leaves this reviewer questioning. I would have thought that the frequency of prescription would have been an important factor except when therapeutics and cost were paramount but specifics were not provided. The spelling of rivaroxaban is incorrect throughout the manuscript.

July 21, 2016
Canadian Medical Association Journal
1867 Alta Vista Dr.
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Dear Editors,
Please consider our manuscript "Development of an essential medicines list for Canada," for publication in the CMAJ.
The CMAJ recently published an Analysis "The case for an essential medicines list for Canada". The Anaslysis noted that while various reports have been written and various task forces assembled, we still do not have a list of essential medicines: "No specific action has been taken after repeated calls for an essential medicines list in Canada, despite recent and past Canadian recommendations and those made in other prosperous jurisdictions, including Australia in 2011 and the US in 2013."
We have taken the first necessary steps in order to develop a list of essential medicines. We started with the World Health Organization's model list of essential medicines that is meant to form the basis for country specific essential medicines list. Our approach involved a multi-leveled peer-reviewed process to create a short list of essential medications for use in Canada. The list

was assessed through retrospective chart review at two clinics to determine whether it supported current prescribing patterns. Our list of 125 medications covered over 90% of prescriptions at the two clinics. Further studies are already in progress to evaluate the coverage and cost of the list with national prescribing data and a randomized control trial is underway that will evaluate the impact of prescribing from the list on health outcomes, medication access, and costs to the health system.
We have improved the manuscript based on feedback from the editor and peer reviewers for our previous submission CMAJOpen-2015-0133. We now describe our list as a preliminary one and we have outlined some of the further steps needed to finalize it. The recent Analysis has drawn attention to the need for this process to get started. We think CMAJ readers should know about the work that has already been done on this important issue.
This manuscript describes original work and is not under consideration by any other journal.
Thank you for your consideration,

Dr. Nav Persaud, MD, MSc
Associate Scientist, Li Ka Shing Knowledge Institute
St. Michael's Hospital

1. Adaptation of WHO list
a. Who worked on adapting the list? Please include initials.
*****We have added these.**
b. How many authors looked at each entry in the 2013 WHO Essential Medicines list?
*****Two.**
c. What resources informed the decisions to remove meds from the WHO list (e.g., how was it determined that another medication had a better tolerated route of administration)?
*****We have clarified this in the text. We have also explained in the text that the purpose of the first part of the process was to generate a first complete draft list for further development based on peer reviewer input and prescribing patterns. In the limitations section, we also added the following statement: "Although the first draft of the list was based on an informal process, any inappropriate additions should have been addressed by the peer reviews and any inappropriate omissions should have been addressed by the peer reviews and the prescribing audit"**
e. How were disagreements handled?
*****We have clarified that disagreements were resolved through discussion.**
f. Similarly, what specifically was the process to add meds to the list?
***** We have clarified this in the text. We have also explained in the text that the purpose of the first part of the process was to generate a first complete draft list for further development based on peer reviewer input and prescribing patterns. In the limitations section, we also added the following statement: "Although the first draft of the list was based on an informal process, any inappropriate additions should have been addressed by the peer reviews and any inappropriate omissions should have been addressed by the peer reviews and the prescribing audit"**
g. What were the inclusion criteria for additions?
***** We have clarified this in the text. We have also explained in the text that the purpose of the first part of the process was to generate a first complete draft list for further development based on peer reviewer input and prescribing patterns. In the limitations section, we also added the following statement: "Although the first draft of the list was based on an informal process, any inappropriate additions should have been addressed by the peer reviews and any inappropriate omissions should have been addressed by the peer reviews and the prescribing audit"**

2. Peer reviewer feedback
a. Please include time frames for various components of this step.
*****We have added these details.**
b. Again, what was the specific process for additions, removals or replacements to the list?
*****We have clarified that it was up to the peer reviewers to decide if they thought medications should be added, removed or replaced.**

c. First recruitment strategy: how many were contacted from each college? All comers or primary care physicians?
*****The numbers are in the text (50 physicians,25 nurses and 25 pharmacists).[[[***We have to verify these numbers before resubmission***]]] Yes we only contacted primary care physicians.**
d. Second recruitment strategy: it's not clear what your inclusion criteria were. You wanted reviewers with extensive experience in these areas?
*****We clarified in the text that we found these peer reviewers by searching Canadian journals.**
e. We are assuming the 60 peer reviewers referred to the "selected" reviewers?
*****Yes and we have made this more clear by rewording the sentence and promoting it within the paragraph.**
f. Third recruitment strategy: what kind of "direct advertising" are you referring to? In which provinces or cities did this take place?
*****We have clarified that the meetings were only in Toronto and we have specified the recipients of the e-mail.**
g. How many on the SMH mailing list?
*****We have added this (60).**

3. Clinician-Scientist review
a. How were these chosen and how many? Just the 3? Who? Background and expertise?
*****There were 5 total clinician-scientists but only 3 attended each meeting. We have added this. We have also further explained in parentheses the background and experiences.**
b. Who developed the questions on efficacy and safety and performed the literature searches?
*****We have added this.**
c. Were the searches only on changes to the original WHO list or were meds that remained from the WHO list also investigated?
*****Yes only the changes were addressed, not the medications from the WHO list. We have added this to the text.**

d. Meeting: when was this convened? Any sponsorship? Were only the panel of 3 clinician-scientists and the research team included? Did the research team contribute to the decision-making?
*****We have added to the text: "The meetings took place in the summer of 2015. The meetings involved the research team (NP, HA, MT) who facilitated the discussion but did not vote and three voting clinician-scientists. There was no sponsorship of the meetings."**
e. What criteria or framework was used to determine the strength of the recommendation by each panel member?
*****GRADE was used for the level of evidence. We used a modified nominal group technique for the recommendations. Both are cited.**
f. How were disagreements handled?
*****Since there were three clinician-scientists, there was always a majority.**

4. Identification and addition of commonly prescribed medications
a. Why did you allow equivalent medications? Will the final list allow for equivalencies?
*****The purpose of an essential medicines list is to include only the needed medicines. So if a prospective new medicine is equivalent to a medicine already on the list (e.g. same class, same efficacy, similar safety profile), it will not be added.**
b. What criteria determined whether medications were "frequently prescribed"?
*****We ranked them so we have changed this to "most frequently prescribed"**

5. Audit of the list
a. How was individual patient-level coverage determined?
*****We have added this to the end of the methods section.**

6. Interpretation
a. Please include comparison with other international literature.
*****We have compared the list with a similar lists in Sweden, the United Kindgom and with the WHO's list.**
b. Please temper claims (e.g., The small size of the list WILL allow clinicians to learn more information about fewer drugs and could improve clinician prescribing appropriateness.)
*****We have removed "will" from this sentence and replaced it with "might". We have added this statement to the limitations section: "The list will only be useful if it is accepted and implemented by the public, clinicians and decision makers. Further work is needed to determine how acceptable essential medicines lists are to these stakeholders in Canada."**

7. General
a. Please be careful to add qualifier "preliminary" or "proposed" when discussing your essentials medicine list.
*****We have added "preliminary" to the title and abstract. The text also refers to the list as "preliminary".**