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Are age-appropriate antibiotic formulations missing from the WHO list of essential medicines for children? A comparison study

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ABSTRACT

Objective There is a global call for formulations, which are better suited for children of different age categories and in a variety of settings. One key public health area of interest is age-appropriate paediatric antibiotics. We aimed to identify clinically relevant paediatric formulations of antibiotics listed on pertinent formularies that were not on the WHO Essential Medicines List for Children (EMLc).

Methods We compared four medicines lists versus the EMLc and contrasted paediatric antibiotic formulations in relation to administration routes, dosage forms and/or drug strengths. The additional formulations on comparator lists that differed from the EMLc formulations were evaluated for their added clinical values and costs.

Results The analysis was based on 26 EMLc antibiotics. Seven oral and two parenteral formulations were considered clinically relevant for paediatric use. Frequently quoted benefits of oral formulations included: filling the gap of unmet therapeutic needs in certain age/weight groups (phenoxymethylpenicillin and metronidazole oral liquids, and nitrofurantoin capsules), and simplified administration and supply advantages (amoxicillin dispersible tablets, clyndamycin capsules, cloxacillin tablets, and sulfamethoxazole+trimethoprim tablets). Lower doses of ampicillin and cefazolin powder for injection could simplify the dosing in newborns and infants, reduce the risk of medical errors,

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and decrease the waste of medicines, but may target only narrow age/weight groups.

Conclusions The identified additional formulations of paediatric antibiotics on comparator lists may offer clinical benefits for low-resource settings, including simplified administration and increased dosing accuracy. The complexity of both procuring and managing multiple strengths and formulations also needs to be considered.

What is already known on this topic?

- Age-appropriate paediatric formulations are essential to enable accurate, safe and acceptable drug administration across the diverse paediatric population.
- The WHO List of Essential Medicines for Children reflects priority therapeutic needs of children, and can be used as a model list by national health authorities for medicines selection.

What this study adds?

- Additional age-appropriate formulations of paediatric antibiotics exist globally, suitable for paediatric use in low resource settings.
- They could facilitate and simplify the treatment of children, particularly at younger age.

INTRODUCTION

Millions of children die every year from preventable or treatable infections, such as pneumonia, diarrhoea, malaria, tuberculosis, HIV/AIDS and neonatal complications.1 ,2 Many of these deaths could be avoided with the use of safe and affordable age-appropriate medicines.3 ,4 The response to medications in children is different from that of adults, and it may also vary across age groups due to their development phases.5 ,6 That implies that strengths and dosing regimens, tablet sizes and volume of parenteral medicines need to be well adapted to children's age.7–10 As a global action to improve access to child-specific medicines, the WHO Essential Medicines List for Children (EMLc) was released on the 30th anniversary of the general EML in 2007.11 Essential medicines are those that satisfy the priority healthcare needs of the population. They are selected based on public health relevance, evidence on clinical efficacy and safety, and comparative cost-effectiveness.12 Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality, and at a price the individual and the community can afford.12 So, the aim of the EMLc is to recognise special needs for medicines in children, and to promote the inclusion of paediatric medicines in national procurement programmes.11

Even with these systematic efforts to respond to paediatric therapeutic needs, more work lies ahead.13 One key public health area of interest in the field of infectious diseases are child-specific antibiotics, due to their potential to fight bacterial infections, including pneumonia and neonatal sepsis that are among leading causes of death in early life.3 ,14–16

A first step in improving the availability of age-appropriate formulations of paediatric antibiotics is to obtain up-to-date information if more formulations exist globally, but are not on the EMLc. Therefore, the aim of this study was to compare

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the antibiotic formulations on relevant medicines lists versus the EMLc, and identify potential new clinically relevant products for paediatric use in low-resource settings.

METHODS

Four medicines lists were compared with the EMLc in respect to their paediatric formulations, focusing on the EMLc antibiotics: (1) the British National Formulary for Children 2014/2015, (2) the Dutch Kinderformularium (Formulary for Children) 2015, (3) the Australian Pharmaceutical Benefits Scheme and (4) the Management Sciences for Health (MSH)/WHO International Drug Price Indicator Guide 2014.17–20 The first three medicine lists originate from high-income countries, which are known for their comprehensive, high quality healthcare systems and good availability of paediatric medicines. The MSH/WHO guide corresponds to a global burden of diseases in children. The fifth edition of the EMLc from 2015 was used as a standard reference list for our comparison.13 The analysis focused on EMLc antibiotics in section 6: Anti-infectives, subsection 6.2: Antibacterials (6.2.1: β-lactam medicines and 6.2.2: Other antibacterials).13 ,21

For the purpose of our comparison, three parameters were used to define the formulations: (1) administration routes, (2) dosage forms and (3) drug strengths. We assessed whether the formulations on the comparator lists differed from the EMLc formulations in any of the parameters. Our findings were arranged to indicate how many EMLc formulations per antibiotic were missing on each of the lists, and how many formulations were an addition to the EMLc.

Importantly, EMLc employs the main terms for oral solid dosage forms, such as tablets, capsules, and so on. Thus, the comparison was made at the EMLc level of detail, although comparator lists are more specific (ie, scored, crushable, chewable, dispersible tablets). Besides, our interest was on the lower paediatric age bands, as the EMLc corresponds to clinical needs of children up to 12 years of age, and comparator lists mostly refer to children up to 18 years.

The additional formulations on the comparator lists that differed from the EMLc formulations were extracted for further analysis. They were checked for their compliance with WHO rules on age and weight restrictions—which are established on the basis of drug efficiency and safety data within the age/weight ranges, suitable administration routes, and/or drug content, as described in the WHO model formulary (MF) for children.21

Ultimately, formulations that countered WHO rules, and/or had been excluded on similar grounds from previous EMLc (2007–2013) were disqualified. The remaining formulations were evaluated for their relevance in paediatric care according to: (1) formulations' added value in clinical practice (ie, unmet needs in certain age/weight group, easier dosing or drug administration, and disease importance) and (2) logistical, supply chain and financial advantages (ie, no need for refrigeration/cold chain, and less drug wastage). Three authors (CR, EZ, MWP) independently appraised all potential new formulations for their relevance, and documented each opinion in a narrative form. Inter-rater agreements were calculated.

The relevance of each formulation was categorised into four groups by author VI: (1) major relevance (unmet needs in certain age/weight group), (2) medium relevance (easier dosing or drug administration, no need for refrigeration/cold chain, less drug wastage), (3) little relevance (narrow age range, few therapeutic indications), and (4) no relevance (unreliable drug administration, uncommon formulation use). A

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randomly selected subset of six formulations was scored independently by author AKM-T to validate the scoring.
Finally, all EMLc antibiotics were classified into five categories: (1) Antibiotics with additional formulations on comparator lists, compliant WHO clinical decisions, with clinical relevance, (2) Antibiotics with additional formulations on comparator lists, compliant WHO clinical decisions, with little or no clinical relevance, (3) Antibiotics with additional formulations on comparator lists, but not compliant with WHO clinical decisions, (4) Antibiotics with no additional formulations on comparator lists, and (5) Antibiotics absent on comparator lists.
The costs of the additional formulations with clinical value and their corresponding formulations on the EMLc (ie, same dosage forms, different drug strengths, or different dosage forms, same drug strengths) were compared, using the prices from the MSH/WHO International Drug Price Indicator Guide 2014.20

RESULTS

Table 1 presents the quantitative summary of paediatric formulations listed on the comparator lists and the EMLc for all 26 EMLc antibiotics. All antibiotics existed on at least one of the comparator lists, but numerous discrepancies existed between the EMLc and the four individual lists including many missing or additional formulations (see online supplementary table S1). Subsequently, 16 antibiotics with 40 additional formulations were selected for further analysis. Of those, 22 formulations were excluded, because 21 of them had potential contradictions with WHO rules, and one formulation was removed from the EMLc in 2008.

[TABLE 1]

[SUPPLEMENTARY DATA]
[archdischild-2016-311933supp.pdf]

The remaining 13 antibiotics with 18 new potential WHO-compatible formulations were selected for the clinical evaluation. Seven antibiotics had formulations with an oral, seven with a parenteral and one with a rectal route. The clinical evaluation of these potential new formulations is summarised in table 2. The inter-rater agreement in the assessment of formulations' relevance was around 83% (82% for oral and other formulations, and 85% for injectables). The scoring of formulations by author AKM-T showed no discrepancies in categorisation between the two authors.

[TABLE 2]

All seven oral formulations were considered to have major or medium added value for improved use of antibiotics in children. Frequently quoted reasons for clinical benefits included: filling the gap of unmet therapeutic needs in certain age/weight groups (phenoxymethylpenicillin oral liquid, metronidazole oral liquid and nitrofurantoin capsules), and simplified administration and logistical and supply chain advantages (amoxicillin dispersible tablets, clindamycin capsules, cloxacillin tablets and sulfamethoxazole+trimethoprim tablets).

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The judged value of parenteral formulations for the EMLc ranged from no to medium value. The existing doses of injections on the EMLc were generally seen as sufficient for all ages. For ampicillin and cefazolin powder for injection, lower doses were expected to simplify the dosing in younger children, reduce the risk of medical errors, and decrease the waste of medicines. The drawbacks included: narrow target age/weight groups for the new strengths, and impractical supply system burdened with non-availability, high prices and non-reimbursement. The formulations with new administration routes (doxycycline injections, gentamycin intrathecal injections and intravenous infusion, metronidazole suppositories) were not recommended for clinical practice due to their uncommon use, age restrictions or unreliable drug absorption routes (table 2).

The final classification of additional antibiotic formulations according to their clinical relevance is presented in table 3. Nine antibiotic formulations were considered to be clinically relevant for paediatric use, while seven formulations were classified to have little or no clinical relevance.

[TABLE 3]

Regarding prices, the identified lower strengths injections on the comparator lists cost the same (ampicillin), or twice less (cefazolin) compared with the twice higher strength phials on the EMLc. The prices of all six oral formulations from the comparator lists were available, except for clindamycin capsules. They show that two formulations (metronidazole, sulfamethoxazole+trimethoprim) have costs similar to the twice higher strength formulations on the EMLc, three formulations (phenoxymethylpenicillin, amoxicillin, cloxacillin) cost twice as less as the higher strength formulations and one formulation (nitrofurantoin) costs twice as much (table 4).

[TABLE 4]

DISCUSSION AND CONCLUSIONS

This study provides an overview of the differences in age-appropriate formulations of paediatric antibiotics between four comparator lists and the EMLc.

In summary, seven oral formulations from the comparator lists were regarded as potential solutions for better tolerated and more efficient therapy, since they simplify drug administration and enhance dosing accuracy in children. Two lower strength oral liquids could be used in children below 4 years of age, who currently have unmet needs for suitable EMLc formulations. Five solid oral forms were seen as alternatives for the oral liquids on the EMLc in children with no swallowing difficulties. Their advantages include accurate dosing, stability, taste masking, easy transport and no need for manipulation before use.22 ,23 Dispersible tablets (DTs) may add to the treatment possibilities as they are palatable and easy to administer in younger children with swallowing difficulties. This is in line with the WHO statement in 2008 that flexible oral solid formulations are most optimal formulations

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for use in children, particularly in lower-income, middle-income countries.24 ,25 Amoxicillin DT 250 mg is the United Nations new recommended treatment for pneumonia in children under the age of 5 years, and the lower strength DT may further expand paediatric options.3

Parenteral antibiotics are important for paediatric, and especially neonatal care, but our clinical assessments put less value on their clinical benefits.26 ,27 As indicated, while lower doses of injections may simplify the dosing in neonates and infants, and reduce the waste of medicines, the target age/weight groups for the new strengths may be too narrow.

It is also important to consider the financial implications that these new formulations may have for low-income countries. Our cost comparisons between corresponding antibiotic formulations showed that half of all new oral and parenteral formulations could decrease the cost of treatment, and have a favourable budget impact.

The strength of our study is the use of diverse lists to depict existing therapeutic options globally. The main limitations are the small sample of evaluators and the narrative description of formulations' clinical relevance, although a high inter-rater agreement was reached. Our evaluation criteria and the proposed categorisation represent an early attempt to translate relevant clinical principles into measurable operational components. Further development of a user-friendly instrument, and its validation and testing are needed to verify our tool's consistency and reliability.

Besides the aforementioned benefits, introducing more formulations on the lists may lead to a complex procurement of multiple strengths and formulations, and less efficient drug management, including prescribing.12 The EMLc is not envisaged as a comprehensive list of all marketed formulations and strengths for children. Nonetheless, it is important to find a suitable platform to share up-to-date information about available age-appropriate paediatric formulations and their advantages and shortcomings, and advocate for their rational use in line with relevant formularies and treatment guidelines. Besides, it is vital to consider the barriers for the implementation of new formulations at the field level, as listing in the WHO EML does not always translate into demand for the medicines at country level.28–30

Concluding, the present study identified relevant age-appropriate formulations of paediatric antibiotics that exist. The progress made in developing new formulations needs to be extended for the benefit of children globally.

FOOTNOTES

- Contributors VI, HGL, LvD and AKM-T conceptualised the study, and formulated its study design and methods. VI collected the data, performed the comparison analysis and wrote the manuscript. AKM-T and HGL supervised the analysis, writing of the manuscript and ensured the quality of the study results. CR, EZ and MWP provided clinical insights and interpretation of the study variables and findings. All authors contributed to the revision of the manuscript, and have approved the submitted versions of the manuscript.

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- Competing interests None declared.
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REFERENCES

1 United Nations Inter-agency Group for Child Mortality Estimation (UN IGME). Levels and trends in child mortality 2015. UNICEF, WHO, World Bank, UN-DESA Population Division, 2015.http://www.childmortality.org/files_v20/download/IGME%20Report%202015_9_3%20LR%20Web.pdf
2 Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet 2015;385:430–40.
3 World Health Organization. Priority live-saving medicines for women and children 2012. Geneva: World Health Organization, 2012 (WHO/EMP/MAR/2012.1): http://apps.who.int/iris/bitstream/10665/75154/1/WHO_EMP_MAR_2012.1_eng.pdf?ua=1
4 Bhutta ZA, Das JK, Walker N, et al. Interventions to address deaths from childhood pneumonia and diarrhoea equitably: what works and at what cost? Lancet 2013;381:1417–29.
5 Kearns GL, Abdel-Rahman SM, Alander SW, et al. Developmental pharmacology—drug disposition, action, and therapy in infants and children. N Engl J Med 2003;349:1157–67.
6 Fernandez E, Perez R, Hernandez A, et al. Factors and mechanisms for pharmacokinetic differences between pediatric population and adults. Pharmaceutics 2011;3:53–72.
7 European Medicines Agency. Guideline on pharmaceutical development of medicines for paediatric use. EMA/CHMP/QWP/805880/2012 Rev. 2. 1 August 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/07/WC500147002.pdf.
8 Breitkreutz J, Boos J. Paediatric and geriatric drug delivery. Expert Opin Drug Deliv 2007;4:37–45.
9 World Health Organization. Development of paediatric medicines: points to consider in formulation. Geneva, Switzerland: World Health Organization, 2012. WHO Technical Report Series, No. 970, Annex 5.
10 Tuleu C, Breitkreutz J. Educational paper: formulation-related issues in pediatric clinical pharmacology. Eur J Pediatr 2013;172:717–20.
11 World Health Organization. The selection and use of essential medicines. Report of the WHO Expert Committee, October 2007 (including the Model List of Essential Medicines for Children). Technical Report Series 950. Geneva: WHO, 2008. http://apps.who.int/iris/bitstream/10665/43887/1/WHO_TRS_950_eng.pdf
12 World Health Organization. Essential medicines. http://www.who.int/medicines/services/essmedicines_def/en/
13 World Health Organization. The selection and use of essential medicines. Report of the WHO Expert Committee, 2015 (including the 5th Model List of Essential Medicines for Children). Technical Report Series 994. Geneva: WHO, 2015. http://apps.who.int/iris/bitstream/10665/189763/1/9789241209946_eng.pdf?ua=14
14 Nair H, Simoes EAF, Rudan I, et al. Global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: a systematic analysis. Lancet 2013;381:1380–90.
15 Zaidi AK, Ganatra HA, Syed S, et al. Effect of case management on neonatal mortality due to sepsis and pneumonia. BMC Public Health 2011;11(Suppl 3):S13.

16 European Medicines Agency. Inventory of paediatric therapeutic needs, infectious diseases. EMA/PDCO/287222/2012. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/05/WC500166168.pdf
17 National Institute for Health and Care Excellence (NICE). British National Formulary for Children (BNFc) 2014/2015. http://www.evidence.nhs.uk/formulary/bnfc/current
18 Nederlands Kenniscentrum voor Farmacotherapie bij Kinderen (Dutch Knowledge for Pharmacotherapy in Children). Kinderformularium.— in Dutch. https://www.kinderformularium.nl/
19 Australian Government Department of Health. The Pharmaceutical Benefits Scheme. http://www.pbs.gov.au/pbs
20 Management Sciences for Health. Drug Price Indicator Guide 2014. http://erc.msh.org/mainpage.cfm?file=1.0.htm&module=DMP&language=English
21 World Health Organization. WHO model formulary for children 2010. Geneva:WHO, 2010. http://www.who.int/selection_medicines/list/WMFc_2010.pdf
22 Ivanovska V, Rademaker CM, van Dijk L, et al. Pediatric drug formulations: a review of challenges and progress. Pediatrics 2014;134:361–72.
23 van Riet-Nales DA, de Jager KE, Schobben AF, et al. Safe and effective pharmacotherapy in infants and preschool children: importance of formulation aspects. Arch Dis Child 2016;101:662–9.
24 World Health Organization. 17th meeting of the Expert Committee on Selection and Use of Essential Medicines. Report of the Informal Expert Meeting on Dosage Forms of Medicines for Children. December 2008. http://www.who.int/selection_medicines/committees/expert/17/application/paediatric/Dosage_form_reportDEC2008.pdf
25 World Health Organization. Development of pediatric medicines: points to consider in formulation. WHO Technical Report Series, No. 970, 2012, Annex 5.
26 Coffey P, Kelly K, Baqui A, et al. Case study: injectable antibiotics for treatment of newborn sepsis. 1–24 p. United Nations Commission on Commodities for Women's and Children's Health, 2012. http://pdf.usaid.gov/pdf_docs/pnady703.pdf
27 Darmstadt GL, Batra M, Zaidi AK. Parenteral antibiotics for the treatment of serious neonatal bacterial infections in developing country settings. Pediatr Infect Dis J 2009;28:S37–42.
28 Robertson J, Forte G, Trapsida J, et al. What essential medicines for children are on the shelf? Bull World Health Organization 2009;87:231–7.
29 Gitanjali B, Manikandan S. Availability of five essential medicines for children in public health facilities in India: a snapshot survey. J Pharmacol Pharmacother 2011;2:95–9.
30 Balasubramaniam R, Beneragama BV, Sri Ranganathan S. A national survey of availability of key essential medicines for children in Sri Lanka. Ceylon Med J 2011;56:101–7.

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TABLES

Table 1 Quantitative summary of antibiotic formulations on comparator lists and the Essential Medicines List for Children (EMLc)

Name of EMLc antibiotic	EMLc number of formulations	Summary 4 lists number of additional formulations
6.2.1 β-lactam medicines Core list		
Amoxicillin	4	5
Amoxicillin+clavulanic acid	3	9
Ampicillin	2	5
Benzathine benzylpenicillin	2	0
Benzylpenicillin	2	0
Cefalexin	3	0
Cefazolin	1	1
Ceftriaxone	2	1
Cloxacillin	2	2
Phenoxymethylpenicillin	2	1
Procaine benzylpenicillin	2	0
6.2.1 β-lactam medicines Complementary list		
Cefotaxime	1	0
Ceftazidime	2	1
Imipenem and cilastatin	2	0
6.2.2 Other antibacterials Core list		
Azythromycin	3	0
Chloramphenicol	4	0
Ciprofloxacin	3	0
Doxycycline	4	1
Erythromycin	2	3
Gentamycin	2	4
Metronidazole	6	2
Nitrofurantoin	2	1
Sulfamethoxazole+trimethoprim	4	1
Trimethoprim	3	0
6.2.2 Other antibacterials Complementary list		
Clindamycin	3	1
Vancomycin	1	2

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Table 2 Summary of clinically added value of potential new formulations of antibiotics

Name of product/dosage form/strength	Clinically added value	Reason for classification
Oral formulations		
Phenoxymethylpenicillin powder 125 mg/5 mL	Major	New low strength formulation can fill the gap of unmet therapeutic needs in young children and neonates.
Metronidazole oral liquid 125 mg/5ml	Major	
Nitrofurantoin capsules 50 mg	Major	New intermediate strength formulation can fill the gap between lower strength syrup, and higher dose capsule/tablet.
Cloxacillin tab/capsule 250 mg	Medium	
Sulfamethoxazole+trimethoprim tablet 200 mg+40 mg	Medium	It offers simplified administration and supply/stock, by replacing same-strength syrup in young children without swallowing difficulties.
Clindamycin capsule 75 mg	Medium	
Amoxicillin dispersible tab 125 mg	Medium	It offers simplified administration and supply/stock, by replacing same-strength syrup in young children with swallowing difficulties.
Parenteral formulations		
Ampicillin powder for injection 250 mg	Medium	Lower strength injection would be appropriate for younger children.
Cefazolin powder for injection 500 mg	Medium	
Cloxacillin powder for injection 250 mg	Little	Lower strength injection would be appropriate for younger children, but it has minor clinical relevance.
Ceftriaxone powder for injection 500 mg	Little	New intermediate dose allows easy dosing with less spill of antibiotics, but it has minor clinical relevance.
Ceftazidime powder for injection 500 mg	Little	
Doxycycline injection 20 mg/mL	No value	It is a proposed new route, but oral forms are sufficient. It has few indications for use in children, and it is age restricted.
Gentamycin intrathecal injection 5 mg/mL, and intravenous infusion 800 µg/mL, 1 mg/mL, 3 mg/mL	No value	No added value of infusion bags/intrathecal formulation, the available injection strengths suffice for all children.
Other formulations		
Metronidazole suppository 500 mg	No value	It is a proposed new route in case of vomiting or refusal of oral liquids. It is unsuitable for initiating treatment of serious conditions, due to slow absorption and low plasma concentrations.

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Table 3 Classification of antibiotics regarding discrepancy formulations and their clinical relevance

Categories	Antibiotics
Antibiotics with additional formulations on comparator lists, compliant with WHO clinical decisions, with clinical relevance	Amoxicillin dispersible tablets, ampicillin powder for injection, cefazoline powder for injection, cloxacilline tablets, phenoxymethyl penicillin oral liquid, metronidazole oral liquid, nitrofurantoin capsules, sulfamethoxazole+trimetoprim tablets, clindamycin capsules.
Antibiotics with additional formulations on comparator lists, compliant with WHO clinical decisions, with little or no clinical relevance	Cloxacilline powder for injection, ceftriaxone powder for injection, ceftazidime powder for injection, doxycycline injection, gentamycin intrathecal injection and infusion, metronidazole suppository.
Antibiotics with additional formulations on comparator lists, but not compliant with WHO clinical decisions	Amoxicillin injection, amoxicillin +clavulanic acid powder for suspension and powder for injection, ampicillin suspension and capsules, erythromycin injections and infusion, vancomycin capsules.
Antibiotics with no discrepancy formulations on comparator lists	Benzathine benzylpenicillin, benzylpenicillin, cefalexin, procaine benzylpenicillin, cefotaxime, chloramphenicol, imipenem and cilastatin, azytromycin, ciprofloxacin, trimetoprim.
Antibiotics absent in comparator lists	/

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Table 4 Price comparison of additional formulations and corresponding formulations on the Essential Medicines List for Children (EMLc)

Drug name	Price of additional formulations with clinical value	Price of corresponding formulations on EMLc
Oral formulations		
Phenoxymethylpenicillin	Powder 125 mg/5 mL $0.47/bottle	Powder 250 mg/5mL $0.71/bottle
Metronidazole	Oral liquid 125 mg/5 mL $0.77/bottle	Oral liquid 200 mg/5 mL $0.8/bottle
Nitrofurantoin	Capsules 50 mg $0.03/capsule	Capsules 100 mg $0.01/capsule
Cloxacillin	Tab/capsule 250 mg $0.02/tablet	Tab/capsule 500 mg $0.04/tablet
Sulfamethoxazole +trimethoprim	Tablet 200 mg+40 mg $0.013/tablet	Syrup 200 mg+40 mg $0.29/bottle **Tablet 400 mg+80 mg** $0.012/tablet
Amoxicillin	Dispersible tab 125 mg $0.02/tablet	Powder for syrup 125 mg/5 mL $0.39/bottle Dispersible tab 250 mg $0.03/tablet
Parenteral formulations		
Ampicillin	Powder for injection 250 mg $0.12/phial	Powder for injection 500 mg $0.12/phial
Cefazolin	Powder for injection 500 mg $0.27/phial	Powder for injection 1 g $0.4/phial

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Supplementary file 1: Detailed list on formulations on the EMLc and comparison lists

WHO EMLc	UK BNFc	ABPS	Kinderformularium	MSH/WHO Guide
6.2.1 BETA - LACTAM MEDICINES				
Amoxicillin J01CA04				
Powder for oral liquid 125mg/5ml, 250mg/5ml **Solid oral dosage form** 250mg, 500 mg	**Pediatric suspension** 125mg/1.25mL 125mg/5ml **Capsules** 250mg, 500mg **Injection** 250mg, 500mg, 1g, 2g vial	**Powder for oral liquid** 125 mg/5 mL (100 mL), 250 mg/5 mL (100 mL), **Capsules** 250mg, 500mg	**Powder for suspension** 25 mg/mL, 50 mg/mL **Capsule/ Tablet dispersible** 250 mg, 500 mg **Powder for inj.** 250 mg, 500 mg, 1g	**Powder for oral liquid** 125mg/5ml, 250mg/5ml **Solid oral dosage form** 250mg, 500 mg **Tablet dispersible** 125 mg
Amoxicillin + Clavulanic acid J01CR02				
Oral liquid 125mg +31.25mg/5ml 250mg+62.5mg/ml **Tablet** 500mg +125mg	**Tablet** 250mg+125mg 500mg+125mg **Oral suspension** 125mg+31.25mg/5ml 250mg+62.5mg/5ml **Powder for inj.** 500mg+100mg, 1000g+200mg **Powder suspension** 400mg+57mg/5ml	**Powder for oral liquid** 125 mg+31.25mg/5ml **Tablets** 500mg+125mg	**Powder for suspension** 100mg+12.5mg/ml (8:1) **Powder for inj.** 250mg+25mg, 500mg+50mg, 1000mg+100mg, 2000mg+200mg (10:1) 500mg+100mg, 1000mg+200mg (5:1) **Tab** 500mg+125mg (4:1)	**Oral liquid** 125mg +31.25mg 250mg+62.5mg **Tablets** 250mg+125mg 500mg+125mg
Ampicillin J01				
Powder for inj 500mg, 1g in vial	**Oral suspension** 125mg/5ml, 250mg/5ml	**Powder for inj** 500mg, 1g	**No**	**Capsules** 250mg, 500mg **Injection**

	Capsules 250mg, 500mg **Injection** 500mg			250mg, 500mg
Benzathine benzylpenicillin J01				
Powder for injection 900mg benzylpenicillin (=1.2 milion IU)/ 5ml 1.44g benzylpenicillin (=2.4 milion IU)/5ml	**No**	**Pre-filled syringe, single use** 900mg in 2.3ml	**Powder for injection** 1.2 milion IU/5ml vial	**Powder for injection** 1.2 milion IU/5ml vial, 2.4 milion IU/5ml vial
Benzylpenicillin J01CE01				
Powder for injection 600mg, 3g in vial	**Powder for injection** 600mg, 3g	**Injection** 600mg, 3g	**Powder for injection** 600mg	**Injection** 600mg, 3g
Cefalexin J01DB01				
Powder reconstitution with water: 125mg/5ml, 250mg/5ml **Solid oral dosage form** 250mg	**Powder for oral liquid** 125mg/5ml, 250mg/5ml **Capsule/Tablet** 250mg	**Powder for oral liquid** 125mg/5ml, 250mg/5ml **Capsule** 250mg	**No**	**Powder for oral liquid** 125mg/5ml, 250mg/5ml **Capsule** 250mg
Cefazolin J01DB04				
Powder for injection 1g in vial	**No**	**Injection** 500mg, 1g	**Powder for injection** 500mg, 1g	**Powder for injection** 500mg, 1g
Ceftriaxone J01DD04				
Powder for injection 250mg, 1g in vial	**Powder for injection** 250mg, 1g	**Powder for injection** 500mg, 1g	**Powder for injection** 500mg, 1g	**Powder for injection** 500mg, 1g
Cloxacillin J01				
Powder for injection 500mg in vial **Powder for oral liquid**	**No**	**No**	**No**	**Powder for injection** 250mg, 500mg in vial **Powder for oral liquid**

125mg/5ml **Capsule** 500mg, 1g				125mg/5ml **Capsule** 250mg, 500mg
Phenoxymethylpenicillin J01				
Powder for oral liquid 250 mg/5ml **Tablet** 250mg	**Powder for oral liquid** 125/5ml, 250 mg/5ml **Tablet** 250mg	**Powder for oral liquid** 125 mg/5ml, 250mg/5ml **Capsule/Tab** 250mg	**No**	**Powder for oral liquid** 125/5ml, 250 mg/5ml **Cap/Tab** 250mg
Procaine benzylpenicillin J01				
Powder for injection 1g (=1 million IU), 3g (=3 million IU) in vial	**No**	**Injection (syringes)** 1g	**No**	**Powder for injection** 1g (=1 million IU), 3g (=3 million IU) in vial
Cefotaxime J01DD01				
Powder for injection 250mg per vial	**No**	**No**	**Powder for injection** 250mg	**No**
Ceftazidime J01DD02				
Powder for injection 250mg, 1g in vial	**Powder for injection** 500mg, 1g	**No**	**Powder for injection** 500mg, 1g	**Powder for injection** 250mg, 1g in vial
Imipenem and cilastatin J01DH51				
Powder for injection 250mg + 250mg in vial 500mg + 500mg, in vial	**Powder for infusion** 500mg + 500mg	**No**	**Powder for infusion** 500mg + 500mg	**Powder for injection** 500mg + 500mg
6.2.2 OTHER ANTIBACTERIALS				
Azythromycin J01DH51				
Capsules 250mg, 500mg **Oral liquid** 200mg/5ml	**Capsules/Tablets** 250mg, 500mg **Oral liquid** 200mg/5ml	**Tablets** 500mg **Powder for oral liquid** 200mg/5ml	**Tablets** 250mg, 500mg **Oral liquid** 40mg/ml	**Tab/Cap** 250mg, 500mg **Oral liquid** 200mg/5ml

Chloramphenicol J01				
Capsules 250mg **Oral liquid** 150mg/5ml **Oily suspension for injection** 0.5g/ml in 2mL **Powder for injection** 1g	**Capsules** 250mg **Powder for injection** 1g	**No**	**No**	**Tab/Cap** 250mg **Oral liquid** 150mg/5ml **Powder for injection** 1g
Ciprofloxacin J01MA02				
Tablet 250mg **Oral liquid** 250mg/5ml **Solution for IV infusion** 2mg/ml	**Tablet** 250mg **Oral liquid** 250mg/5ml **Solution for IV infusion** 2mg/ml	**No**	**Tablet** 250mg **Oral liquid** 250mg/5ml **Solution for IV infusion** 2mg/ml	**Tablet** 250mg **Oral liquid** 250mg/5ml **Solution for IV infusion** 2mg/ml
Doxycycline J01AA02				
Solid oral dosage form 50mg, 100mg **Oral liquid** 25mg/5ml, 50mg/5ml	**Capsules** 50mg, 100mg	**No**	**Tablet/Dispersible tablets** 100mg **Injection** 20mg/ml	**Tab/Cap** 100mg
Erythromycin J01FA01				
Solid oral dosage form 250mg **Powder for oral liquid** 125mg/5ml	**Cap/ Tab** 250mg **Powder for oral liquid** 125mg/5ml, **IV infusion** 1g	**Tablet enteric** 250mg **Injection** 1g	**Tab/Tablet enterosolubile** 250mg **Granules for oral suspension** 25mg/ml **Powder for infusion** 1g	**Cap/ Tab** 250mg **Powder for oral liquid** 125mg/5ml **IV infusion 0,5g**
Gentamycin J01FA01				
Injection 10mg, 40mg/ml	**Injection** 10mg/ml, 40mg/ml, **Intrathecal injection** 5mg/ml	**Injection** 80mg/2ml	**Injection** 10mg/ml, 40mg/ml	**Injection** 10mg/ml, 40mg/ml

	IV infusion 800mcg/ml, 1mg/ml, 3mg/ml			
Metronidazole P01AB01				
Injection 500mg/100ml **Oral liquid** 200mg/5ml **Tablet** 200mg to 500mg	**No**	**Injection** 500mg/100ml **Oral liquid** 200mg/5ml **Tablet** 200mg, 400mg **Suppository** 500mg	**Infusion** 5mg/ml **Oral liquid** 40mg/ml **Tablet** 250mg to 500mg	**Injection** 5mg/ml **Oral liquid** 125mg/5ml, 200mg/5ml **Tablet** 200mg to 500mg **Suppository** 500mg
Nitrofurantoin J01XE01				
Oral liquid 25mg/5ml **Tablet** 100mg	**Oral liquid** 25mg/5ml **Tablet/cap** 100mg **Capsules** 50mg	**Capsules** 50mg, 100mg	**Capsules with regulated release /Cap**100mg **Capsules** 50mg **Suspension** 5mg/ml	**Cap/ Tab** 50mg, 100mg **Oral liquid** 25mg/5ml
Sulfamethoxazole + trimethoprim J01				
Oral liquid 200mg+40mg/5ml **Tablet** 100mg+20mg, 400mg+80mg **Injections** 80mg+16mg/ml	**No**	**Oral liquid** 200mg+40mg/5ml	**No**	**Oral liquid** 200mg+40mg/5ml **Tablet** 100mg+20mg, 200mg+40mg, 400mg+80mg **Injections** 80mg+16mg/ml
Trimethoprim J01EA01				
Oral liquid 50mg/5ml **Tablet** 100mg, 200mg	**Oral liquid** 50mg/5ml **Tablet** 100mg, 200mg	**No**	**Tablet** 100mg, 300mg	**No**
Clindamycin J01FF01				
Oral liquid 75mg/5ml	**Liquid** 75mg/5ml	**No**	**Powder for oral**	**Tab/cap** 150mg

Capsule 150mg **Injection** 150mg/ml	**Capsule** 75mg, 150mg **Injection** 150mg/ml		**suspension** 15mg/ml **Capsule** 150mg **Injection** 150mg/ml	**Injection** 150mg/ml
Vancomycin J01XA01				
Powder for injection 250mg in vial	**Capsule** 125mg, 250mg	**Capsule** 125mg, 250mg	**Capsule** 250mg	**No**