PEER REVIEW HISTORY

This paper was submitted from another journal to BMJ Paediatrics Open but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Paediatrics Open. The paper was subsequently accepted for publication at BMJ Paediatrics Open.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	Public health relevance of medicines developed under paediatric legislation in Europe and the United States: a systematic mapping study
AUTHORS	Volodina, Anna Jahn, Albrecht Jahn, Rosa

VERSION 1 – REVIEW

REVIEWER	Pragnadyuti Mandal
REVIEW RETURNED	11-Feb-2024

GENERAL COMMENTS	In the manuscript in Page 4 (line3 &4, paragraph 1) it is reported that "the codes obtained were mapped to the most detailed DALY causes in children (0-14 years, total DALYs and rate) for each country and globally. Mapping was done using Institute for Health Metrics and Evaluation (IHME) tool (used DALYs per 100000, 0-14 years)". The researchers did not consider late adolescents (age band 15-18 years) for analysis and reporting. The disease profile, DALY causes in 15-18 years and mapping of the sampled medicines to the DALYs of the target conditions in late adolescents were not revealed. The European Pediatric Regulation came into force in European Union (EU) to improve the health of children in Europe by facilitating the development and availability of medicines for children aged 0-17 years. So the 15-18 years age group should also be considered for analysis (if possible, in future studies) rationalizing the importance of developmental window of childhood and adolescent consistent with newer understanding of neurodevelopment but also global shifts in the timing of key social role positions. At a global level, relative transition in epidemiology by age and socio-demographic development resulted in communicable disease burden increasingly shifting from children younger than 5 years to older children and adolescents which have been revealed in studies and particularly observed in the defined timeline of 1990-2019. Analysis in trends in 2019 has revealed that the impressive gains in the early childhood mortality have not been extended to older children and adolescents. Tuberculosis and HIV both have been emerging as important cause of infectious disease

	burden in children and adolescence. Excess mortality-to-incidence (MIR) for HIV has been reported for males aged 15-19 years in low socio-demographic settings. So it is preferable that during mapping of sampled medicines to the DALYs of the target condition(s), age group division should be done and data should be expressed in the disaggregated manner which should include the 15-18 years age group to fulfill the pediatric health needs.

REVIEWER	Dr. Maraisha Philogene Boston Children's Hospital
REVIEW RETURNED	24-Feb-2024

GENERAL COMMENTS	The authors presented an interesting and well-written study assessing the impact of European Union and United States pediatric legislation on the availability and access to pediatric medicine globally, with a focus on the potential impact of sample of medications from the EMA and FDA on the global burden of pediatric diseases, utilizing DALYs and asses their status on essential medication list. The study is significant as there continues to be a need for incentives in research and development in pediatric care globally, and a need for expansion of access to medication for pediatric patients, but it is important that it correlates with the needs of the global pediatric population. Recommendations: 1. Research Gap and Limitations: Although this study highlights the discrepancy in medication and global disease burden in the pediatric population, neonatal disorders were shown to have the highest burden. Neonatal disorders include prematurity, hypoxic ischemic encephalopathy, and neonatal sepsis. For these disorders, non-pharmacological intervention and health system strengthening are often required to improve outcomes, which cannot be captured by the authors' study as they are mapping only medications. The authors mention this briefly in the conclusion, but I would recommend highlighting this as a reason for the possible discrepancy, as it could be misleading to the reader.

REVIEWER	Dr. Surangi Jayakody University of Warwick Faculty of Science Engineering and Medicine, Health Sciences
REVIEW RETURNED	27-Feb-2024

GENERAL COMMENTS	An important area of enquiry. However, some areas of the article need to be improved. The topic and the study aim/objectives should be consistent. The topic is stated as 'public health relevance', which is fairly broad. Suggest altering the topic to reflect the study objectives. What is already known about the topic? What does the study add? What the authors mentioned is quite broad. Need to be specific. What is meant by 'benefited'? In which aspects? Abstract - methods sections needs to be strengthened. Systematic mapping studies are conducted to create a map of wide research in a particular subject area. The justification for

	selecting the design for the current study should have been strengthened. When conducting a SMS, it's a good practice to follow and report five essential steps. The authors have mentioned some, but a few important points are lacking. 1. Study planning: Why did you choose systematic mapping? Reason for including selected countries (few reasons were given, however, need to be strengthened.) 2. Search strategy: This should be clearly stated. What databases used, any keywords or search terms, and how did you access them? Inclusion and exclusion criteria, selection process, whether its independent selection, etc. 3. Data extraction- More details needed 4. Classification- mentioned 5. data analysis and mapping- mentioned Satisfactory discussion and conclusion. Whilst there is evidence of critical analysis and reflection, some issues require further exploration. There is evidence of originality of thought, although some areas are underdeveloped and managed in an unimaginative/ illogical way.

REVIEWER	Dr. Jennifer Walsh Jenny Walsh Consulting Ltd
REVIEW RETURNED	29-Feb-2024

GENERAL COMMENTS	Interesting research into the impact of EU and US paediatric regulations on the development of paediatric medicines globally. Introduction Suggest you refer to "new" medicinal products (or medicines instead of "novel" medicines. (The requirement also includes medicines covered by a patent or supplementary protection certificate). Method Please include year of EML and EMLc. Method/Results Can you please comment on the inclusion of e.g., maternal disorders, STD excluding HIV, gynaecological disorders and substance use disorders, taking into account their relevance for the majority of paediatric patients? (It is recognised that they could be applicable to older adolescents). What are considered to be oral disorders? Did you evaluate off-patent drugs in your analysis? (e.g. PUMAs in Europe). Discussion Are you able to comment on or refer to the differences between incentives for the development of new paediatric medicines and those for developing paediatric medicines of off-patent drugs?

	Note, medicines on the EML and EMLc can only be added through the submission of new applications and after thorough review by the Expert Committee considering evidence of clinical benefit as well as cost and supply. There is quite often a lag time between a new licence approval and adoption on the list (if appropriate). Can you comment paediatric regulations or progress towards paediatric medicine development in other markets, e.g. Japan, China? What about new initiatives to increase the development of and access to paediatric medicines e.g. GAP-f? An additional point to consider is if a new medicine is needed for a particular indication. For example, anxiety disorders may be supported by other interventions such as CBT. Of note, some of the (old) medicines for such disorders were removed from the EMLc as they were considered to be no longer appropriate. Your results also show a lack of neonatal medicines which I understand is a recognised gap due the challenges of conducting research in this group of patients. Access to medicines and other factors could also be considered. For example, diarrhoeal diseases are a huge killer in LMICs (as noted in S1) and some of this could potentially be attributed to limited access to ORS and/or lack of sanitation. Another interesting reference on the EU paediatric regulation: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7884470/ Toma 2021

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1 Pragnadyuti Mandal

Question 1.1:

In the manuscript in Page 4 (line3 &4, paragraph 1) it is reported that “the codes obtained were mapped to the most detailed DALY causes in children (0-14 years, total DALYs and rate) for each country and globally. Mapping was done using Institute for Health Metrics and Evaluation (IHME) tool (used DALYs per 100000, 0-14 years)”.

The researchers did not consider late adolescents (age band 15-18 years) for analysis and reporting. The disease profile, DALY causes in 15-18 years and mapping of the sampled medicines to the DALYs of the target conditions in late adolescents were not revealed.

The European Pediatric Regulation came into force in European Union (EU) to improve the health of children in Europe by facilitating the development and availability of medicines for children aged 0-17 years. So the 15-18 years age group should also be considered for analysis (if possible, in future studies) rationalizing the importance of developmental window of childhood and adolescent consistent with newer understanding of neurodevelopment but also global shifts in the timing of key social role positions.

At a global level, relative transition in epidemiology by age and socio-demographic development resulted in communicable disease burden increasingly shifting from children younger than 5 years to older children and adolescents which have been revealed in studies and particularly observed in the defined timeline of 1990-2019. Analysis in trends in 2019 has revealed that the impressive gains in the early childhood mortality have not been extended to older children and adolescents. Tuberculosis and HIV both have been emerging as important cause of infectious disease burden in children and adolescence. Excess mortality-to-incidence (MIR) for HIV has been reported for males aged 15-19 years in low socio-demographic settings.

So it is preferable that during mapping of sampled medicines to the DALYs of the target condition(s), age group division should be done and data should be expressed in the disaggregated manner which should include the 15-18 years age group to fulfill the pediatric health needs.

Response:

Thank you for this comment. It is correct that older adolescents from 15 to less than 18 years old were not included in the DALYs evaluation. This is because we worked with the Global Burden of Disease (GBD) database which has pre-defined age ranges. These age ranges do not include the age category of 0-18 years, which would be aligned with the regulatory definition of paediatric population. It also does not include a stand-alone age category of 15-18 years that we could use together with the age group 0-14 years. Out of the available age categories we selected the age group of 0-14 years for DALYs analysis as the most critical for age-appropriate drug research and development.

We thank you for the proposal to perform the age group division and express the data in the disaggregated manner. We will consider this proposal for future studies. For this manuscript we have now included the following sentence in the Limitations section:

“The exclusion of contraceptives and symptomatic treatments, i.e. pain killers, and the paediatric age group from 15 to 18 years of age from the DALYs mapping may have underestimated the responsiveness of the studied medicines sample to paediatric needs.”

Finally, we would like to emphasize that we made an effort to adress the health needs of older adolescents by reviewing the Essential Medicines Lists for both children as well as adults. The study reports the following:

“Methods:

To account for the difference in the paediatric population between the EMLc (up to 13 years) and paediatric legislation (up to 18 years), and to capture essential medicines for adolescents, we included the EML in our review. “

[…]

Results:

“Of the 26 medicines included only in the EML, 7 were for adolescent use for mental disorders, emergency contraception or HIV/AIDS pre-exposure prophylaxis.”

Reviewer: 2

Dr. Maraisha Philogene, Boston Children's Hospital

Comments to the Author

The authors presented an interesting and well-written study assessing the impact of European Union and United States pediatric legislation on the availability and access to pediatric medicine globally, with a focus on the potential impact of sample of medications from the EMA and FDA on the global burden of pediatric diseases, utilizing DALYs and asses their status on essential medication list. The study is significant as there continues to be a need for incentives in research and development in pediatric care globally, and a need for expansion of access to medication for pediatric patients, but it is important that it correlates with the needs of the global pediatric population.

Question 2.1:

Research Gap and Limitations: Although this study highlights the discrepancy in medication and global disease burden in the pediatric population, neonatal disorders were shown to have the highest burden. Neonatal disorders include prematurity, hypoxic ischemic encephalopathy, and neonatal sepsis. For these disorders, non-pharmacological intervention and health system strengthening are often required to improve outcomes, which cannot be captured by the authors' study as they are mapping only medications. The authors mention this briefly in the conclusion, but I would recommend highlighting this as a reason for the possible discrepancy, as it could be misleading to the reader.

Response:

Thank you for this comment which we agree with. In fact, we elaborated on this point in earlier drafts but then removed it to respect the word count limit of the Journal. Your comment suggests that this message is in fact critical and essential for the readers and we therefore add the following text in the Discussion and Conclusion:

Discussion

[…]

Our study also highlights that successful drug development does not always result in practical use. For example, Australia and Canada were the only countries with a negligible burden of vaccine-preventable diseases in our study. These findings underscore the relevance of health system and other barriers that affect access to existing medicines, particularly in LMICs (~~29~~35). ~~Public health efforts aimed at securing access to available treatments need to continue.~~ Reducing access barriers and increasing coverage of approved medicines is therefore critical. The same applies to access to surgery, mental health services, and other non-pharmacological interventions, which may be required to address some of the included paediatric conditions, such as injuries, congenital birth defects or mental disorders. Our findings also underscore the relevance of diseases related to poor living conditions and unhealthy environments, including enteric infections and nutritional deficiencies. Addressing these requires the provision of access to safe water and sanitation, food security, and health education. Public health interventions beyond pharmaceutical policies thus remain indispensable in reducing paediatric disease burden and need to continue (36-37).

[…]

Conclusion

Medicines developed under the paediatric legislation in the EU and US are only partially responsive to paediatric health needs and exhibit a disproportionate focus on NCDs. To be considered for wider implementation, paediatric incentives and obligations should therefore be more targeted towards paediatric health needs. International harmonisation of legislation and alignment with global research priorities could further strengthen its impact on child health and support ongoing efforts to improve access to authorised treatments. ~~Efforts should be made to ensure global access to authorised paediatric medicines.~~ Finally, health interventions beyond improving access to medicines are needed to achieve a global reduction of paediatric disease burden.

Reviewer: 3

Dr. Surangi Jayakody, University of Warwick Faculty of Science Engineering and Medicine

Question 3.1:

An important area of enquiry. However, some areas of the article need to be improved. The topic and the study aim/objectives should be consistent. The topic is stated as 'public health relevance', which is fairly broad. Suggest altering the topic to reflect the study objectives.

Response:

Thank you for this proposal. We believe that the original title is appropriate. However, we have considered the suggestion of the reviewer and developed an alternative title to reflect the study objectives as following:

Responsiveness of medicines developed under paediatric legislation in Europe and the United States to health needs in other countries: a systematic mapping study

For the final title, we will follow the advice of the Editor(s).

Question 3.2:

What is already known about the topic? What does the study add? What the authors mentioned is quite broad. Need to be specific. What is meant by 'benefited'? In which aspects?

Response:

Thank you for this comment. We revised respective text as following:

“What is already known on this topic

Paediatric legislation in the European countries and the United States has stimulated research and development of medicines for children. According to impact assessments, the number ~~availability~~ of paediatric medicines in these countries has increased ~~benefited~~. However, there are no studies to assess the potential impact on the childhood burden of disease beyond these countries and globally.

What this study adds

Emerging treatments do not reflect the disease burden in high-income countries and diverge even further from the needs in resource-constrained settings. Nevertheless, they offer more treatment options for select high-burden conditions, such as universally occurring infections and debilitating non-communicable diseases. They are also important contributors to the WHO lists of essential medicines. To achieve a better public health impact paediatric legislation should be expanded internationally, harmonised and tailored to global research priorities in children."

Question 3.3:

Abstract - methods sections needs to be strengthened.

Response:

Thank you for this comment. We have revised the Methods in the Abstract as following:

"Methods

We searched EU and US regulatory databases for medicines with approved indications resulting from completed paediatric development between 2007 and 2018. Of 195 medicines identified, 187 could be systematically mapped to the burden of the target disease for six study countries (Australia, Brazil, Canada, Kenya, Russia, South Africa) and globally, using Disability Adjusted Life Years (DALYs). All medicines were also screened for inclusion on the World Health Organisation Model List of Essential Medicines (EML) and the EML for children under 13 years (EMLc)."

We also revised the Results in the Abstract to remain within the word count limit.

Question 3.4:

Systematic mapping studies are conducted to create a map of wide research in a particular subject area. The justification for selecting the design for the current study should have been strengthened. When conducting a SMS, it's a good practice to follow and report five essential steps. The authors have mentioned some, but a few important points are lacking.

1. Study planning: Why did you choose systematic mapping? Reason for including selected countries (few reasons were given, however, need to be strengthened.)

2. Search strategy: This should be clearly stated. What databases used, any keywords or search terms, and how did you access them? Inclusion and exclusion criteria, selection process, whether its independent selection, etc.

3. Data extraction- More details needed

Response: Thank you for this question. We have revised the Methods section and substantiated it with further details as requested. Please refer to pages 3-4 of the revised manuscript.

Question 3.4 cont´d:

4. Classification- mentioned

5. data analysis and mapping- mentioned

Satisfactory discussion and conclusion. Whilst there is evidence of critical analysis and reflection, some issues require further exploration.

There is evidence of originality of thought, although some areas are underdeveloped and managed in an unimaginative/ illogical way.

Response: thank you, assessment noted.

Reviewer: 4

Dr. Jennifer Walsh, Jenny Walsh Consulting Ltd

Question 4.1:

Interesting research into the impact of EU and US paediatric regulations on the development of paediatric medicines globally.

Introduction
Suggest you refer to "new" medicinal products (or medicines instead of "novel" medicines. (The requirement also includes medicines covered by a patent or supplementary protection certificate).

Response:

Thank you for this comment. We agree to use “new medicines” instead of “novel medicines” and have implemented this change throughout the manuscript.

Question 4.2:

Method
Please include year of EML and EMLc.

Response: Thank you for this comment. We have now added the year of EML and EMLc in the “Methods” section (page 4) as following:

“The INN search of the full sample was performed in the 23rd EML and the 9th EMLc from 2023.”

Furthermore, the year of EML and EMLc has been added in “Results” section (page 9) in Table 6.

Question 4.3:

Method/Results
Can you please comment on the inclusion of e.g., maternal disorders, STD excluding HIV, gynaecological disorders and substance use disorders, taking into account their relevance for the majority of paediatric patients? (It is recognised that they could be applicable to older adolescents).

Response:

Thank you for this question. It should be noted that DALY causes were used without modification, as defined in the Global Burden of Disease study. We concur that some DALY causes contain conditions with varying prevalence across the paediatric population (e.g. substance use disorders), while others could be considered universal (e.g. influenza). We are happy to clarify why we analyse and report all DALY causes as defined by the Global Burden of Disease study, including maternal disorders, STD excluding HIV, gynaecological disorders and substance use disorders.

The EU/US Paediatric legislation defines children as those from 0 to less than 17 years (US)/less than 18 years (EU), a diverse patient population with a wide range of health issues. This diversity makes it difficult to justify an exclusion of a DALY cause with confidence/without being subjective.

Furthermore, the study aimed to map and characterize medicines resulting from the EU/US legislation irrespective of the disease area. It was not designed to sample medicines with DALY causes relevant to a majority of patients. No selection of indications was made at the time of sampling, consequently no selection of DALY causes from the GBD database was deemed justified.

We were also aware that one of the criticisms of the EU legislation was the development of paediatric medicines for adult conditions. This was another important argument for analysing and reporting all DALYs causes as defined by the Global Burden of Disease study, regardless of how relevant they might be to the majority of children.

Finally, this study looks at countries that have different maturity levels of health care, diverse disease profile, regulatory system, and are different in many other ways. Mindful of these country differences, we refrained from pre-specifying DALYs causes for analysis. As seen from the study results, DALY cause that may not be relevant in Canada (e.g. “Sexually transmitted diseases excluding HIV/AIDS”) is of relevance in Kenya and South Africa.

To summarise, we included all DALY causes to account for the diversity of health conditions in the patient population, international nature of the study and to characterise all sampled medicines most comprehensively.

Question 4.4:

What are considered to be oral disorders?

Response:

As stated in the Attachment 1_Global Burden of Disease tool, oral disorders are mapped with the following ICD-10 codes:

K00-K08.499: Disorders of tooth development and eruption, Retained and impacted teeth, Dental caries, Other diseases of the dental hard tissues, Diseases of the pulp and periapical tissue, Gingivitis and diseases of the periodontium, Other diseases of the gingiva and edentulous alveolar ridge, Dentofacial anomalies, Other diseases of the teeth and periodontium

K08.8-K14.9, Cysts of the oral region, not elsewhere classified, Other diseases of the jaw, Diseases of the salivary glands, Stomatitis and related diseases, Other diseases of the lip and oral mucosa, Diseases of the tongue M26-M27.9: Dentofacial anomalies [including malocclusion], Other diseases of jaws

Z01.2-Z01.21: Examination of the teeth

Z13.84 Special procedures to examine for other specified diseases or disorders

- Dental diseases

Z96.5: Presence of dental root or lower jaw implants

The GBD tool is described in the Methods section and is referenced in the manuscript (reference 14).

Question 4.5:

Did you evaluate off-patent drugs in your analysis? (e.g. PUMAs in Europe).

Response:

We sampled all EU medicines that had Paediatric Investigation Plans and were approved for use in children by 2018, as long as they were not withdrawn due to safety concerns at the time of sampling in 2021. The sampling process did not differentiate between new and off-patent medicines and the sample included at least one PUMA medicine.

Question: 4.6

Discussion

Are you able to comment on or refer to the differences between incentives for the development of new paediatric medicines and those for developing paediatric medicines of off-patent drugs?

Response:

For the purpose of the Response letter, we can comment that EU incentives for off-patent medicines have had limited results and can be considered ineffective in encouraging industry engagement. This is a public health issue because many medicines used off-label in children are old, off-patent medicines.

They are given in inappropriate formulations; in some countries they are not reimbursed. This affects patient access and adherence to necessary treatments and requires new approaches from policy makers and other relevant stakeholders to stimulate the development of age-appropriate treatments after patent expiry.

We have added the following sentence in the Discussion in response to this question:

"Nonetheless, fostering needs-driven R&D for paediatric medicines requires complementary financing mechanisms directed at the development of original paediatric medicines beyond the scope of paediatric legislation. This could be particularly relevant for off-patent medicines where the incentives of the EU legislation were shown to be insufficient (23). Efforts to define missing medicines were undertaken in the past (31-32) and could serve as a sound basis for policy development in this area."

Question 4.7:

Note, medicines on the EML and EMLc can only be added through the submission of new applications and after thorough review by the Expert Committee considering evidence of clinical benefit as well as cost and supply. There is quite often a lag time between a new licence approval and adoption on the list (if appropriate).

Response:

Thank you for that clarification. We agree that processes such as EML application and review take time. As we sampled medicines authorised in children up to 2018 and reviewed the last EML and EMLc from 2023, we felt that we had at least partially accounted for a possible time lag between new authorisation and adoption of the list. However, we agree and cannot exclude that more sampled medicines may be included in the EMLs in future.

Question 4.8:

Can you comment paediatric regulations or progress towards paediatric medicine development in other markets, e.g. Japan, China?

Response:

Thank you for this question. Paediatric regulations in other countries are beyond the study scope. To address this question, we have included the following sentence in the limitations:

"Research in other geographical regions is recommended to further refine policy recommendations."

Question 4.9:

What about new initiatives to increase the development of and access to paediatric medicines e.g. GAP-f?

Response: thank you for this question. We agree that such initiatives are crucial in improving availability of pharmaceutical treatments for children. We added the following sentence in the Discussion in response to this question:

"Finally, alongside with regulatory policies, global initiatives and research collaborations such as the Global Accelerator for Paediatric Formulations Network (GAP-f) and the International Neonatal Consortium will continue to play a critical role in facilitating development and access to paediatric medicines (33-34)."

Question 4.10:

An additional point to consider is if a new medicine is needed for a particular indication. For example, anxiety disorders may be supported by other interventions such as CBT. Of note, some of the (old) medicines for such disorders were removed from the EMLc as they were considered to be no longer appropriate.

Response:

Thank you for this comment, which we absolutely support. We addressed the importance of non-pharmaceutical interventions for child health by adding the following paragraph to the discussion (please also refer to response to question 2.1 from the Reviewer 2):

"**Discussion**

[…]

Our study also highlights that successful drug development does not always result in practical use. For example, Australia and Canada were the only countries with a negligible burden of vaccine-preventable diseases in our study. These findings underscore the relevance of health system and other barriers that affect access to existing medicines, particularly in LMICs (29). ~~Public health efforts aimed at securing access to available treatments need to continue.~~ Reducing access barriers and increasing coverage of approved medicines is therefore critical. The same applies to access to surgery, mental health services, and other non-pharmacological interventions, which may be required to address some of the included paediatric conditions, such as injuries, congenital birth defects or mental disorders. Our findings also underscore the relevance of diseases related to poor living conditions and unhealthy environments, including enteric infections and nutritional deficiencies. Addressing these requires the provision of access to safe water and sanitation, food security, and health education. Public health interventions beyond pharmaceutical policies thus remain indispensable in reducing paediatric disease burden and need to continue (36-37).

[…]

Conclusion

Medicines developed under the paediatric legislation in the EU and US are only partially responsive to paediatric health needs and exhibit a disproportionate focus on NCDs. To be considered for wider implementation, paediatric incentives and obligations should therefore be more targeted towards paediatric health needs. International harmonisation of legislation and alignment with global research priorities could further strengthen its impact on child health and support ongoing efforts to improve access to authorised treatments. ~~Efforts should be made to ensure global access to authorised paediatric medicines.~~ Finally, health interventions beyond improving access to medicines are needed to achieve a global reduction of paediatric disease burden."

Question 4.11:

Your results also show a lack of neonatal medicines which I understand is a recognised gap due the challenges of conducting research in this group of patients.

Response:

We agree that neonates are a challenging subset of the paediatric population for research. A well-developed clinical research infrastructure and innovate research approaches are required to facilitate the R&D in this vulnerable group, and regulatory policies alone will not address all the hurdles. We included the following paragraph in the Discussion in response to this comment, to highlight that efforts beyond regulatory are needed:

"Finally, alongside with regulatory policies, global initiatives and research collaborations such as the Global Accelerator for Paediatric Formulations Network (GAP-f) and the International Neonatal Consortium will continue to play a critical role in facilitating development and access to paediatric medicines (33-34)."

Question 4.12:

Access to medicines and other factors could also be considered. For example, diarrhoeal diseases are a huge killer in LMICs (as noted in S1) and some of this could potentially be attributed to limited access to ORS and/or lack of sanitation.

Response:

Thank you for this comment, which we agree with. We addressed the importance of strengthening access to available treatments and non-pharmaceutical interventions in the Discussion and Conclusion, please refer to the response to question 4.10 above.

Question 4.13:

Another interesting reference on the EU paediatric regulation:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7884470/
Toma 2021

Response:

Indeed, this is an extremely valuable paper which we have now included in this manuscript (please see reference 11) and referenced in the past in another publication on paediatric medicines, please see: Suitability of paediatric legislation beyond the USA and Europe: a qualitative study on access to paediatric medicines | BMJ Public Health