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Title	Development of a provisional essential medicines list for children in Canada: consensus process
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Reviewer 1	Dr. James Feinstein
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General comments and author response	This manuscript outlines the process by which the authors (The CLEAN Meds Project, www.cleanmeds.ca) created a provisional short-list of essential medications for use in Canadian children. The CLEAN Meds Project was initially conceived to create an essential medications list for Canadian adults and subsequently studied for the effect of providing patients with free and convenient access to this carefully selected list. This type of process and medication list has precedent in various other countries, and is akin to this reader's own experience in the US serving on a Medicaid Pharmacy & Therapeutics committee to generate preferred drug lists. There is evidence to show that these essential lists may improve efficacy and safety when prescribers choose and write prescriptions for medications on selected lists. The authors should be commended on providing a transparent, publicly available process by which they arrived at their recommended essential list, and the authors have recommended continual updating of the essential medication list for use in Canadian children. Ultimately, this manuscript should be published to document the process and help guide other countries/institutions as they generate their own lists of essential medications. RESPONSE: We appreciate and thank the esteemed reviewer's overall positive viewpoint on the worthiness and importance of our work. The manuscript would be enhanced by considering the following suggestions: 1. Page 8, Methods: Consider revising the current Figure 1 to more comprehensively describing the process described by the Method section sub-headers. Only the bottom 3 left-hand boxes in the current figure describe the pediatric portion performed in this paper; the top portion relating to adults has been described elsewhere and is irrelevant to this manuscript. This would free space to include more detailed information in Figure 1 to mirror the Method section sub-headers and show the process flow/timeline. Currently, it is difficult to determine the process flow/timeline from just the text of the Methods section. RESPONSE: We have revised Figure 1 as per this suggestion. 2. Page 8, Methods: In the Implications section, the authors discuss and compare their process to other countries' processes to develop essential medication lists. If any of the other countries' processes were used to inform the design of the process in the current manuscript, this should be detailed or at least introduced in the Methods section. RESPONSE: Our process was based on guidance from the World Health Organization. The processes used by other countries to develop essential medicines lists were not used to inform the design process in the current manuscript. 3. Page 9, Lines 122-125: Please clarify whether those research team members deciding equivalence had clinical or pharmaceutical expertise to do so. RESPONSE: We have clarified that the research team members deciding equivalence were a physician and a pharmacist (p.8, line 206). 4. Page 9, Lines 130-131: How many peer reviewers participated through the website? Also, please clarify if these reviewers from the website were separate from the peer reviewers described in the paragraph staring on line 141. RESPONSE: Four peer reviewers participated through the website; they are the same as described in the paragraph starting on line 141. 5. Page 10, Lines 148-149: Response rates are typically included in the Results section. Four "peer reviewers" seems like a very low number for community input? Perhaps discuss in limitations section and suggest ways to increase clinician input through website? RESPONSE: Response rates are now in the results section. We include the small

	number of peer reviewers as a limitation (p.16, line 339-346). Direct advertising of the website to clinicians has been added to the limitations section as a way to increase clinician input through the website (p.16, line 339). 6. Page 10, Lines 157-158: Unclear what “health technology assessment reports” are or how they contribute to review of medications. RESPONSE: Health technology assessments are evaluations of the clinical effectiveness, cost-effectiveness, and the ethical, legal, and social implications of health technologies on patient health and the health care system. Health technologies include prescription drugs. Specifically, we gathered evidence from health technology assessment reports from the Canadian Agency for Drugs and Technologies in Health (CADTH). We have specified this to the methods section. 7. Page 11, Lines 167-168: States that 5 clinician-scientists agreed and participated, but then the following sentence says that 3 clinician-scientists plus 1 NP voted. Please resolve discrepancy. RESPONSE: There were a total of 5 clinician scientists for the two meetings (March 23, 2017 and March 30, 2017). 3 voting members were present at each meeting. One of the clinician scientists was present at both meetings. This is now clarified (p.7 lines 166-175, and p. 9 line 211). 8. Page 12, Lines 196-197: What is the Ontario Public Drug Programs? Why was this used or valid for use in identification and addition of commonly prescribed medications? RESPONSE: Ontario Public Drug Programs is a branch of the Ontario Ministry of Health and Long-term Care and includes the publicly funded drug programs in Ontario. Prescribing information for the province is available from Ontario Public Drug Programs. We have added an explanation in the methods section (p. 8, line 200). 9. Page 13, Lines 216-218: Perhaps provide an example or two of what the patient/community board recommended? RESPONSE: We specify that the community guidance panel provided input on the criteria and the knowledge translation strategy (p. 9, lines 221-224). 10. Page 13, Results: Consider organizing the sub-headers in the same order as presented in the methods section to improve clarity and readability. RESPONSE: We have re-organized the Results section as suggested (p. 12). 11. Page 14, Line 230: While the list is freely available on cleanmeds.ca, would still be useful to include a table of the essential medication list (as the authors did with the adult list in the published manuscript “Development of a preliminary essential medicines list for Canada.” RESPONSE: A table of the list of essential medicines for children in Canada is now included as an appendix. 12. Figure 1: See earlier comments about keeping only bottom 3 left-hand boxes and making the pediatric portion more detailed. Also, consider providing a few examples of medication additions/replacements/deletions. RESPONSE: We have revised Figure 1 accordingly (p. 11). 13. Table 1: Why is “Development Process Decribed” for Canada “No” – isn’t that what the authors are doing? Maybe leave blank. RESPONSE: This is now blank. The table is now an appendix. 14. Page 19, Lines 314-318: This is a substantial limitation, but less concerning because, as the authors state, the essential list will be updated in an annual iterative process. Maybe reduce concerns by suggesting how future reviews should at minimum include representation from x, y, and z types of clinicians. RESPONSE: We have added the suggestion that future reviewers should include representation from various types of clinicians (p.16, lines 342-344). 15. Page 19, Lines 319-323: Again, perhaps reduce concerns about this limitation by suggesting how one might monitor for inappropriate prescribing?

	Or, maybe add a citation or two to compare to practices in other countries. This reader sits on a Medicaid Pharmacy & Therapeutics review committee and we operate in a very similar manner to the clinician-scientist panel. We are mandated to: The P&T Committee shall consist of a minimum of nine Committee members, but no more than thirteen members, appointed by the Executive Director of the Department. The P&T Committee membership shall include: 1. Four pharmacists; 2. Two Medicaid member representatives; 3. One physician who specializes in the practice of psychiatry; 4. One physician who specializes in the practice of pediatrics; 5. One physician who specializes in the treatment of clients with disabilities; 6. Four physicians from any other medical specialty. B. Physicians and pharmacists must be licensed and actively practicing while a member of the P&T Committee. C. The Department shall solicit recommendations for P&T Committee members from professional associations, client advocacy groups and other Medical Assistance Program stakeholders. D. The P&T Committee may meet and conduct business when at least any nine members are appointed to the P&T Committee. A majority of the appointed P&T Committee members constitute a quorum for the transaction of business at any P&T Committee meeting. E. P&T Committee members must disclose, at the beginning of any P&T Committee meeting, any conflicts of interest that would make it difficult to fulfill P&T Committee duties in an objective manner. RESPONSE: As the reviewer suggested, we have added a discussion of how this can be avoided and we also mention that this is not a new issue. 16. Page 19, Lines 330-331: The list should be continuously revised based on new evidence by who? RESPONSE: We have clarified that the list should be continuously revised by peer reviewers and clinician scientists based on new evidence (p. 16, line 359).
Reviewer 2	Dr. David G. Bailey
Institution	Lawson Health Research Institute, London Health Sciences Centre, London, Ont.
General comments and author response	The authors have developed a provisional short list of essential medications for children using a four-step process that involved a small group of Canadian clinicians and clinician – scientists. The purpose would be to allow other clinicians to learn more about fewer number of medications and thereby improve the appropriateness of their prescribing habits. 1. While I applaud this rationale, few clinical studies are conducted in children to assess efficacy / safety because of ethical concerns. Most decisions about use in children are based on data from the adult experience, which may not always be appropriate. I feel that this is an important concern to emphasize. Thus, I would suggest that a key aspect for including a medication in this list would be the existence of reliable and supportive peer reviewed clinical data about use in children. Since the authors did state that literature searches for efficacy and safety were conducted, they appear to be aware this issue. It is also mentioned in Limitations. However, these searches were only performed for suggested additions, subtractions or substitutions by the peer reviewers and not for medicines that remained from the WHO list. I am suggesting that the authors emphasize the pertinence of this point in the manuscript and perform a comprehensive literature search on all of the drugs as a way of solidifying confidence in their list by the reader. RESPONSE: We have added an explicit mention of this limitation in the limitations section: “We reviewed only the evidence for suggested changes; some medications on the WHO model list of essential medicines may not be well studied in children despite reviews conducted by the WHO. The list may include medicines from the WHO model list that are not effective or harmful.” (p.15, lines 334-337). 2. It would be important to know whether newly marketed drugs have been excluded from the list. In this case, prescribing information is based only on data from tightly controlled drug trials in adults. This does not account for the less frequent but very important safety aspects that become evident in the much greater and diverse patient population of the real world. The relevance of this concern is apparent in the attached publication (Lexchin J. New Drugs and Safety: What Happened to New Active Substances Approved in Canada Between 1995 and 2010? Arch Intern Med 2012;172(21):1680-1) and the accompanying commentary. The key messages are that a quarter of all newly marketed drugs will subsequently receive a serious adverse drug warning or be removed from the market. Moreover, a third of them will have this same fate if they were given pre-marketing priority review. An adequate duration of

	post marketing experience should be at least 5 years. The better situation would be when the drug is off patent and available through a generic manufacturer. In this case, potential concerns about the influence of pharmaceutical companies in the decision-making process would be further reduced. This aspect appears relevant because the final decision on the most current version is ultimately determined by a small number of clinicians, who seemed to have declared no conflict of interest, and has the possibility to affect the prescribing habits of a wide range of physicians. RESPONSE: Newly marketed drugs have not been excluded from the list. However, most of the medication from the WHO list are old. There are benefits and drawbacks of a list that contains mostly older medicines. 3. Value of this process of getting input from the community is questionable. RESPONSE: The community members provided guidance on the process and not the selection of individual medications. We have explained this in the Methods section. 4. The current website mentioned in the manuscript seems to be in the early stages of development. Although it provides a list of drugs, other indicated aspects like suggested additions, subtractions or substitutions, and literature search questions, search strategies and evidence report were not apparent despite the indication that they had been included. Moreover, the provisional list could not be found in alphabetical order or therapeutic area or include contraindications, drug interactions or cautions, adverse effects, dosing information, monitoring, and the source of the suggestion as stated. RESPONSE: To see a list of the medications in alphabetical order, click “for children” on the home page. Clicking on a medication will show you the source of the suggestion. Click “List by therapeutic area” to view the medications by therapeutic area. Click “Suggest changes to the list” to suggest a change or to view previous suggested additions, subtractions or substitutions, literature search questions, search strategies and evidence reports. Contraindications, drug interactions or cautions, adverse effects and dosing information will not be included on the website for each medication on the child list as some medications are not approved for use in children. This was included in the manuscript in error (these are only available for medications on the adult list). The manuscript has now been edited (p. 14, lines 323-324).