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Highlights

- The WHO Essential Medicines List includes Access essential antibiotics
- ESGAP defined Forgotten antibiotics, old drugs still useful for some indications
- We investigated which Access and Forgotten antibiotics are nationally approved
- The study sample included 28 low- and middle-income countries
- Access antibiotics are mostly approved, whereas Forgotten antibiotics are not

ACCEPTED MANUSCRIPT

Essential and Forgotten antibiotics: an inventory in low- and middle-income countries

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ABSTRACT

Background: The WHO Essential Medicines List (EML) includes 'Access' antibiotics, judged essential to treat common infections. ESGAP defined a list of 'Forgotten' antibiotics, some old and often off-patent antibiotics, which possess particular value for specific indications.

Objective: To investigate which EML 'Access' and 'Forgotten' antibiotics are approved at national level in a sample of low- to middle-income countries (LMICs).

Methods: The scientific committee used a consensus procedure to select 26 EML 'Access' and 15 'Forgotten' antibiotics. Paediatric formulations were explored for 14 antibiotics. An internet-based questionnaire was circulated to 40 LMICs representatives. Antibiotics were defined as approved if an official drug regulatory agency and/or the Ministry of Health licensed their use, making them at least theoretically available on the market.

Results: We surveyed 28 LMICs (Africa: 11, Asia: 11, America:6). Nine EML 'Access' antibiotics (amoxicillin, ampicillin, benzylpenicillin, ceftriaxone, clarithromycin, ciprofloxacin, doxycycline, gentamicin and metronidazole) were approved in all countries, 26/26 in more than two thirds. Among 'Forgotten' antibiotics only 1/15 was approved in more than two thirds of countries. The median number of approved antibiotics per country was 30 [interquartile range: 23-35]. 6/14 paediatric formulations (amoxicillin, amoxicillin-clavulanic acid, oral antistaphylococcal penicillin, cotrimoxazole, erythromycin and metronidazole) were approved in more than two thirds of countries.

Conclusions: EML 'Access' antibiotics and the most frequently used formulations for paediatrics were approved in the vast majority of the 28 surveyed LMICs. This was not the case for many 'Forgotten' antibiotics, despite their important role, particularly in areas with high prevalence of multidrug-resistant bacteria.

Keywords: Access; Antibiotic access; low- and middle-income countries; antibiotic stewardship; survey

1. BACKGROUND

Balancing access and excess is one of the most urgent and complex challenges currently facing antibiotic use worldwide, particularly in low- and middle-income countries (LMICs) [1].

Reliable access to efficacious medicines is a human right and a health priority; it is considered a cornerstone in the achievement of sustainable human development and has been included by the United Nations in Millennium Development Goal 8E [1–4]. Nonetheless, inequity of access to antimicrobials remains a global public health problem [1]. It was recently estimated, for example, that adequate provision of antibiotics could avert 75% of deaths attributable to community-acquired pneumonia in children younger than 5 years, equivalent to 445,000 deaths [5].

The World Health Organization (WHO) Essential Medicines List (EML) was developed in order to provide guidance to country health systems for selecting priority drugs to be provided to the population [6,7]. The WHO-EML was updated in 2017 (20th edition for adult, 6th edition for children) [8,9], with re-categorisation of antibiotic agents into groups labelled ‘Access’, ‘Watch’ and ‘Reserve’, to highlight both the need for measures guaranteeing access to these essential antibiotics, and for stewardship programmes to promote responsible use. ‘Access’ antibiotics are those most frequently used to treat common bacterial infections, hence those which should be available everywhere.

At the same time, misuse and overuse of antibiotics is threatening their efficacy, in both high income countries (HICs) and LMICs [10], calling for antibiotic stewardship (ABS) efforts. In 2011, the ESCMID Study Group for Antimicrobial stewardship (ESGAP) examined the availability of so called ‘Forgotten antibiotics’ in selected HICs [11]. These are old and often off-patent antibiotics, selected for their unique value in targeting specific pathogens or in specific clinical indications (Appendix A). In clinical practice, ‘Forgotten’ antibiotics offer the possibility of treating certain infections with narrower-spectrum agents (e.g. pivmecillinam for cystitis), and/or provide therapeutic options for difficult-to-treat infections due to multidrug resistant (MDR) pathogens (e.g. IV fosfomycin for

carbapenem-resistant bacteria). A follow-up ESGAP study in 2015 found that the availability of these 'Forgotten' antibiotics (again in the HIC setting) was further decreased [12].

Neither the availability of WHO-EML 'Access' antibiotics, nor that of 'Forgotten' antibiotics has been detailed in LMICs. Because the approval by an official drug regulatory agency and/or the Ministry of Health is the first step in enabling an official and regulated supply of an antimicrobial in a given country, our study investigated which antibiotics are officially approved among WHO-EML 'Access' antibiotics and 'Forgotten' antibiotics in a large number of LMICs.

2. METHODS

This was an international, Internet-based, cross-sectional survey. The final questionnaire was in English and was hosted on SurveyMonkey® (Palo Alto, CA, USA). It is available in Appendix B.

2.1 Definitions

An antibiotic was defined as approved if a country's official drug regulatory agency and/or the Ministry of Health approved its use, making it at least theoretically available on the market. The inclusion in the national Essential Medicines List was considered as a form of official approval. Only formulations for systemic use, i.e. oral, intramuscular (IM) and intravenous (IV) routes of administration were considered.

Paediatric formulations were defined as those specifically intended for paediatric use, i.e. dispersible tablets, syrups, and powders for reconstitution as syrups [13]. Antibiotics usually administered to children using smaller doses of the same formulation intended for adults (e.g. IV formulations) were not considered as specifically intended for paediatric use.

2.2 Antibiotic selection

A consensus procedure via an Internet-based questionnaire was developed within the scientific committee, to come up with a short list of antibiotics to explore (see the list of authors for members of the scientific committee). The full list of WHO-EML 'Access' and ESGAP 'Forgotten' antibiotics was not used, since collecting data on these 54 antibiotics was considered to be too much work for the respondents. The antibiotics we included were considered by the scientific committee to be those most interesting for LMICs, with a high level of agreement ($\geq 80\%$) among the experts.

A total of 41 antibiotics were selected (Table 1), while 13 antibiotics were rejected (Appendix C). Selected antibiotics included: a) 24 WHO-EML 'Access' antibiotics; b) 15 'Forgotten' antibiotics; c) imipenem and erythromycin (which are listed as alternatives to meropenem and clarithromycin respectively in the EML). Eight of the WHO-EML 'Access' antibiotics (Table 1) were also originally included in the 'Forgotten' antibiotics list [11,12]. These antibiotics, as well as erythromycin and imipenem, are included among WHO-EML 'Access' antibiotics in the further paragraphs and figures. Among the antibiotics included in the study, 14 had formulations specifically intended for paediatric use [13].

A pilot version of the survey was circulated to the Scientific Committee to assess it for clarity and time requirement.

2.3 Survey deployment and double checking of results

A convenience sample of 40 national LMICs' contacts with recognised expertise in the field of the study was selected and received the invitation to participate. These national contacts were part of the scientific committee for 6 countries (Argentina, Brazil, India, Namibia, Nigeria, South Africa), or were chosen among the professional networks of the members of the scientific committee. One person per country was contacted. The questionnaire was circulated from October to December 2017 and one reminder was sent to non-responders.

In order to ensure the reliability of collected data, respondents were asked to provide one or more official source document and/or website to support their answers, mainly national formularies, drug regulatory agency websites or the national Essential Medicines List. These documents/websites were double checked by one of the researchers (GT or GL) to ensure accuracy. Country representatives were contacted in case of discrepancy.

2.4 Data analysis

Data were reported as numbers and percentages or medians and interquartile range [IQR], as appropriate.

The Mann–Whitney U test was used for comparisons between different groups (different continents and different income groups), using the software Prism 5.0 (GraphPad Software, La Jolla, CA, USA).

3. RESULTS

3.1 Study participants

The invitation to participate was sent to 40 national contacts and 28 (70%) accepted to participate: 11 (39%) from Africa, 11 (39%) from Asia, 6 (22%) from America (Table 2). Five (18%) countries were classified as low income countries (LIC, gross national income - GNI - per capita: \$1,005 or less), 10 (36%) as low middle-income countries (LoMIC, GNI per capita: \$1,006 to \$3,955), and 13 (46%) as upper middle-income countries (UpMIC, GNI per capita: \$3,956 to \$12,235) [14]. The respondents are listed in the Acknowledgement section and their complete affiliations are detailed in the Appendix D.

3.2 Approval of antibiotics

Figure 1 shows the number of countries having approved each of the WHO-EML ‘Access’ antibiotics and ‘Forgotten’ antibiotics.

Among the WHO-EML 'Access' antibiotics, 9/26 (35%) were approved in all countries (amoxicillin, ampicillin, benzylpenicillin, ceftriaxone, clarithromycin, ciprofloxacin, doxycycline, gentamicin, metronidazole), and all (100%) were approved in more than two thirds of countries. Among the 'Forgotten' antibiotics not included in the 'Access' list, only 1/15 (cefepime) was approved in more than two thirds of countries.

Figure 2 shows the number of antibiotics approved per country. The median number was: 30 [interquartile range 23-35] overall; 24 [23-27] in Africa; 31 [28-36] in America; 34 [23-37] in Asia; 24 [23-30] in LIC; 25 [21-36] in LoMIC; 31 [30-36] in UpMIC. Medians were not significantly different among continents and different income groups (data not shown).

3.3 Approval of antibiotics specifically intended for paediatric use

Figure 3 shows the number of countries having approved a formulation specifically intended for paediatric use for each of the WHO-EML 'Access' antibiotics and 'Forgotten' antibiotics.

Six out of fourteen antibiotics (43%; amoxicillin, amoxicillin-clavulanic acid, cotrimoxazole, erythromycin, metronidazole, oral antistaphylococcal penicillin) were approved in more than two thirds of countries.

Figure 4 shows the number of formulations specifically intended for paediatric use approved per country.

The median number was: 8 [interquartile range 7-9] overall; 8 [7-10] in Africa; 7 [5-8] in America; 8 [7-11] in Asia; 7 [7-11] in LIC; 8 [8-10] in LoMIC; 7 [5-8] in UpMIC. Information about paediatric formulations was not available for Vietnam.

3.4 Double checking of results

The results were double checked by investigators in 21/28 cases (75%), consulting official source documents and websites provided by respondents. Double checking was not possible in 3 cases because of linguistic barriers (China, Iran, Vietnam) and in 4 cases because of a lack of electronic versions of source documents, or websites (Azerbaijan, Nepal, Panama, Thailand). The list of documents and websites is provided in Appendix E.

4. DISCUSSION

This large international survey gives an overview on the official approval by local drug regulatory agencies and/or the Ministries of Health of 41 useful antibiotics, including paediatric formulations, in a sample of 28 LMICs from 3 continents. The explored antibiotics were selected among those included as ‘Access’ antibiotics in the EML by WHO in 2017 [8,9], and those included in the list of ‘Forgotten’ antibiotics in the ESGAP studies by Pulcini et al. in 2011[11] and 2015 [12]. We found that most of the WHO-EML ‘Access’ antibiotics are approved in the 28 surveyed LMICs, including the most clinically relevant paediatric formulations; on the contrary many ‘Forgotten’ antibiotics are not approved in these countries.

This study assessed if a given systemic antibiotic was approved for human use in a given country. We did not aim to collect information about effective availability at different levels of each country’s health care system. The appraisal of drug availability is challenging for several reasons: health care systems in LMICs are known to have complex organisations, with different levels of health care provision (e.g. reference hospitals, district hospitals, peripheral primary health care facilities), having different aims and therefore providing different assortments of medications [15,16]; private for-profit health care providers are variably present and do not necessarily follow the policies implemented in the public system [17]; the circulation of drugs in the informal sector may be significant and difficult to assess [18]; other relevant actors in the non-profit sector may adhere to independent drug policies

and provide their own supply channels [19–21]; drug shortages and troubles in supply chain may affect effective access, particularly in remote and poorest areas [22]. Availability therefore needs to be assessed on a country-by-country basis. For example, a report by the Ministry of Health and Social Welfare of Tanzania showed that there are more than 25 stakeholders involved in the procurement of medicines in that country [19]. This complex scenario revealed that investigations of drug approval is an important first step, since the approval by the local drug authority is needed to further enable a reliable and regulated access to a given antibiotic in a particular country.

Our study demonstrated that overall LMICs comply with WHO-EML, since the vast majority of ‘Access’ antibiotics were approved by an official drug regulatory agency and/or the Ministry of Health (Figure 1). Actually the list of ‘Access’ antibiotics was published in March 2017 and amended in August 2017, hence we can rather argue that surveyed countries complied with the previous WHO-EML (2015 version) [23]. However, as illustrated in Table 1, the vast majority of this ‘Access’ antibiotics were already listed as ‘Core antibiotics’ in the previous WHO-EML, with the exception of few antibiotics (cefotaxime, clindamycin, carbapenems and vancomycin) which were anyway in the ‘Complementary list’ [23].

The situation is significantly different for ‘Forgotten’ antibiotics. Our study explored the approval of 23 ‘Forgotten’ antibiotics; 8 were included also among the WHO-EML ‘Access’ antibiotics and were approved in the large majority of countries (Figure 1); on the other hand, the remaining 15 ‘Forgotten’ antibiotics were approved only in a minority of countries (Figure 1). ‘Forgotten’ antibiotics can have a role in daily practice in different clinical situations: enabling reduction in the use of other broader spectrum and sometimes less effective antimicrobials (e.g. antistaphylococcal penicillins, oral fosfomicin, pivmecillinam); offering the opportunity to treat MDR pathogens (e.g. aztreonam, IV fosfomicin, polymyxins, temocillin and many others); acting as niche agent for specific pathogens (e.g. ampicillin-sulbactam for *Acinetobacter baumannii*, spectinomycin for *Neisseria gonorrhoeae*, tobramycin for *Pseudomonas aeruginosa*) (Appendix A) [4,11,24]. This can be of added value in LMICs, where prevalence of MDR bacteria is often very high, calling for both effective treatments

and antibiotic stewardship efforts [25–27]. The availability of these mainly out-of-patent products is threatened by a vicious circle including low economic incentives; limited market size; low level of scientific evidence (particularly on pharmacokinetics/pharmacodynamics and clinical efficacy); low use by physicians; and absence of inclusion in guidelines [4,11,24].

The last version of the WHO-EML marked a step forward since 3 of these ‘Forgotten’ antibiotics (ertapenem, teicoplanin and ticarcillin-clavulanic acid) were included in the newly designed ‘Watch’ category and 5 (aztreonam, cefepime, colistin and polymyxin B, IV fosfomycin) in the ‘Reserve’ group [6]. This is a significant change compared to the previous WHO-EML list [23] and could help improve the availability of these molecules for selected conditions.

Overall American and Asian countries, as well as countries classified as upper middle-income countries approved more antibiotics than African countries and lower income countries. These data suggest that countries having higher incomes could guarantee access to more antibiotics, even if these differences were not statistically significant, probably due to the relatively small number of explored countries.

Concerning formulations specifically intended for paediatric use (Figures 3 and 4), the antibiotics more frequently used for the most common paediatric bacterial infections (amoxicillin, amoxicillin-clavulanic acid, antistaphylococcal penicillins, macrolides, cotrimoxazole and metronidazole) were approved in the majority of countries. However some countries approved the use of few paediatric formulations, suggesting that the availability of appropriate paediatric drugs could be threatened in some settings. Due to the enormous impact on children’s health of proper access to medicines [5] and the paucity of data about the availability of paediatric drugs, this aspect urgently deserves further efforts in research, as well as targeted policies.

There is still a long way to go. Coordinated efforts with multi-stakeholder approaches will be needed to improve antimicrobial availability in LMICs. Areas include: continuous monitoring of the

availability of all antibiotics included in the WHO-EML; consideration of the possible role of 'Forgotten' antibiotics in these settings; access gap analysis; strengthening of health systems; promotion of universal health coverage; promotion of alternative economic models to delink payments for antimicrobials from the volumes sold; and the evaluation of the potential role and feasibility of a Global Antibiotic Access and Conservation Fund [1,4,28,29].

This study has some limitations. Only one respondent was contacted for each country, thus the reliability of some of the collected data could be questioned. However, respondents provided one or more official document and/or website as source to corroborate their answers and these texts were double checked by the investigators in 75% of cases; all discrepancies were discussed and solved. The study investigated the approval of paediatric formulations overall, without detailing if different types of formulations (intended for children of different age groups) were approved. We did not distinguish between the approval of an antibiotic by a drug regulatory agency and/or the Ministry of Health and the inclusion in the national EML, even if this difference could influence the effective drug availability. We did not collect data on how many brands and/or generics are approved for each antibiotic, to avoid excessive workload for the respondents. It is however possible that if only a limited number had been approved, this would indicate greater vulnerability, when compared to many approvals per medicine. Finally we screened a sample of 28 countries, and our results cannot be generalized to other countries. Our sample nevertheless included countries from 3 continents, with a good geographic distribution and a huge variability in terms of health care, demographic and econometric characteristics (Table 2).

In conclusion, most of the WHO-EML 'Access' antibiotics are approved in the 28 surveyed LMICs, including the most relevant paediatric formulations. On the contrary, many 'Forgotten' antibiotics are not approved in these countries, despite their important role in some specific clinical conditions, particularly in areas with high prevalence of MDR bacteria. The WHO-EML therefore seems to have a very positive impact regarding approval of antibiotics at national level. Further studies are needed to verify in each LMIC if approved antibiotics are effectively available in daily clinical practice, with

reliable supply chain, affordable prices, and acceptable formulations, at different levels of the health care system.

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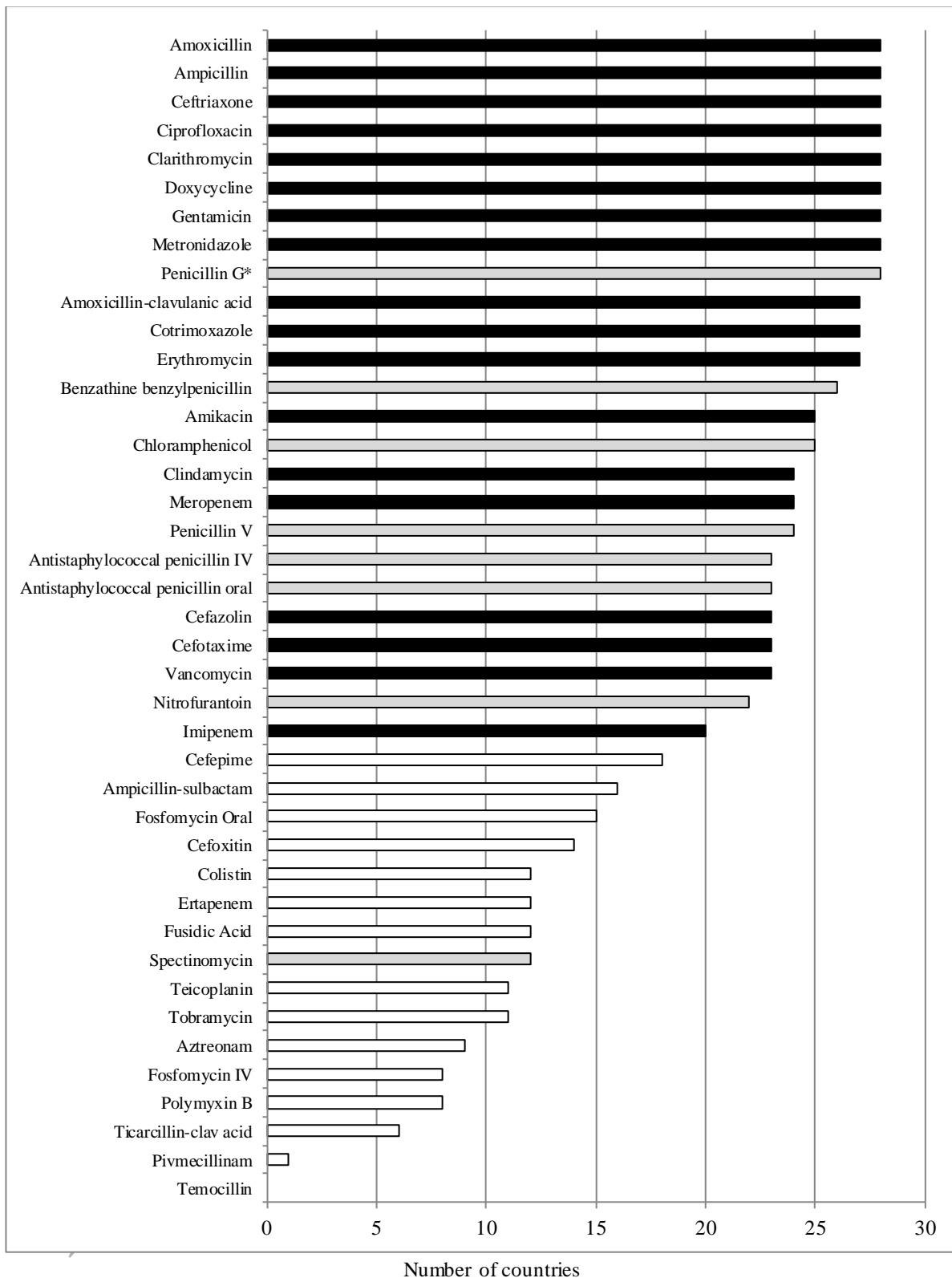


Figure 1. WHO-EML ‘Access’ antibiotics and ‘Forgotten’ antibiotics approved in the 28 surveyed countries

Black bars: antibiotics included in the WHO-EML ‘Access’ list

Grey bars: antibiotics included in both WHO-EML ‘Access’ and ‘Forgotten’ antibiotics list

White bars: antibiotics included in the ‘Forgotten’ antibiotics list

WHO-EML: World Health Organization Essential Medicines List; IV: intravenous

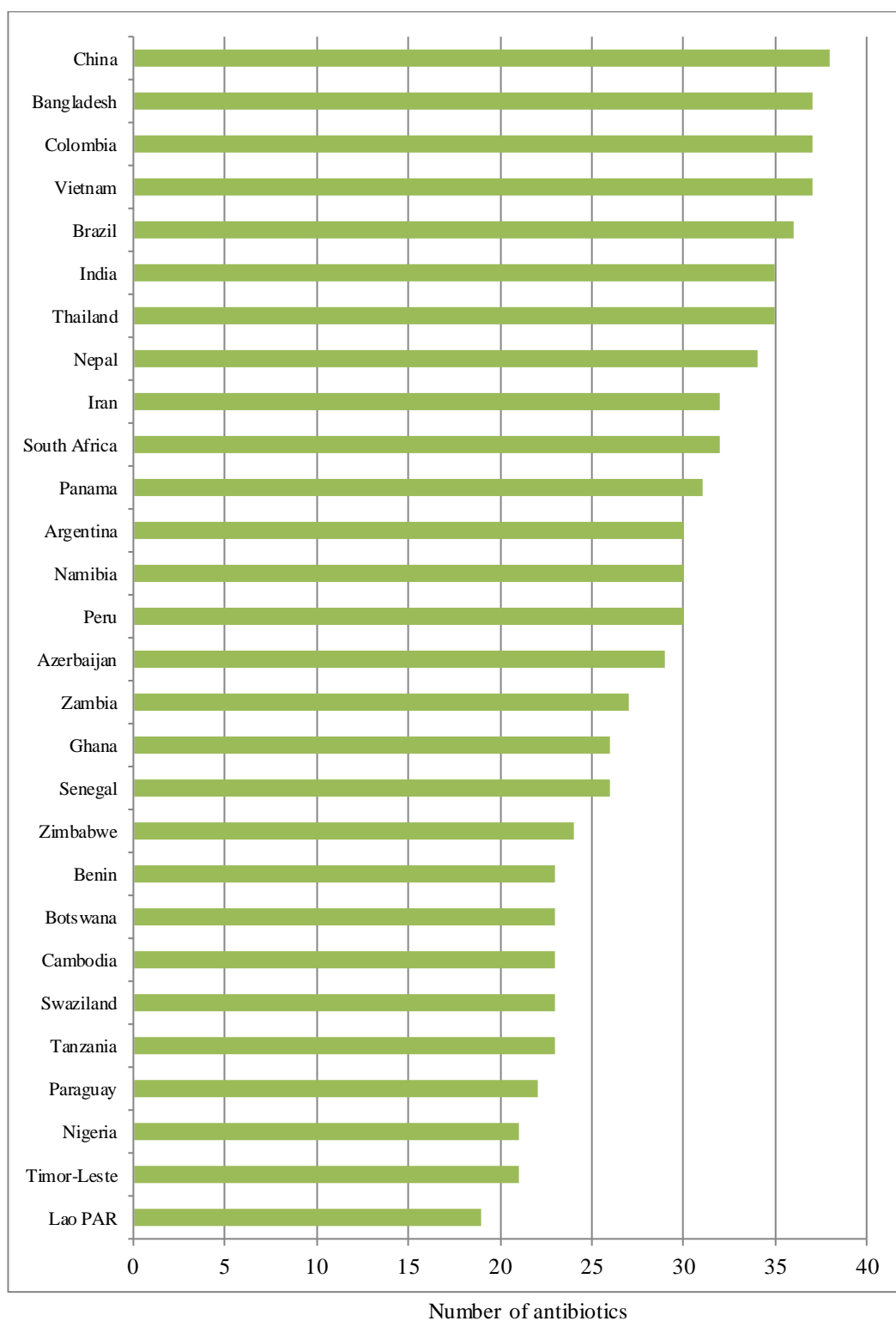


Figure 2. Number of the 41 WHO-EML 'Access' antibiotics and 'Forgotten' antibiotics approved per country (out of 41 antibiotics)

WHO-EML: World Health Organization Essential Medication List

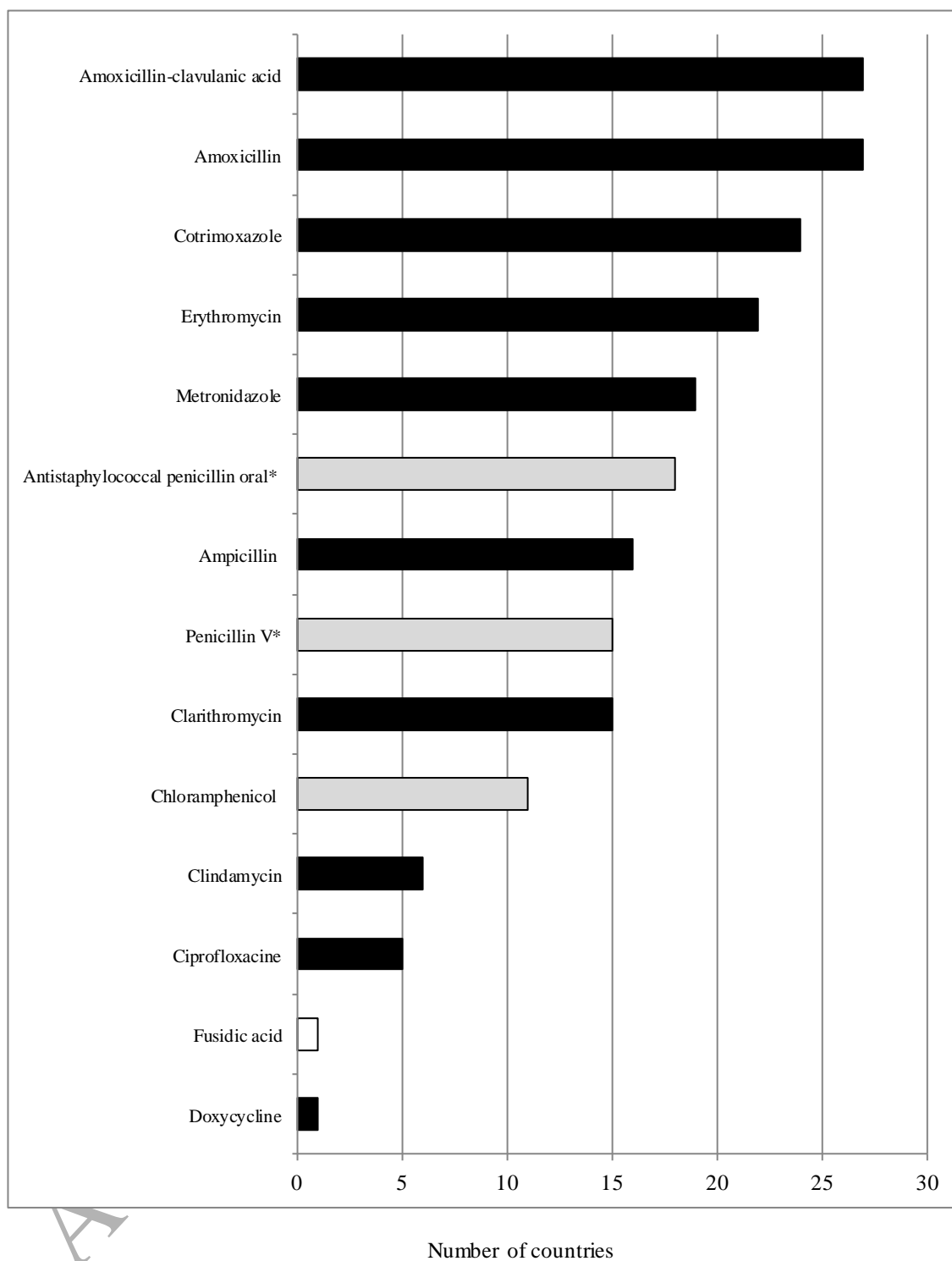


Figure 3. Approval of antibiotics specifically intended for paediatric use in the 28 surveyed countries

Black bars: antibiotics included in the WHO-EML 'Access' list

Grey bars: antibiotics included in both WHO-EML 'Access' and 'Forgotten' antibiotics list

White bars: antibiotics included in the 'Forgotten' antibiotics list

WHO-EML: World Health Organization Essential Medicines List

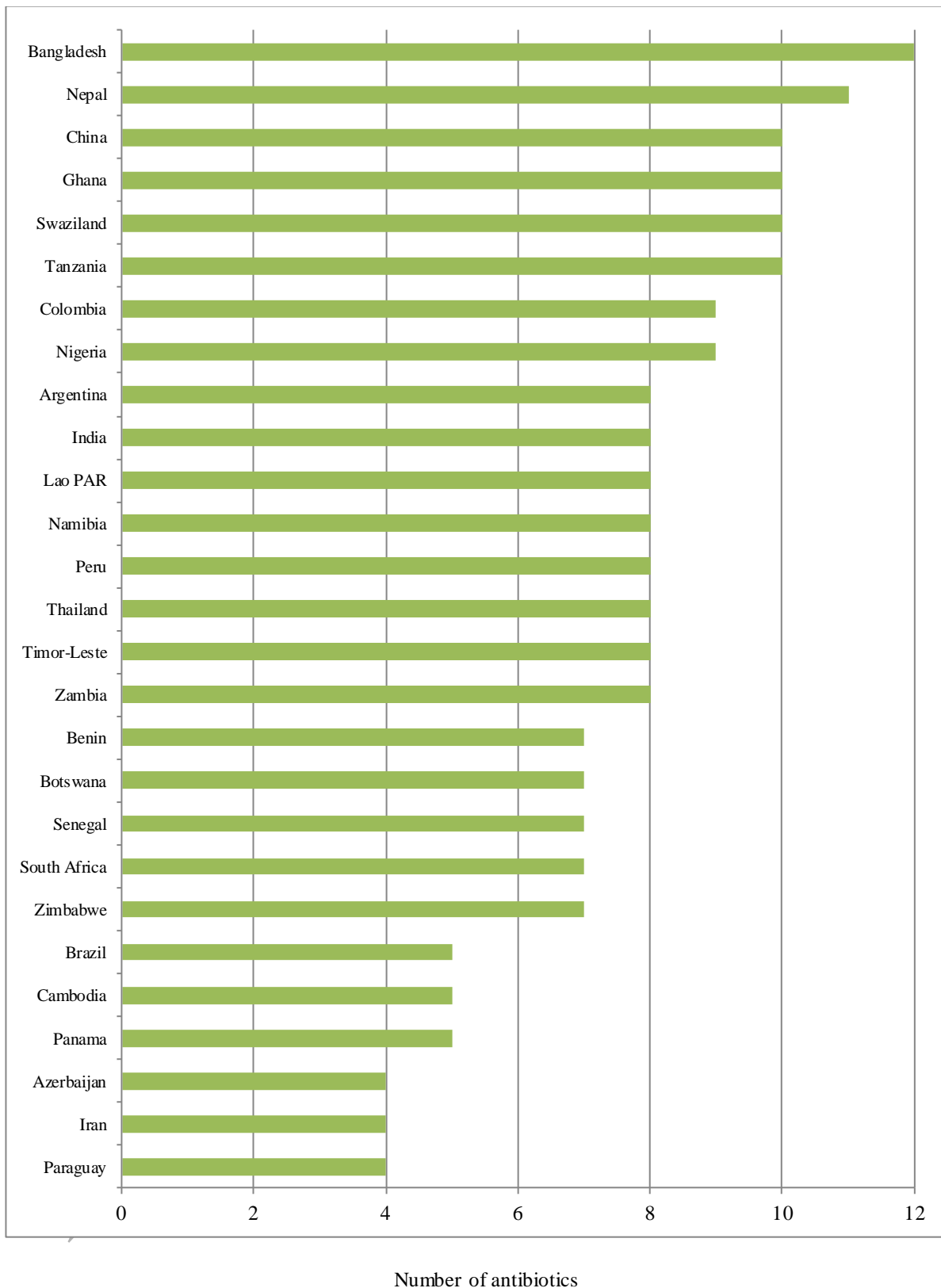


Figure 4. Number of formulations specifically intended for paediatric use approved per country (out of 12 antibiotics)

Table 1. List of the 41 included antibiotics

Antibiotic (in alphabetical order)	WHO-EML (2017) [6]			Former WHO-EML (2015) [23]		Forgotten antibiotics list
	Access antibiotics list	Watch antibiotics list	Reserve antibiotics list	Core list	Complementary list	
Amikacin	X				X*	
Amoxicillin†	X			X		
Amoxicillin-clavulanic acid†	X			X		
Ampicillin †	X			X		
Ampicillin-sulbactam						X
Antistaphylococcal penicillins IV	X**			X**		X
Antistaphylococcal penicillins oral †	X**			X**		X
Aztreonam			X			X
Benzathine benzylpenicillin	X			X		X
Benzylpenicillin (Penicillin G)	X			X		X
Cefazolin	X			X		
Cefepime			X			X
Cefotaxime	X	X			X	
Cefoxitin						X
Ceftriaxone	X	X		X		
Chloramphenicol†	X			X		X
Ciprofloxacin†	X	X		X		

Clarithromycin† (and erythromycin† as an alternative)	X	X		X		
Clindamycin†	X				X	
Colistin			X			X
Cotrimoxazole†	X			X		
Doxycycline†	X			X		
Ertapenem		X				X
Fosfomycin IV			X			X
Fosfomycin Oral						X
Fusidic Acid†						X
Gentamicin	X			X		
Meropenem (and imipenem as an alternative)	X	X			X***	
Metronidazole†	X			X		
Nitrofurantoin	X			X		X
Phenoxymethylpenicillin (Penicillin V) †	X			X		X
Pivmecillinam						X
Polymyxin B			X			X
Spectinomycin	X			X		X
Teicoplanin		X				X

Temocillin						X
Ticarcillin-clavulanic acid		X				X
Tobramycin						X
Vancomycin	X	X			X	

WHO-EML: World Health Organization Essential Medicines List

IV: intravenous

† Antibiotics existing in formulations specifically intended for paediatric use, i.e. dispersible tablets, syrups, powders for reconstitution as syrups [13]

* Included only as reserve second line drug for the treatment of multidrug resistant tuberculosis

** Cloxacillin

*** Imipenem

Table 2. List of the 28 surveyed low- and middle-income countries

Country	Continent	GNI per capita Group¹	HDI² (rank on 188 screened countries)
Benin	Africa	LIC	167
Botswana		UpMIC	108
Ghana		LoMIC	139
Namibia		UpMIC	125
Nigeria		LoMIC	152
Senegal		LIC	162
South Africa		UpMIC	119
Swaziland		LoMIC	148
Tanzania (United Republic of)		LIC	151
Zambia		LoMIC	139
Zimbabwe		LIC	154
Argentina	America	UpMIC	45
Brazil		UpMIC	79
Colombia		UpMIC	95
Panama		UpMIC	60
Paraguay		UpMIC	110
Peru		UpMIC	87
Azerbaijan	Asia	UpMIC	78
Bangladesh		LoMIC	139
Cambodia		LoMIC	143
China		UpMIC	90
India		LoMIC	131

Iran (Islamic Republic of)		UpMIC	69
Lao People's Democratic Republic		LoMIC	138
Nepal		LIC	144
Thailand		UpMIC	87
Timor-Leste		LoMIC	133
Vientam		LoMIC	115

1. GNI: Gross National Income. Classification by income according to The World Bank [14].

- UpMIC: upper middle-income countries (GNI per capita: \$3,956 to \$12,235)
- LoMIC: low middle-income countries (GNI per capita: \$1,006 to \$3,955)
- LIC: low income countries (GNI per capita: \$1,005 or less)

2. HDI: Human development index. This is a composite indicator including a health dimension (life expectancy at birth), an education dimension (mean of years of schooling for adults aged 25 years and more and expected years of schooling for children of school entering age) and a standard of living dimension (gross national income per capita). The rank in the table refers to 188 screened countries (the higher the better). The HDI is endorsed by the United Nations Development Programme [30,31].