PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Evaluation of rational prescribing in paediatrics
AUTHORS	Choonara, Imti

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Dr. kalle hoppu Institution and Country: Museokatu 40 A 7, Helsinki, 00100, Finland Competing interests: None
REVIEW RETURNED	16-Feb-2021

GENERAL COMMENTS	A well written editorial on an important topic, but I have one comment: The author writes “In order to facilitate rational prescribing, the WHO has produced an Essential List of Medicines”. This is a too simple and “strong” statement. The primary aim of the Essential List of Medicines (EML) is to provide access to appropriate, available, affordable, and quality essential medicines. As stated by Dr Mariângela Simão, WHO Assistant Director- General, Medicines, Vaccines and Pharmaceuticals when opening the 22nd meeting of the World Health Organization (WHO) Expert Committee on the Selection and Use of Essential Medicines in 2019 (see Reference 10), the EML is primarily a tool for policy-makers to optimize selection and use of medicines at the national level to ensure access in the context of universal health coverage (UHC). That the EML is not primarily targeted for prescribing is evident from the lack of indications (except to some extent in the AWaRe classification) and dosing recommendations. The real tools of the WHO for rational prescribing are the WHO Guidelines. These are made using stringent methods for systematic evaluation of research data. EML and Rational Use of Medicines should be distinguished from each other, recognizing their distinct albeit complementary purposes. While in the background the EML is based as much as possible on evidence, the EML Expert Committee does not assess evidence systematically the way a WHO Guideline Development Group does. For example, at the time of a pandemic, there may be an acute need to have at least some medicine available for treatment of a severe disease, and to guide procurement. Then the WHO may recommend use of something that is not backed by strong evidence, like in the case of oseltamivir, which was included in the EML for treatment of the pandemic influenza virus pH1N1 in a Supplementary Meeting of the WHO Expert Committee in January 2010. The decision was based on the available evidence of the potential benefit of oseltamivir in specific patient groups and the expected prevalence of pandemic H1N1 in the coming seasons. The Committee noted the absence of RCT evidence for effectiveness and safety of all antivirals in the pandemic, as well

	as raising questions about whether any antiviral would meet the definition of an essential medicine. The 2017 Expert Committee recommended that oseltamivir be considered for deletion in 2019 unless new information supporting its use in seasonal and pandemic outbreaks is provided. However, the decision was not made in 2019, pending an ongoing update of the WHO Guidelines for clinical management of influenza (the updated Guideline is still not available although scheduled for 2018). So, oseltamivir is still on the EML although its use is questionable and can hardly be considered evidence based rational use. Regarding the Access, Watch and Reserve (AWaRe) classification of antibiotics on the EML, the WHO Expert Committee in 2019 recommended that specific listing of antibiotics in the EML and the allocation of antibiotics to the different AWaRe groups should be distinguished from each other, recognizing their distinct albeit complementary purposes. The comments above are not meant to be included in any way in the editorial, which is not on the topic of EML, but I would recommend changing the wording of the editorial to better reflect the different purposes of EML, rational use of medicines and the AWaRe classification.

REVIEWER	Reviewer name: Dr. Michael Rieder Institution and Country: Western University Schulich School of Medicine and Dentistry, Paediatrics, Canada Competing interests: None
REVIEW RETURNED	24-Feb-2021

GENERAL COMMENTS	This manuscript describes the issue of rational prescribing in paediatrics and reviews steps that have been made to improve prescribing as well as problems that remain. The issue of rational prescription drug use is germane to all patients but is of particular import in paediatrics, in part due to the frequent use of off-label drugs and in part due to the relative paucity of research in this area. The author reviews the issue of rational prescribing briefly and then describes steps that have taken to address this including the WHO Essential Medicines for Children list. The special case of neonates is considered and recommendations made. This brief manuscript is timely and provides concrete steps to move forward. The author might want to consider adding context by referencing drug utilization in children and youth notably the sharp increase in many countries in the use of psychotropic medications for children and youth (BMC Psychiatry 16, 12 (2016). https://doi.org/10.1186/s12888-016-0716-x, JAMA. 2018;319(19):2009-2020, Eur J Clin Pharmacol 2019 Oct;75(10):1333-1346). As well, while this is clearly an issue for low and medium resource countries, the issue of biologics and high cost drugs might be noted for high income countries, which is an emerging issue that will only become more problematic with time (Pediatr September 2017, 140 (3) e20171095). In terms of interventions, one area that might be discussed is the contribution - or lack thereof - of education in rational prescribing. It has been identified for some time that newly qualified physicians

	are lacking in knowledge/skill to guide optimal (or indeed rational) prescribing, and this is more markedly the case when prescribing for children (Br J Clin Pharmacol. 2012 Oct; 74(4): 644–661). It might be worth a few lines to consider on how house officers and practicing physicians can be better trained in rational prescribing.

REVIEWER	Reviewer name: Dr. Antonio Clavenna Institution and Country: IRCCS - Istituto di Ricerche Farmacologiche Mario Negri, Laboratory for Mother and Child Health, Department of Public Health, Italy Competing interests: None
REVIEW RETURNED	20-Feb-2021

GENERAL COMMENTS	The editorial addresses a relevant issue: the rational prescribing in paediatrics. I agree with Professor Choonara on the need for appropriate and applicable tools and indicators for monitoring the appropriateness of drug prescribing in children and adolescents. Until now, there is no consensus on which kind of tool could be used, and the examples cited in the editorial have some limitations and are not easily and widely applicable. The WHO classification of antibiotics reported in EML(c) can be helpful, even if it is developed mainly for low/middle income countries. A few studies suggested the use of the percentage of prescriptions covered by amoxicillin (and/or the by narrow spectrum antibiotics) as potential indicators for monitoring and comparing the appropriateness of antibiotic prescribing in European countries (de Bie S, et al Pediatr Infect Dis J. 2016;35(12):1317-1323; Piovani D, et al. BMJ Paediatr Open. 2017 Sep 11;1(1):e000169). Finally, since the editorial is mainly focused on discussing the rational prescribing of antibiotics, I would like to suggest to clarify it in the title.

VERSION 1 – AUTHOR RESPONSE

Dear Karel,
Many thanks for the helpful comments from the reviewers. I have tried to address them all
Reviewer: 1

Comments to the Author
A well written editorial on an important topic, but I have one comment:

The author writes "In order to facilitate rational prescribing, the WHO has produced an Essential List of Medicines". This is a too simple and "strong" statement. The primary aim of the Essential List of Medicines (EML) is to provide access to appropriate, available, affordable, and quality essential medicines. As stated by Dr Mariângela Simão, WHO Assistant Director- General, Medicines, Vaccines and Pharmaceuticals when opening the 22nd meeting of the World Health Organization (WHO) Expert Committee on the Selection and Use of Essential Medicines in 2019 (see Reference 10), the EML is primarily a tool for policy-makers to optimize selection and use of medicines at the national level to ensure access in the context of universal health coverage (UHC). That the EML is not primarily targeted for prescribing is evident from the lack of indications (except to some extent in the AWaRe classification) and dosing recommendations. The real tools of the WHO for rational prescribing are the WHO Guidelines. These are made using stringent methods for systematic evaluation of research data. EML and Rational Use of Medicines should be distinguished from each other, recognizing their distinct albeit complementary purposes.

While in the background the EML is based as much as possible on evidence, the EML Expert Committee

does not assess evidence systematically the way a WHO Guideline Development Group does. For example, at the time of a pandemic, there may be an acute need to have at least some medicine available for treatment of a severe disease, and to guide procurement. Then the WHO may recommend use of something that is not backed by strong evidence, like in the case of oseltamivir, which was included in the EML for treatment of the pandemic influenza virus pH1N1 in a Supplementary Meeting of the WHO Expert Committee in January 2010. The decision was based on the available evidence of the potential benefit of oseltamivir in specific patient groups and the expected prevalence of pandemic H1N1 in the coming seasons. The Committee noted the absence of RCT evidence for effectiveness and safety of all antivirals in the pandemic, as well as raising questions about whether any antiviral would meet the definition of an essential medicine. The 2017 Expert Committee recommended that oseltamivir be considered for deletion in 2019 unless new information supporting its use in seasonal and pandemic outbreaks is provided. However, the decision was not made in 2019, pending an ongoing update of the WHO Guidelines for clinical management of influenza (the updated Guideline is still not available although scheduled for 2018). So, oseltamivir is still on the EML although its use is questionable and can hardly be considered evidence based rational use.

Regarding the Access, Watch and Reserve (AWaRe) classification of antibiotics on the EML, the WHO Expert Committee in 2019 recommended that specific listing of antibiotics in the EML and the allocation of antibiotics to the different AWaRe groups should be distinguished from each other, recognizing their distinct albeit complementary purposes.

The comments above are not meant to be included in any way in the editorial, which is not on the topic of EML, but I would recommend changing the wording of the editorial to better reflect the different purposes of EML, rational use of medicines and the AWaRe classification.

Thank you. I have rephrased the section and mentioned the WHO guidelines.

Reviewer: 2

Comments to the Author
The editorial addresses a relevant issue: the rational prescribing in paediatrics.
I agree with Professor Choonara on the need for appropriate and applicable tools and indicators for monitoring the appropriateness of drug prescribing in children and adolescents.
Until now, there is no consensus on which kind of tool could be used, and the examples cited in the editorial have some limitations and are not easily and widely applicable.
The WHO classification of antibiotics reported in EML(c) can be helpful, even if it is developed mainly for low/middle income countries.
A few studies suggested the use of the percentage of prescriptions covered by amoxicillin (and/or the by narrow spectrum antibiotics) as potential indicators for monitoring and comparing the appropriateness of antibiotic prescribing in European countries (de Bie S, et al Pediatr Infect Dis J. 2016;35(12):1317-1323; Piovani D, et al. BMJ Paediatr Open. 2017 Sep 11;1(1):e000169).
Finally, since the editorial is mainly focused on discussing the rational prescribing of antibiotics, I would like to suggest to clarify it in the title.
Thank you. I have mentioned the quality indicators and referenced one of the papers. I have not changed the title, as I have included a paragraph about psychotropic medicines as requested by reviewer 3.
Reviewer: 3

Comments to the Author
This manuscript describes the issue of rational prescribing in paediatrics and reviews steps that have been made to improve prescribing as well as problems that remain.

The issue of rational prescription drug use is germane to all patients but is of particular import in paediatrics, in part due to the frequent use of off-label drugs and in part due to the relative paucity of research in this area. The author reviews the issue of rational prescribing briefly and then describes steps that have taken to address this including the WHO Essential Medicines for Children list. The special case of neonates is considered and recommendations made.

This brief manuscript is timely and provides concrete steps to move forward. The author might want to consider adding context by referencing drug utilization in children and youth notably the sharp increase in many countries in the use of psychotropic medications for children and youth (BMC Psychiatry 16, 12 (2016). https://doi.org/10.1186/s12888-016-0716-x, JAMA. 2018;319(19):2009-2020, Eur J Clin Pharmacol 2019 Oct;75(10):1333-1346). As well, while this is clearly an issue for low and medium resource countries, the issue of biologics and high cost drugs might be noted for high income countries, which is an emerging issue that will only become more problematic with time (Pediatr September 2017, 140 (3) e20171095).

In terms of interventions, one area that might be discussed is the contribution - or lack thereof - of education in rational prescribing. It has been identified for some time that newly qualified physicians are lacking in knowledge/skill to guide optimal (or indeed rational) prescribing, and this is more markedly the case when prescribing for children (Br J Clin Pharmacol. 2012 Oct; 74(4): 644–661). It might be worth a few lines to consider on how house officers and practicing physicians can be better trained in rational prescribing.

Thank you. I have added a paragraph about psychotropic meds and also mentioned education in the last concluding paragraph