Workstream 2:

Review the Essential Medicine List: EML and EMLc for gaps

Summary Report on the Review of the EML to Identify Medicines that have Potential Therapeutic Utility in Children but are not included on the EMLc

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Table of Contents

1. Introduction

Essential medicines are those that satisfy the priority healthcare needs of the population and are intended to be available in functioning health systems at all times, in appropriate dosage forms, of assured quality and at prices individuals and health systems can afford. Every two years since 1977, the World Health Organization (WHO) has published the Model List of Essential Medicines (EML), intended as a guide for countries or regional authorities to adopt or adapt in accordance with local priorities and treatment guidelines, for the development of national essential medicines lists. In 2007, the WHO published its first Model List of Essential Medicines for Children (EMLc), an evidence-based list of medicines for children up to and including the age of 12 years. The EMLc has since been updated every two years, with the most recent one published in October 2021.

Under the framework of the WHO-hosted Global Accelerator for Paediatric Formulations Network, WHO is currently carrying out a comprehensive and thorough review of the EMLc to inform the next update of the list in 2023. One of the activities within the project is the review of the EML to identify medicines that have potential therapeutic utility in children but that are not currently included on the EMLc. This report provides a summary of the method applied and results of the comparison of medicines on the EML and EMLc and recommended next steps to facilitate the 2023 EMLc update.

2. Method

The Model Lists are available in electronic format (eEML) (eEML - Electronic Essential Medicines List (essentialmeds.org)) from which data may be exported in PDF, Excel, or Word formats. In addition, filters may be applied according to target population (age and sex). The EML and EMLc are also available in PDF report format, where medicines are listed according to therapeutic area. Medicines with more than one therapeutic use may be listed in more than one section.

2.1 Identification of medicines on the EML that are not listed on the EMLc

Medicines listed on the EML which are not on the EMLc were identified by exporting four separate medicine lists from the eEML (2019 version) into Excel, by applying the relevant target population filter, as follows:

- Any (all ages, no filter)
- Adolescents and adults
- 1 month to 12 years
- Neonates

The lists were then combined to generate a master spreadsheet that showed for each medicine, the age group(s), formulation(s) and indication(s) of listing.

Each line (i.e., medicine, formulation, indication, target population) of the master spreadsheet was then manually checked and compared with the eEML to ensure consistency and validate the results.

A second quality check of the master spreadsheet was conducted by interrogating and comparing with the PDF EMLc (2019) to confirm consistency of the results. Any

discrepancies in results were identified and rectified during this manual check, to ensure accuracy.

Appropriate filters were then applied to the validated and quality-checked master spreadsheet to extract a list of medicines and indications which were included on the EML but not included on the PDF EMLc (2019).

2.2 Identification of medicines for potential consideration for addition to the EMLc

All medicines in sections known to be excluded from the EMLc due to the absence of therapeutic need in children, (e.g., contraceptives, ovulation inducers, uterotonics, medicines for Parkinsonism, etc.) were identified and excluded from further review.

Each of the remaining medicines and their indications were then reviewed and assessed for their potential suitability for inclusion on the EMLc by interrogating product Labels/Summary of Product Characteristics (SmPCs) from the US Food and Drug Administration (FDA) and UK Medicines for Healthcare Regulatory Authority (MHRA), which were considered to represent Stringent Regulatory Authorities (SRAs). SmPCs published by the Australian Therapeutic Goods Administration (TGA) or European Medicines Agency (EMA) were interrogated if limited or conflicting information was available from the FDA and MHRA, for example, apparent discrepancies in approved age limits and indications.

On occasion, internet searches were also conducted when further information was required to assist with the evaluation. For example, information on the prevalence and potential burden of a particular condition in children aged below 12 years was sought, to help understand its relevance in paediatric patients. The EMA lists of Paediatric Therapeutic Needs were also evaluated for information (Needs for paediatric medicines | European Medicines Agency (europa.eu).

Medicines for which a product licence was available for patients aged below 12, and medicines that were not indicated for children aged 12 years and below were classified accordingly in the spreadsheet. Medicines for which utility in paediatric patients was less clear, for example, due to a lack of information on product Labels/SmPCs, were classified separately.

The updated edition of the EMLc was published in late 2021 (EMLc 2021). Since the above review had considered the 2019 edition of the EMLc, medicines previously identified as having potential for addition to the EMLc were reviewed for their inclusion in the PDF EMLc 2021. This review also considered therapeutic equivalents, where specified on the EMLc 2021.

For full details of the data collection and management approach, refer to Appendix A.

3. Results

3.1 Identification of medicines on the EML that are not listed on the EMLc

A total of 492 medicines and medicine combinations, and over 1200 indications were compiled into the combined master spreadsheet (“EML-lists-combined checked-filters_MASTER_FINALV1”) from the separate eEML exported spreadsheets. According to

the eEML target population filters, 34 of the 492 medicines were listed as being indicated for children aged 1 month to 12 years, whilst 11 were indicated for neonates.

A copy of the combined master spreadsheet is provided in Appendix B.

The application of appropriate filters to the combined master spreadsheet successfully extracted a list of medicines and indications that were included on the EML but not on the EMLc. A total of 214 medicines were identified for further review. It should be noted that some of these medicines were included on the EMLc but for different indications compared to the EML, and these differences were noted in the spreadsheet comments fields.

3.2 Identification of medicines for potential addition to the EMLc

The results of the review of the potential paediatric therapeutic utility of medicines identified as being on the EML but not on the EMLc, and compared against the EMLc 2021 are provided in the spreadsheet below:

"EML_medicines_not on_EMLc2019_checked_with EMLc2021_MASTER-FINALV1_2022"

EML_medicines_not
_on_EMLc2019_chec

(Please note, it is recommended any links are disabled)

Medicines that were identified from the review of the EMLc 2019 as having utility in patients aged 12 years and below, and that were already added to the EMLc in 2021 were highlighted in green. Medicines identified as having clear utility in paediatric patients (≤ 12 years) based on their SRA authorisation for use in children as per their SmPC/Label, that had not been added in the 2021 update were highlighted in yellow. Medicines that were identified as potentially having utility in paediatric patients (≤ 12 years) but requiring further information to evaluate their benefit were highlighted in pink. For example, where a medicine was not indicated for paediatric patients, but where the SmPC/Label stated the product "may be used in children".

Medicines that were identified for potential addition from the review of the EMLc 2019, which were added to the EMLc 2021 are listed in Table 1 ("green"). This includes therapeutic alternatives as shown.

Table 1
Medicines identified for potential addition to the EMLc according to product licence labelling and that were added in 2021

Medicine Name	Comments
Beclometasone (respiratory)	Included as a therapeutic alternative to budesonide
Carbimazole	Included as a therapeutic alternative to methimazole
Clotrimazole (topical)	Included as a therapeutic alternative to miconazole (topical)
Daclatasvir	Included for treatment of chronic hepatitis C
Dalteparin	Included as a therapeutic alternative to enoxaparin
Darbepoetin alfa	Included as a therapeutic alternative for erythropoiesis stimulating agents
Epoetin alfa	Included as a therapeutic alternative for erythropoiesis stimulating agents
Epoetin beta	Included as a therapeutic alternative for erythropoiesis stimulating agents
Epoetin theta	Included as a therapeutic alternative for erythropoiesis stimulating agents
Ergocalciferol	Included as a therapeutic alternative to colecalciferol
Etanercept	Included as a therapeutic alternative to adalimumab
Gleceprevir + Pibrentasvir	Included for treatment of chronic hepatitis C
Indometacin	Included as a therapeutic alternative to ibuprofen IV (preterm infants)
Infliximab	Included as a therapeutic alternative to adalimumab
Podophyllotoxin (topical)	Included as a therapeutic alternative to podophyllum resin
Polygeline	Included as a therapeutic alternative to dextran 70
Sofosbuvir	Included for treatment of chronic hepatitis C
Sofosbuvir + Velpatasvir	Included for treatment of chronic hepatitis C

Medicines that were identified as having therapeutic utility in paediatric patients aged 12 years or below based on their SmPC/Label but were not added to the EMLc 2021, and hence could be considered for inclusion on the EMLc, are listed in Table 2 (“yellow”).

Several statins were identified in this group of medicines, which according to SRA product licences, are indicated for older paediatric patients aged from 8-10 years. (The minimum recommended age for atorvastatin, fluvastatin, and simvastatin is 10 years (boys Tanner Stage II and above and girls who are at least one year post-menarche), whilst that for pravastatin is 8 years). Atorvastatin, fluvastatin, lovastatin and pravastatin are specified as therapeutic alternatives to simvastatin on the EML. Although according to their product labels these medicines may potentially have limited utility for the age population covered by the EMLc (patients aged 0-12 years), they could be considered for inclusion.

Table 2
Medicines identified for potential future consideration for addition to the EMLc according to product licence labelling

Medicine Name	Indication[1]	Minimum Age[1]
Amlodipine	Hypertension	From 6 years
Atorvastatin	Familial hypercholesterolaemia	From 10 years
Atracurium	Skeletal muscle relaxant	From 1 month
Budesonide + Formoterol (respiratory)	Asthma	From 6 years
Fentanyl patches	Chronic (cancer) pain (patients on opioid therapy)	From 2 years
Fluvastatin	Familial hypercholesterolaemia	From 9/10 years
Losartan	Hypertension	From 6 years
Mesalazine	Ulcerative colitis	From 5/6 years
Pravastatin	Familial hypercholesterolaemia	From 8 years
Selenium sulfide (topical)[2]	Seborrhoeic dermatitis	From 2 years
Simvastatin	Familial hypercholesterolaemia	From 10 years
Sodium nitroprusside	Antihypertensive crisis	No minimum age specified
Sulfasalazine[2]	Ulcerative colitis	From 6 years[3]

[1] According to SRA product licence SmPC/Label; [2] May also potentially have utility in other indications (e.g., "may be used…" stated on label); [3] Tablets are listed on the EML and are indicated for patients aged 6 years and above in some labels. A suspension is available for patients aged from 2 years, which is not listed in the EML.

Table 3 lists medicines and their indications that are on the EML but not the EMLc, that may potentially have utility in paediatric patients (≤ 12 years), and could be considered for inclusion on the EMLc, but for which further information, and/or opinion from paediatric and disease area experts is required ("pink"). According to SRA SmPCs/Labels, these medicines do not appear to be approved for paediatric use for these indications, although they "may be used", suggesting some data may be available. This list excludes antiretrovirals since this group of medicines is undergoing a separate review.

Table 3
Medicines on the EML that may have therapeutic utility in children

Medicine Name	Indication
Amidotrizoate	Diagnostic agent
Calcium	Nutritional supplement
Ephedrine	Anaesthesia local
Golimumab	Juvenile idiopathic arthritis
Ipratropium bromide (respiratory)	Asthma
Latanoprost	(Paediatric) Glaucoma
Methylthioninium chloride	Acquired methaemoglobinaemia
Pegylated interferon alfa (2a/2b)	Chronic hepatitis C
Penicillamine	Exposure to noxious substances
Pilocarpine	(Paediatric) Glaucoma
Sodium nitrite	Exposure to noxious substances
Sodium thiosulphate	Exposure to noxious substances
Timolol	(Paediatric) Glaucoma
Tranexamic acid	Haemorrhage
Verapamil	Supraventricular tachyarrhythmia

Indications that are listed for specific medicines on the EML but are not listed for these medicines on the EMLc, that may be applicable to paediatric patients (≤ 12 years), but require further evaluation are shown in Table 4 (“pink”).

Table 4
Potential additional indications for medicines listed on the EMLc

EMLc Medicine Name	Potential Additional Indication(s)
Clarithromycin	In combination with ceftriaxone, cefotaxime, or amoxicillin + clavulanic acid for bacterial pneumonia; *H pylori*
Digoxin	Cardiac arrhythmia
Hydrochlorothiazide	Hypertension
Lidocaine	Ventricular tachyarrhythmia
Paclitaxel	Kaposi sarcoma
Pentamidine	Pneumocystosis
Ribavirin	Chronic hepatitis C
Vinblastine	Kaposi sarcoma

4. Discussion

The review and comparison of medicines on the EML with those on the EMLc 2019 identified approximately thirty medicines for potential consideration for inclusion in the EMLc, according to their product licences.

It is encouraging to note that the review of the EMLc 2021 showed that nearly two thirds of the medicines identified to be considered for potential addition from the initial review had been included, some of which were listed as therapeutic alternatives for medicines currently on the list.

The interrogation of stringent regulatory agency product labelling enabled medicines licensed for paediatric use to be identified, i.e., where sufficient safety and efficacy data in paediatric patients have been generated. However, it is recognised that many medicines, especially those which are off-patent, are used off-label for paediatric patients, and this aspect was not investigated. The unlicensed use of a medicine does not preclude its inclusion on the EMLc; however, clear evidence of efficacy and safety and comparative cost-effectiveness are required. The aim of this activity was to identify medicines to be further evaluated of their appropriateness for the EMLc, and not to perform a systematic review of their safety and efficacy in the paediatric population. It should also be noted that some medicines may be manipulated (for example tablet crushing) to facilitate dosing, and medicine dosage form acceptability was not formally assessed during this exercise.

5. Recommendations and Next steps

It is recommended that EML Expert Committee historical records (since 2007) regarding all the medicines and their indications that have been identified above for consideration for potential addition to the EMLc (Tables 2 to 4) are reviewed to establish if they have been previously evaluated and discussed regarding their inclusion on the EMLc. Any which have been recently evaluated and concluded to be unsuitable for addition may not require any further action. Indeed, medicines previously identified as having no or limited therapeutic benefit in children should be excluded from further review.

The remaining medicines should be grouped according to therapeutic area and prioritised according to potential therapeutic need and discussed with relevant paediatric and disease area experts to determine if their inclusion on the EMLc should be further investigated, and if new evidence on their safety and efficacy should be re-evaluated.

6. Conclusions

The review of the EML to identify medicines that have potential therapeutic utility in children but that are not currently included on the EMLc has been successfully completed.

Thirty-one medicines on the EML were initially identified for potential addition to the EMLc following review of the EMLc 2019. Further evaluation of the EMLc 2021 indicated eighteen of these medicines had been already added. The remaining 13 medicines should be considered for addition to a future update. The review also identified another 23 medicines and/or indications that may have therapeutic utility in children, and which should therefore be evaluated further.

The results of the review will be shared with WHO focal point experts, to facilitate the identification of medicines and indications that should be evaluated for addition to the EMLc.

7. Version control

Version Number	Date	Description of changes
Original Version	25.03.2022	New document
Version 2	17.10.2022	Amendment to wording regarding the priority of statins, following a discussion with WHO cardiovascular team

APPENDIX A

Data collection and management

The Model List of Essential Medicine (EML) is available as a freely accessible, online electronic database (eEML) (eEML - Electronic Essential Medicines List (essentialmeds.org)), that contains key pharmaceutical, clinical and cost information, as well as data related to the status of a medicine as an essential medicine. In addition, the EML and Model List of Essential Medicines for Children (EMLc) are freely available as Technical Documents in PDF format.

The first step in the process to compare the EML and EMLc was to identify medicines listed on the EML which are not on the EMLc. This was achieved in early 2021 by exporting four separate medicine lists from the electronic EML database (eEML) (2019 version) into Excel, by applying the relevant target population filter, as follows:

- Any (all ages, no filter)
- Adolescents and adults
- 1 month to 12 years
- Neonates

The lists were combined to generate a master spreadsheet that showed which age group(s) each medicine, formulation and indication were listed under.

Each line (i.e., medicine, formulation, indication, target population) of the master spreadsheet was then manually checked by the author and compared with information provided on the eEML database for each medicine, to ensure consistency and validate the results.

A second quality check of the master spreadsheet was conducted by interrogating and comparing with the PDF EMLc (2019) to confirm consistency of the results. Any discrepancies in results were identified and rectified during this manual check, to ensure accuracy. This resulted in the production of the final master EML spreadsheet; “EML-lists-combined checked-filters_MASTER_FINALV1” spreadsheet (provided in Appendix B).

Appropriate filters were then applied to the validated and quality-checked final master spreadsheet to extract a list of medicines and indications which were included on the EML but not included on the PDF EMLc (2019), to produce a “EML medicines not on EMLc 2019” spreadsheet.

The second step of the process was to identify medicines on the “EML medicines not on EMLc 2019” spreadsheet for potential consideration for addition to the EMLc. All medicines in sections known to be excluded from the EMLc due to the absence of therapeutic need in children, (e.g., contraceptives, ovulation inducers, uterotonics, medicines for Parkinsonism, etc.) were defined in the “potential EMLc addition” column of the “EML medicines not on EMLc 2019” spreadsheet as “N” (no) and removed from further review.

Each of the remaining medicines and their indications on the “EML medicines not on EMLc 2019” spreadsheet were then reviewed and assessed for their potential suitability for inclusion on the EMLc by interrogating product Labels/Summary of Product Characteristics (SmPCs) from the US Food and Drug Administration (FDA) and UK Medicines for

Healthcare Regulatory Authority (MHRA), to determine if the medicines had been authorised for use in patients aged ≤ 12 years. The FDA and MHRA were considered to represent Stringent Regulatory Authorities (SRAs). SmPCs published by the Australian Therapeutic Goods Administration (TGA), or European Medicines Agency (EMA) were interrogated if limited or conflicting information was available from the FDA and MHRA, for example apparent discrepancies in approved age limits and indications.

On occasion, internet searches were also conducted when further information was required to assist with the evaluation. For example, information on the prevalence and potential burden of a particular condition in children aged below 12 years was sought, to help understand its relevance in paediatric patients. The EMA lists of Paediatric Therapeutic Needs were also evaluated for information (Needs for paediatric medicines | European Medicines Agency (europa.eu).

Medicines for which a product licence was available for patients aged below 12 years were defined as “Y” (yes), whilst those for which utility in paediatric patients was less clear, for example, due to a lack of information on product Labels/SmPCs, were defined as “TBC” (to be confirmed). Medicines that were not indicated for children aged below 12 years were defined as “N” (no).

The updated edition of the EMLc was published in late 2021 (EMLc 2021). Since the above review had considered the 2019 edition of the EMLc, medicines previously identified as having potential for addition to the EMLc (“EML medicines not on EMLc 2019” spreadsheet) were reviewed for their inclusion in the PDF EMLc 2021. This review also considered therapeutic equivalents, where specified on the EMLc 2021. The results of this final review were recorded in the “Included in EMLc 2021?” column of the spreadsheet.

APPENDIX B

A copy of the combined EML lists spreadsheet is provided below:
EML-lists-combined checked-filters_MASTER_FINALV1

EML_lists_combined
_checked_filters_MA

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