



ORIGINAL ARTICLE

A critical comparison between the World Health Organization list of essential medicines for children and the Brazilian list of essential medicines (Rename)[☆]

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Abstract

Objective: To perform a critical comparison between the Brazilian national essential medicines list (Rename, 2012) with the list of essential medicines for children (LEMC, 2011) of the World Health Organization (WHO), regarding the differences among drugs and formulations listed for children.

Methods: The LEMC drugs were classified into four categories: 1) absent in Rename; 2) included in Rename but without any formulation suitable for children; 3) listed in Rename only in some formulations; 4) present in Rename in all formulations. The missing formulations were analyzed by therapeutic group. Alternatives present in Rename were searched.

Results: From the 261 drugs of interest on the LEMC, 30.3% are absent from Rename, 11.1% are in Rename but without any pediatric formulation, and 32.2% are present in some but not all formulations listed in LEMC. Considering all formulations items listed in the LEMC (n = 577), 349 are missing from Rename, of these 19.6% due to their strength, and 18.5% due to the the dosage form. Useful formulations specific for neonatal care,

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PALAVRAS-CHAVE

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respiratory tract, central nervous system, and anti-infectives, among other groups, are missing.

Conclusion: The lack of age-appropriate formulations of essential medicines for children in Brazil includes important therapeutic groups and indispensable drugs for severe clinical conditions. Some of these products exist in the Brazilian pharmaceutical market, but not in public facilities; others could be produced by national laboratories with commercial interest or stimulated by a specific governmental policy, as in other countries.

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Uma comparação crítica entre a Lista de Medicamentos Essenciais para Crianças da Organização Mundial de Saúde e a Relação Nacional de Medicamentos Essenciais (Rename)

Resumo

Objetivo: Realizar uma comparação crítica entre a Relação Nacional de Medicamentos Essenciais (Rename, 2012) e a Lista de Medicamentos Essenciais para Crianças (LMEC, 2011) da Organização Mundial de Saúde (OMS), com relação às diferenças entre os medicamentos e as formulações listadas para crianças.

Métodos: Os medicamentos da LMEC foram classificados em quatro grupos: 1) não constam na Rename; 2) constam na Rename, porém sem qualquer formulação adequada para crianças; 3) listados na Rename apenas com algumas formulações; 4) constam na Rename em todas as formulações. As formulações que faltam foram analisadas por grupos terapêuticos. As alternativas presentes na Rename foram pesquisadas.

Resultados: Dos 261 medicamentos de interesse listados na LMEC, 30,3% não estão presentes na Rename, 11,1% estão na Rename, mas sem qualquer formulação pediátrica, e 32,3% estão presentes em algumas, mas não todas as formulações listadas na LMEC. Considerando todos os itens de formulações listados na LMEC (n = 577), 349 não constam na Rename, desses, 19,6% devido à intensidade de dosagem, e 18,5% devido à forma farmacêutica. Faltam formulações úteis específicas para cuidado neonatal, trato respiratório e sistema nervoso central, anti-infecciosos, entre outros grupos.

Conclusão: A ausência de formulações adequadas à idade de medicamentos essenciais para crianças no Brasil inclui importantes grupos terapêuticos e medicamentos indispensáveis para quadros clínicos graves. Alguns desses produtos são encontrados no mercado farmacêutico brasileiro, porém não existem em unidades públicas; outros poderiam ser produzidos por laboratórios nacionais com interesse comercial ou estimulados por uma política governamental específica, como é feito em outros países.

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Introduction

The concept of essential medicines is globally accepted as a powerful means of promoting health equity and is instrumentalized by a reference list. By definition, essential medicines are those that satisfy the priority health care needs of the population.¹ The elaboration of a list of essential medicines for children (LEMC) was conducted to correct an injustice that prevailed for 40 years, since the World Health Organization (WHO) general list of essential medicines did not sufficiently contemplate the treatment needs of children. These needs refers to the specificities of children as an heterogeneous group in terms of the physical, metabolic, and psychological processes peculiar to this age group, and to pharmaceutical aspects of formulations that

are critical for the administration in children, such as tablet size, volume of parenteral medicine, and palatability of pediatric oral medications.²⁻⁴

The LEMC embodies a model list to be adapted by nations according to their needs and circumstances. It is a dynamic tool, reviewed and updated periodically by *ad hoc* committees, as has occurred with the main List of Essential Medicines for 40 years. The LEMC, even in its third version (2011), remains incomplete and certainly unsatisfactory due to a lack of appropriate medicines for children in the world. The process of selecting essential medicines is based on worldwide-validated procedures established on the evaluation of existing evidence about efficacy and safety of use, convenience for the patients, and compatibility of the costs with the resources of the patients or the community.⁵

For pediatric medicines, this evaluation is limited by the scarcity of available evidence and of well-performed controlled clinical trials in children, by the limitations of the pharmacokinetic knowledge in different age groups, as well as by the scarcity of appropriate formulations for subgroups in different stages of physiological development, e.g. preterm neonates, full term neonates, infants and toddlers, and older children and adolescents.⁶⁻⁹

Brazil has a national drug policy defined by law¹⁰ that includes the national list of essential medicines (Relação Nacional de Medicamentos Essenciais - Rename) as a tool for its implementation. This instrument is a general list that orients the availability of medicines in the health system nationwide. In the latest versions, Rename has progressively been including medicines and drug formulations for pediatric use.¹¹⁻¹³ Nevertheless, recent studies demonstrate a lack of access to age-adapted formulations in public facilities, as well as the inexistence of some necessary formulations in the Brazilian pharmaceutical market.¹⁴⁻²⁰

The aim of the present study is to critically compare the Rename 2012 with the LEMC 2011, outlining the lack of medicines and formulations for children in the Brazilian reference list to discuss the need for a specific governmental policy to stimulate this area.

Methods

The composition of the Rename 2012¹³ was compared with the composition of the LEMC 2011²¹ in terms of the presence of medicines and formulations suitable for children, by building a spreadsheet using Microsoft Excel 2007[®] software. Two trained reviewers were assigned to compare the lists and build the spreadsheet with the supervision of a clinical pharmacist experienced in pediatric pharmacy.

A pharmaceutical presentation or formulation was considered by definition as a drug product in a determined dosage form and strength. Thus a drug may be presented in more than one formulation. This means that, for instance, tablets, oral dispersible tablets, scored tablets, capsules, cream, ointment, injectable, powder for injectable, as well different strengths of a drug, are considered different formulations. This analysis is justified on some specific characteristics of formulations that are crucial to facilitate the administration and to promote safe and effective use in children.^{2,3}

The products were classified in four categories, depending on the presence or absence of the drug or its pediatric formulation in Rename. The categories are described in "Results". Additionally, for every formulation absent in Rename, it was verified whether this absence was related to the strength of the active ingredient or to the dosage form. The combinations of active ingredients such as "lamivudine + zidovudine" were considered as distinct from formulations of the components separately. The adopted classification of drugs into therapeutic classes was the same as in the WHO list. An analysis was undertaken in order to identify which therapeutic classes are more affected by the absence of formulations for children in Rename.

Furthermore, the formulations present in Rename were searched for pediatric indication in the ANVISA package

inserts compendium, available online (www.anvisa.gov) and reversely identified in LEMC 2011.

The study protocol was approved by the Ethics Committee of the Hospital São José, Fortaleza, Brazil.

Results

In the LEMC 2011, there are 272 different drugs or fixed-dose combinations. For analysis purposes, 11 drugs that did not correspond to the epidemiological needs in Brazil were excluded from the comparison, among them the Japanese encephalitis vaccine and Pentamidine, a drug used in the treatment of West African trypanosomiasis (*T. brucei gambiensis*) and in rare cases of *Pneumocystis jirovecii* pneumonia (PCP) in AIDS patients allergic to cotrimoxazole/trimethoprim. The range of analysis comprised the remaining 261 drugs, considered essential for children in Brazil.

From these 261 drugs found in LEMC 2011, 81 (31.0%) were completely absent from the Brazilian list published in 2012 and classified as category 1; category 2 comprises the 28 (10.7%) drugs present in Rename but without any suitable formulation for child use; in category 3, the 84 (32.2%) drugs present in Rename at least in one formulation included in LEMC; and category 4 comprises 68 (26.1%) drugs present in Rename in all pediatric formulations existing in LEMC.

Regarding pharmaceutical preparations, these 261 selected essential drugs are presented in 577 distinct formulations in LEMC, 350 of which (60.7%) are absent from the Rename list: 113 in terms of strength of the preparation (19.6%), 106 in terms of dosage form (18.4%), and 131 in terms of absence of the active principle (22.7%).

The formulations corresponding to the groups "diagnostic agents" and "ear, nose, and throat conditions in children" are completely absent from the Brazilian list. The categories "vitamins and minerals", "muscle relaxants and cholinesterase inhibitors", "specific medicines for neonatal care", "anticonvulsants/antiepileptics" and "diuretics" have respectively 88.9%, 87.5%, 80.0%, 76.9%, and 75.0% of their formulations missing in Rename.

Among the anti-infective medicines, at least 52.4% of the formulations of each therapeutic subgroup are lacking, mainly in the subgroups "anthelmintic" (78.6%), "antifungal" (73.3%), and "antibacterial medicines" (57.6%). In the "antibacterials" subgroup 64.0% of the subsection "antituberculosis medicines" is missing from the Rename. In the "antiprotozoal" subgroup, both "antitrypanosomal" and "antileishmaniasis" subsections have 75.0% of their formulations absent, and in the subsection "antimalarial" 62.5% of the formulations are absent from Rename 2012.

Tables 1, 2, and 3 discriminate the missing formulations in some relevant therapeutic classes. In these tables, therapeutic alternatives existent in Rename 2012 in the same subgroups are described as drugs or formulations that are absent in LEMC 2011. As explained in the Methods section, Rename does not present the therapeutic indication of drugs; this information was researched in the online package inserts compendium. In the therapeutic group "specific medication for neonatal care", caffeine citrate, prostaglandin E and ibuprofen formulations were

Table 1 Missing formulations for neonatal care, respiratory tract, central nervous system, and their therapeutic alternatives present only in Rename.

Group	Drug	Formulations missing in Rename	Therapeutic alternatives present only in Rename
Specific medicines for neonatal care	Caffeine citrate	Injection: 20 mg/mL	-
	Prostaglandin E	Oral liquid (solution): 20 mg/mL Solution for injection (E1: 0.5 mg/mL in alcohol; E2: 1 mg/mL)	-
Medicines acting on the respiratory tract	Ibuprofen	Solution for injection: 5 mg/mL	-
	Salbutamol sulfate	Injection: 50 mcg/mL in 5-mL ampoule	Formoterol Inhalation powder: 12 mcg Inhalation capsules: 12 mcg Formoterol + Budesonide Inhalation powder: 6 mcg + 200 mcg Inhalation capsules: 6 mcg + 200 mcg
Anticonvulsants/ Antiepileptics	Carbamazepine	Tablet (chewable and scored): 100 mg and 200 mg	-
	Diazepam	Rectal solution	-
	Lorazepam	Parenteral formulation	-
	Phenobarbital	Oral liquid 3 mg/mL	Phenobarbital
	Injection 200 mg/mL	Oral liquid: 40 mg/mL	Injection: 100 mg/mL
	Phenytoin (sodium salt)	Capsule: 25 mg, 50 mg, and 100 mg Tablet: 25 mg and 50 mg Chewable tablet: 50 mg	-
Valproic acid (sodium valproate)	Valproic acid (sodium valproate)	Oral liquid (solution): 40 mg/mL	Valproic acid (sodium valproate)
		Tablet: 100 mg Tablet (enteric-coated): 200 mg	Oral liquid: 50 mg/mL Tablet or capsule: 250 mg Clonazepam Oral solution: 2.5 mg/mL

withdrawn, letting this population without appropriate alternatives for critical conditions. Among medicines acting on the respiratory tract, only one formulation is missing, salbutamol sulfate 50 µg/mL in 5mL ampoule, and Rename presents more alternatives for asthma treatment than LEMC. In the group “anticonvulsant and antiepileptics”, suitable dosage forms and variety of strengths for common drugs (e.g. carbamazepine, diazepam, lorazepam, phenytoin) are missing, but Rename has some useful presentations of phenobarbital and valproic acid.

Discussion

The lack of medicine formulations suitable for children is a worldwide concern, taken into consideration in some developed countries, as well as multilaterally by organizations such as the WHO.²²⁻³⁴

The present study performed an inventory of the missing essential medicines in suitable formulations for children in Rename, using LEMC as a reference. Some of the drugs completely absent in Rename but present in LEMC have minimal or no importance for Brazilian children (such as miltefosine, used in American visceral leishmaniasis), but

others are useful systemic antibiotics, such as vancomycin, ampicillin, and cloxacillin (or its equivalent oxacillin, widely used in Brazil). This was not an exhaustive quantitative or qualitative analysis regarding which drugs and formulations should be considered essential for Brazilian children, rather an attempt to describe the lack of drugs and formulations suitable for children as a relevant problem that deserves the attention of Brazilian health policy makers. It is well-known that the absence of appropriate medicines and formulations for children (drugs duly studied in children, suitable dosage form, and strength) leads to unlicensed and off-label use of medicines and/or to the use of less safe or effective drugs.^{7,35} The lack of specific medication for neonatal treatment, as when comparing Rename to LEMC, forces the use of magistral or extemporaneous preparations, and sometimes the replacement of a drug by a more toxic substitute. The first is exemplified by the use of prepared caffeine citrate as respiratory stimulant, and the second by the use of indomethacin instead of ibuprofen for patent ductus arteriosus.³⁶ Another example relative to neonates is the absence of ampicillin and gentamycin antimicrobials in Rename, which jeopardizes the adequate treatment of *Enterococcus* sp. and *Listeria monocytogenes* systemic infections.³⁷ Such strategies are associated with

Table 2 Missing formulations and therapeutic alternatives present only in Rename: antifungals, anthelmintics, antitrypanosomal.

Group	Drug	Formulations missing in Rename	Therapeutic alternatives present only in Rename
Antifungal	Fluconazole	Capsule: 50 mg	Fluconazole
	Griseofulvin	Capsule or tablet: 125 mg, 250 mg	Capsule: 100 mg
	Nystatin	Oral liquid: 25 mg/mL Lozenge: 100,000 UI Oral liquid (suspension): 10 mg/mL Tablet: 100,000 UI, 500,000 UI	Itraconazole Oral liquid: 10 mg/mL
	Flucytosine	Capsule: 250 mg Infusion: 2.5 g in 250 mL (10 mg/mL)	
Anthelmintics	Levamisole	Tablet: 50 mg, 150 mg	Albendazole Oral suspension: 40 mg/mL
	Mebendazole	Tablet (chewable): 100 mg, 500 mg	
	Niclosamide	Chewable tablet: 500 mg	
	Pyrantel	Oral liquid: 50 mg/mL Tablet (chewable): 250 mg	
	Ivermectin	Tablet (scored): 3 mg, 6 mg	Ivermectin Tablet: 6 mg
	Oxamniquine	Capsule: 250 mg	
	Praziquantel	Tablet: 150 mg	
Antitrypanosomal medicines	Nifurtimox	Tablet: 30 mg, 120 mg, 250 mg	Benznidazole Tablet: 12.5 mg

medication errors and adverse events, as suggested by several studies performed worldwide.^{16-18,38-40} In some therapeutic subgroups, as in the case of “medicines for asthma treatment”, more alternatives are present in Rename compared to LEMC, but there are critical issues. For example, the salbutamol solution for nebulization present in Rename is ten times stronger (500 mcg/mL) than that of LEMC (50 mcg/mL), increasing the possibility of errors. Furthermore, the inclusion of formoterol as a single drug is inconvenient, considering the recognized risk of using isolated long-acting beta2-agonists in asthma.^{41,42}

In the case of the antiepileptic medicines, ethosuximide liquid formulation suitable for children was included in the Rename 2012, and phenytoin is present as oral solution and syrup of 50 mg/mL, but not in chewable tablet, or in 25 mg and 50 mg tablets as in LEMC. In the “antifungals, anthelmintics, and antitrypanosomals” group, the reduced span of antihelmintic drugs in Rename is remarkable, and is inconsistent with the country’s reality. Distinctly from LEMC, pyrantel, niclosamide, and mebendazole are not available. Praziquantel is also present in 150 mg tablets in the LEMC, and niclosamide in chewable tablets. There is still a need in Rename for non-absorbable drugs for intestinal helminths. In the case of the antitrypanosomals, Rename is more complete, and includes benznidazole in 12.5 mg tablets, a dosage not found in LEMC.

Regarding antivirals and antiretrovirals, as a rule, Rename includes most of the available alternatives for antiretroviral therapy compatible with the need of the country, particularly highly active antiretroviral therapy, some in formulations suitable for children. However,

there is a need for more oral solutions and more varied concentrations, as in the LEMC.

Some drugs absent from the Rename compared to the LEMC are important for Brazilian children, such as cloxacillin, a very specific antibiotic against mild to moderate infections by *Staphylococcus aureus*. This drug is often replaced in Brazil by cephalexin, a first-generation cephalosporin with a broader spectrum, effective in community-acquired *Escherichia coli* urinary tract infections. As cephalexin is frequently prescribed to treat *Staphylococcus aureus* skin infections, it induces an undesirable selective pressure over *Escherichia coli*, stimulating an increase in antimicrobial resistance. An example of inadequate formulation is the lack of isoniazid (INH) in liquid presentation of 50 mg/5 mL strength in the Brazilian list. Rename only provides tablets of 100 mg of INH or combined INH/rifampin at 75/150, 100/150, and 200/300mg tablets for children with tuberculosis. A difference in solution strength is also seen in the syrup concentration of prednisolone, which in LEMC is 5 mg/mL and in the Rename is 3 mg/mL. This lower concentration increases costs and reduces treatment compliance, as it requires a greater volume intake.

The differences between Rename and LEMC shown in this study were expected, since the former is a list for current use in general medicine, and the opportunity to include comprehensive pediatric needs is therefore remote. The fact that many formulations present in the LEMC cannot be found in the Brazilian pharmaceutical market should restrict the possibility of their inclusion in a national list. However, it would be desirable that the Rename clearly expressed the need for pediatric medicines in Brazil to

Table 3 Missing formulation and therapeutic alternatives present only in Rename: anti HIV drugs.

Group	Drug	Formulations missing in Rename	Therapeutic alternatives present only in Rename
Antiviral	Aciclovir	Oral liquid: 40 mg/mL	Darunavir
	Didanosine	Buffered powder for oral liquid (solution): 100 mg, 167 mg, 250 mg	Tablet: 150 mg, 300 mg
		Capsule (unbuffered enteric-coated): 125 mg, 200 mg	Fosamprenavir
	Emtricitabine	Tablet (buffered chewable, dispersible): 25 mg, 50 mg, 100 mg, 150 mg, 200 mg	Oral suspension: 50 mg/mL
		Capsule: 200 mg	Tipranavir
	Stavudine	Oral liquid: 10 mg/mL	Oral solution: 100 mg/mL
		Capsule: 15 mg, 20 mg	Zanamivir
	Zidovudine	Capsule: 250 mg	Inhaling powder: 5 mg
		Tablet: 300 mg	
	Efavirenz	Capsule: 50 mg, 100 mg	
	Atazanavir	Solid oral dosage form: 100mg	
	Lopinavir + ritonavir	Capsule: 133.3 mg + 33.3 mg.	
	Ritonavir	Tablet (heat stable): 25 mg, 100 mg	
	Lamivudine + nevirapine + stavudine	Tablet: 150 mg + 200 mg + 30 mg	
		Tablet (dispersible): 30 mg + 50 mg + 6 mg; 60 mg + 100 mg + 12 mg	
	Lamivudine + nevirapine + zidovudine	Tablet: 30 mg + 50 mg + 60 mg;	
		150 mg + 200 mg + 300 mg	
Lamivudine + zidovudine	Tablet: 30 mg + 60 mg		
Ribavirin	Injection for intravenous administration: 800 mg, 1000 mg	Solid oral dosage form: 200 mg, 400 mg, 600 mg	
Oseltamivir	Oral powder: 12 mg/mL		

pharmaceutical companies and health authorities. Besides, some formulations missing in Rename, described in Tables 1, 2, and 3, are already available in private Brazilian pharmacies, as sodium valproate enteric coated tablets, and pyrantel pamoate and mebendazole suspensions. It would be feasible in these cases to provide full access to these formulations at public health facilities if they were included in the Rename list.

Another aspect to be highlighted is that almost 70% of the missing formulations are related to strength and dosage form, suggesting that no technical issues need to be solved, only the lack of commercial interest and marketing concerns. Presently, dosage forms suitable for use in children include a great variety, such as suspensions, syrups, solutions, concentrates, granules, sprinkles, powders, scored or crushable tablets, and the new fast dispersing dosages forms (films, fast-melts, ODTs, minitables, chewable tablets), among others.⁴³ The palatability of medicines is also a field of great research investment, and is recognized as one of the most crucial factors influencing adherence to therapeutic regimens, mainly in young children.³ These technological advances need to be incorporated into these products for the

benefit of Brazilian children. It is well known that research, development, and production of pediatric medicines are not currently goals of the pharmaceutical industry, with the exception of medicines for common diseases such as mild infections and medicines for asthma. Therefore policymaker initiatives are crucial through financial or technical support for research and development,¹ and industrial production of new formulations.^{7,22,26,27,33,34} Costa et al., in a review of medical literature and reports from Brazilian pediatricians, identified 126 formulations necessary in the country, a great proportion of them already present in other marketplaces abroad.¹⁴ As in the present study, the referred formulations included antimicrobials, anti-asthmatics, and analgesics, indispensable drugs for severe clinical conditions such as convulsive disorders (anticonvulsants), cardiovascular diseases, and tuberculosis, as well as drugs for vulnerable age groups such as neonates.

To address the great number of pediatric formulations required to be included in the Rename, the elaboration of a specific list of essential medicines for children in Brazil appears to be a worthy solution. Such an instrument could be part of a broadened policy to stimulate the

development and production of medicines for children in the country. As proposed by Beggs et al.,⁴⁴ the development of a pediatric-specific essential medicines list potentially increases the awareness of the need for pediatric-specific medications and formulations, and highlights areas of priority where medications are lacking. Providing access to these formulations according to the need and promoting their rational use in children are concomitant challenges to be addressed by Brazilian health policies.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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