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Essential and forgotten antibiotics: An inventory in low- and middle-income countries

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ABSTRACT

Background: The World Health Organization Essential Medicines List (WHO-EML) includes 'access' antibiotics, judged essential to treat common infections. The European Society of Clinical Microbiology and Infectious Diseases Study Group for Antimicrobial Stewardship defined a list of 'forgotten' antibiotics, some old and often off-patent antibiotics, which have particular value for specific indications.
Objective: To investigate which WHO-EML 'access' and 'forgotten' antibiotics are approved at national level in a sample of low- to middle-income countries (LMICs).

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Methods: The Scientific Committee used a consensus procedure to select 26 WHO-EML 'access' and 15 'forgotten' antibiotics. Paediatric formulations were explored for 14 antibiotics. An internet-based questionnaire was circulated to 40 LMIC representatives. Antibiotics were defined as approved if an official drug regulatory agency and/or the national ministry of health licensed their use, making them, at least theoretically, available on the market.

Results: Twenty-eight LMICs (11 in Africa, 11 in Asia and six in America) were surveyed. Nine WHO-EML 'access' antibiotics (amoxicillin, ampicillin, benzylpenicillin, ceftriaxone, clarithromycin, ciprofloxacin, doxycycline, gentamicin and metronidazole) were approved in all countries, and all 26 'access' antibiotics were approved in more than two-thirds of countries. Among the 15 'forgotten' antibiotics, only one was approved in more than two-thirds of countries. The median number of approved antibiotics per country was 30 (interquartile range 23–35). Six of 14 paediatric formulations (amoxicillin, amoxicillin-clavulanic acid, oral antistaphylococcal penicillin, cotrimoxazole, erythromycin and metronidazole) were approved in more than two-thirds of countries.

Conclusions: WHO-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 of the 'forgotten' antibiotics, despite their important role, particularly in areas with high prevalence of multi-drug-resistant bacteria.

1. Background

Balancing access and excess is one of the most urgent and complex challenges 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 is included in 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 aged <5 years, equivalent to 445,000 deaths [5].

The World Health Organization Essential Medicines List (WHO-EML) was developed in order to provide guidance to national health systems for selecting priority drugs to be provided to the population [6,7]. 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 the need for measures guaranteeing access to these essential antibiotics, and for stewardship programmes to promote responsible use. 'Access' antibiotics are those used most frequently to treat common bacterial infections, and 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 efforts. In 2011, the European Society of Clinical Microbiology and Infectious Diseases 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 multi-drug-resistant (MDR) pathogens (e.g. intravenous 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 'forgotten' antibiotics has been detailed in LMICs. As approval by an official drug regulatory agency and/or the national ministry of health is the first step in enabling an official and regulated supply of an antimicrobial in a given country, this study investigated which of the WHO-EML 'access' antibiotics and 'forgotten' antibiotics are officially approved 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 national ministry of health approved its use, making it, at least theoretically, available on the market. Inclusion of an antibiotic in the national EML was considered as a form of official approval. Only formulations for systemic use (i.e. oral, intramuscular and intravenous routes of administration) were considered.

Paediatric formulations were defined as those intended specifically 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. intravenous formulations) were not considered as intended specifically for paediatric use.

2.2. Antibiotic selection

A consensus procedure via an internet-based questionnaire was developed by the Scientific Committee to identify 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, as collecting data on all 54 antibiotics was considered to be too much work for the respondents. The antibiotics included were considered by the Scientific Committee to be those of most interest for LMICs, with a high level of agreement (≥80%) among the experts.

In total, 41 antibiotics were selected (Table 1) and 13 antibiotics were rejected (Appendix C).

Selected antibiotics included: (i) 24 WHO-EML 'access' antibiotics; (ii) 15 'forgotten' antibiotics; and (iii) 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

Table 1
List of included antibiotics (n=41).

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[b]	
Amoxicillin[a]	X			X		
Amoxicillin-clavulanic acid[a]	X			X		
Ampicillin[a]	X			X		
Ampicillin-sulbactam						X
Antistaphylococcal penicillins IV	X[c]			X[c]		X
Antistaphylococcal penicillins oral[a]	X[c]			X[c]		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[a]	X			X		X
Ciprofloxacin[a]	X	X		X		
Clarithromycin[a] (and erythromycin[a] as an alternative)	X	X		X		
Clindamycin[a]	X				X	
Colistin			X			X
Cotrimoxazole[a]	X			X		
Doxycycline[a]	X			X		
Ertapenem		X				X
Fosfomycin IV			X			X
Fosfomycin oral						X
Fusidic acid[a]						X
Gentamicin	X			X		
Meropenem (and imipenem as an alternative)	X	X			X[d]	
Metronidazole[a]	X			X		
Nitrofurantoin	X			X		X
Phenoxymethilpenicillin (Penicillin V)[a]	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.
[a] Antibiotics existing in formulations intended specifically for paediatric use (i.e. dispersible tablets, syrups, powders for reconstitution as syrups) [13].
[b] Included only as reserve second-line drug for the treatment of multi-drug-resistant tuberculosis.
[c] Cloxacillin.
[d] Imipenem.

erythromycin and imipenem, are included among the WHO-EML 'access' antibiotics in the following paragraphs and figures.

Among the antibiotics included in this study, 14 had formulations intended specifically 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 LMIC contacts with recognised expertise in the field of study was selected and invited to participate. These national contacts were part of the Scientific Committee for six 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 documents and/or websites to support their answers, mainly national formularies, drug regulatory agency websites or the national EML. 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 ranges (IQR), as appropriate.

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

3. Results

3.1. Study participants

Forty national contacts were invited to participate in this study and 28 (70%) accepted: 11 (39%) from Africa, 11 (39%) from Asia and six (22%) from America (Table 2). Five (18%) countries were classified as low-income countries [LICs, gross national income

Table 2
List of surveyed low- and middle-income countries (n=28).

Country	Continent	GNI per capita group[a]	HDI[b] (rank in 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

GNI, gross national income; UpMIC, upper-middle-income country; LoMIC, low-middle-income country; LIC, low-income country; HDI, human development index.

[a] Classification by income according to the World Bank [14]. UpMICs, GNI per capita: $3956–12,235; LoMICs, GNI per capita $1006–3955; LICs, GNI per capita: ≤$1005.

[b] The HDI is a composite indicator including a health dimension (life expectancy at birth), an education dimension (mean years of schooling for adults aged ≥25 years 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].

(GNI) per capita: ≤$1005), 10 (36%) were classified as low-middle-income countries (LoMICs, GNI per capita: $1006–3955), and 13 (46%) were classified as upper-middle-income countries (UpMICs, GNI per capita: $3956–12,235) [14]. The respondents are listed in the Acknowledgements section and their complete affiliations are detailed in Appendix D.

3.2. Approval of antibiotics

Fig. 1 shows the number of countries with approval for each of the WHO-EML 'access' antibiotics and 'forgotten' antibiotics.

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

Fig. 2 shows the number of antibiotics approved per country. The median number was: 30 (IQR 23–35) overall, 24 (IQR 23–27) in Africa, 31 (IQR 28–36) in America, 34 (IQR 23–37) in Asia, 24 (IQR 23–30) in LICs, 25 (IQR 21–36) in LoMICs and 31 (IQR 30–36) in UpMICs. Medians were not significantly different between continents and different income groups (data not shown).

3.3. Approval of antibiotics specifically intended for paediatric use

Fig. 3 shows the number of countries with approval for a formulation intended specifically for paediatric use for each of the WHO-EML 'access' antibiotics and 'forgotten' antibiotics.

Six of 14 antibiotics (43%: amoxicillin, amoxicillin-clavulanic acid, cotrimoxazole, erythromycin, metronidazole, oral antistaphylococcal penicillin) were approved in more than two-thirds of countries.

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

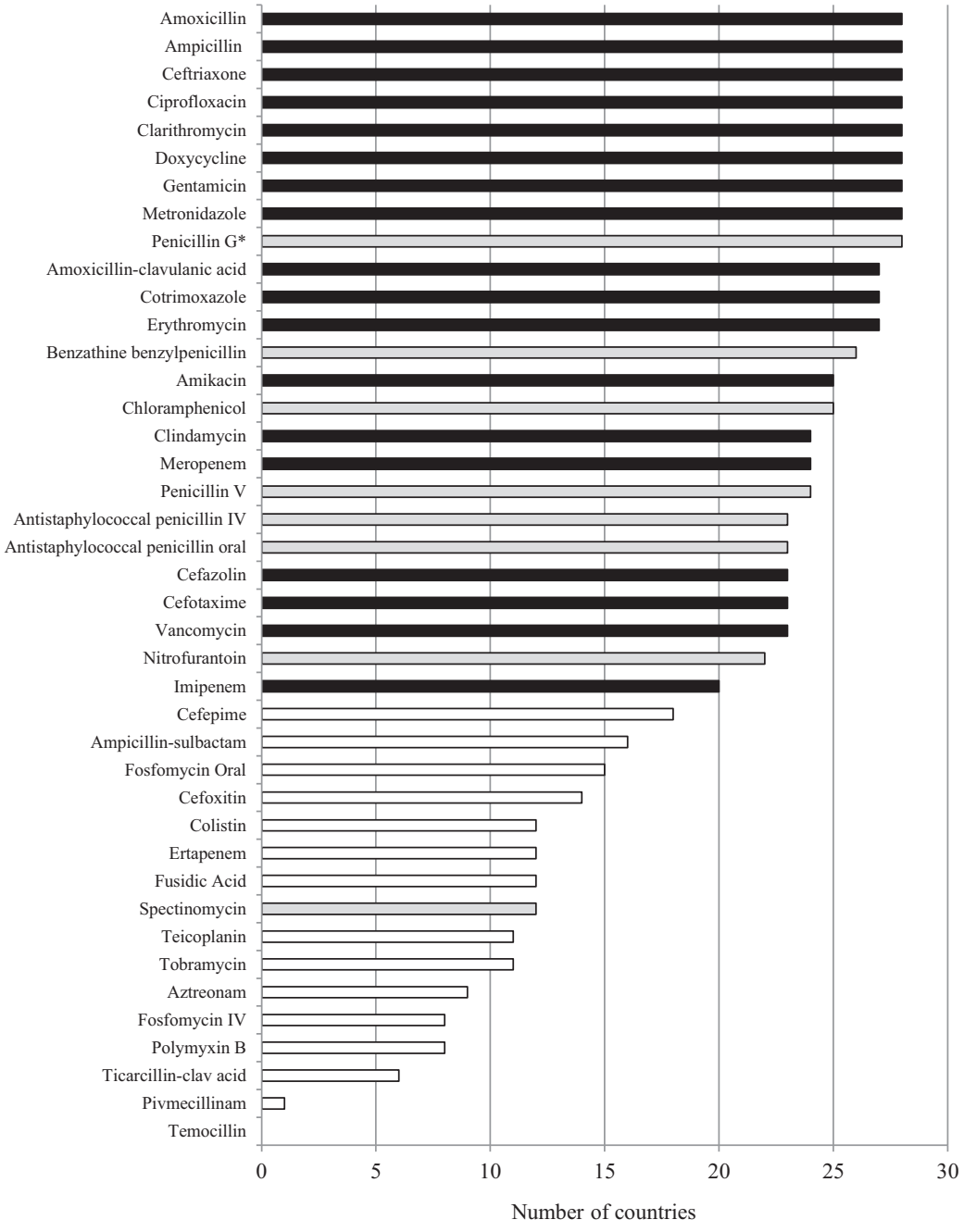
The median number was: eight (IQR 7–9) overall, eight (IQR 7–10) in Africa, seven (IQR 5–8) in America, eight (IQR 7–11) in Asia, seven (IQR 7–11) in LICs, eight (IQR 8–10) in LoMICs and seven (IQR 5–8) in UpMICs. Information about paediatric formulations was not available for Vietnam.

3.4. Double checking of results

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

4. Discussion

This large international survey gives an overview of official approval by local drug regulatory agencies and/or national ministries of health of 41 useful antibiotics, including paediatric formulations, in a sample of 28 LMICs from three continents. The explored antibiotics were selected among those included as 'access' antibiotics



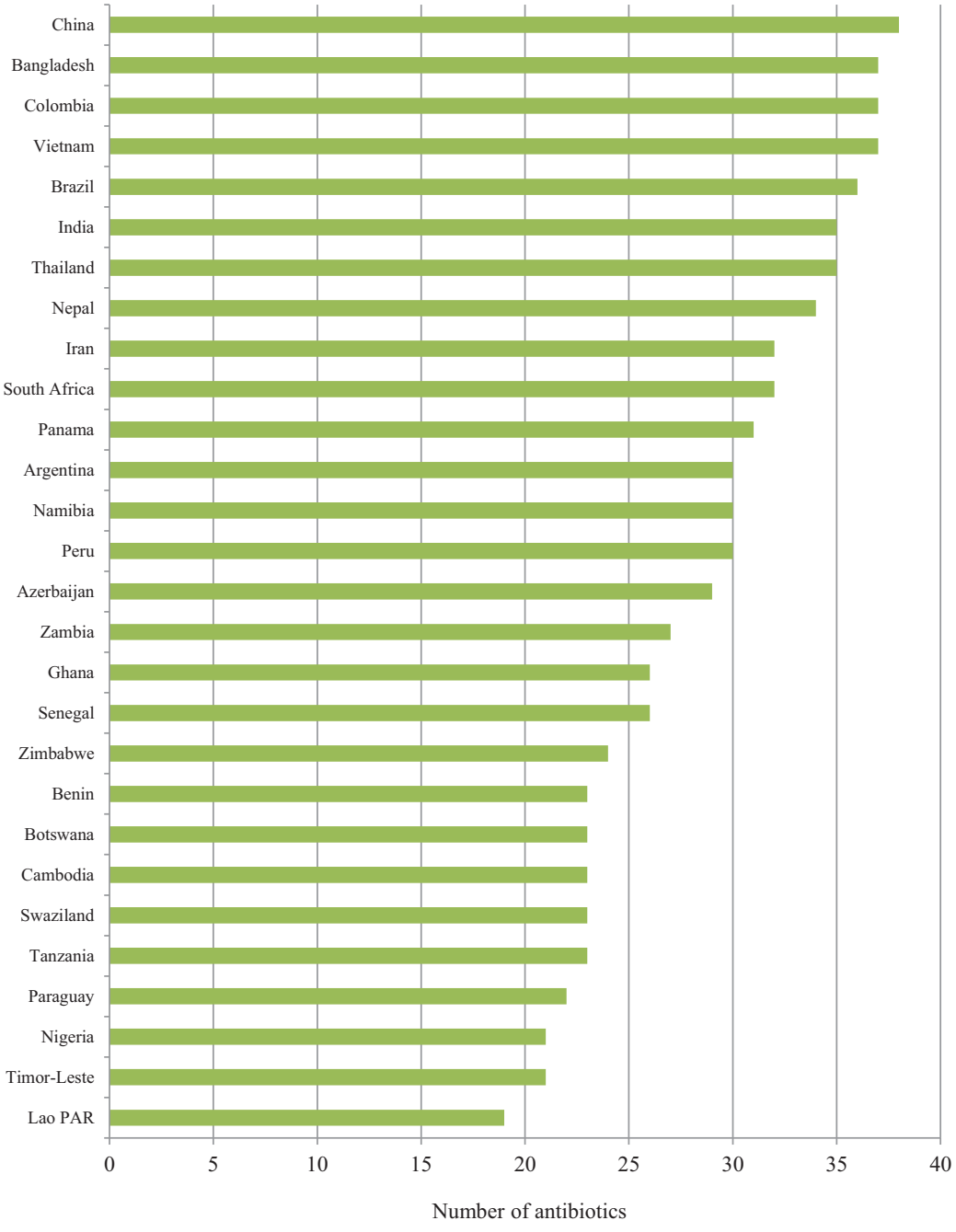
Black bars: antibiotics included in the WHO-EML 'Access' list
Grey bars: antibiotics included in both WHO-EML 'Access' and 'Forgotten' antibiotics list
Withe bars: antibiotics included in the 'Forgotten' antibiotics list

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

Fig. 1. World Health Organization Essential Medicines List (WHO-EML) 'access' antibiotics and 'forgotten' antibiotics approved in the 28 surveyed countries.

in WHO-EML 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]. Most of the WHO-EML 'access' antibiotics were found to be approved in the 28 LMICs surveyed, 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. The authors did not collect information about effective availability at different levels of each country's healthcare system. The appraisal of drug availability is challenging for several reasons: healthcare systems in LMICs are known to have complex organisation, with different levels of healthcare provision (e.g. reference hospitals, district hospitals, peripheral primary healthcare facilities) having different aims and therefore providing different assortments of medications [15,16]; private for-profit healthcare 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



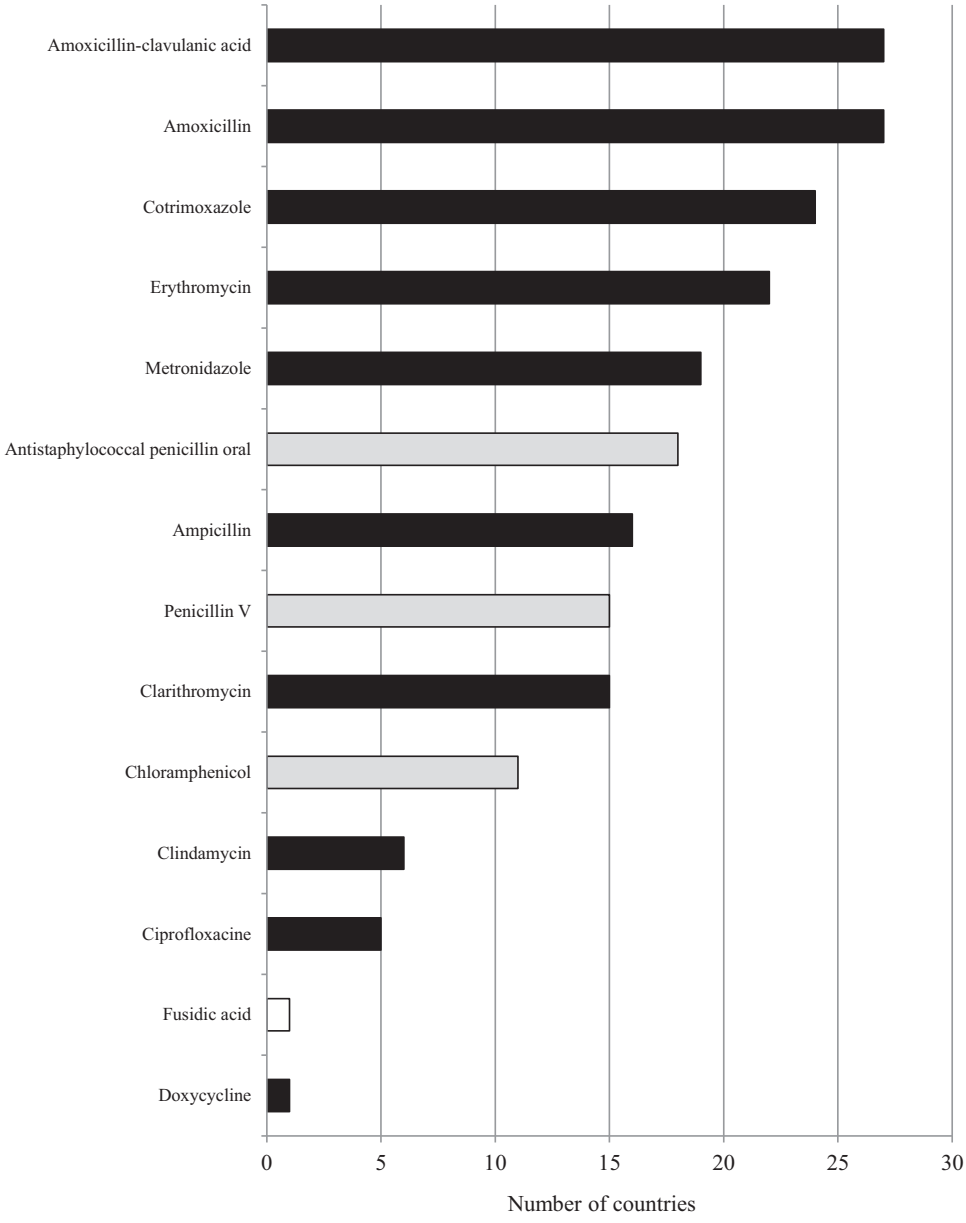
WHO-EML: World Health Organization Essential Medication List

Fig. 2. Number of World Health Organization Essential Medicines List 'access' antibiotics and 'forgotten' antibiotics approved by country (out of 41 antibiotics).

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]; and drug shortages and troubles in the supply chain may affect effective access, particularly in remote and poorest areas [22]. As such, availability 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 investigation of drug approval is an important first step, as approval by the local drug authority is needed to further enable reliable and regulated access to a given antibiotic in a particular country.

This study demonstrated that, overall, LMICs comply with WHO-EML, as the vast majority of 'access' antibiotics were approved by an official drug regulatory agency and/or the national ministry of health (Fig. 1). As the list of 'access' antibiotics was published in March 2017 and amended in August 2017, it could be argued that the surveyed countries complied with the previous WHO-EML (2015 version) [23]. However, as illustrated in Table 1, the vast majority of 'access' antibiotics were already listed as 'core antibiotics' in the previous WHO-EML, with the exception of a few antibiotics (cefotaxime, clindamycin, carbapenems and vancomycin) which were in the 'complementary list' [23].

The situation is significantly different for 'forgotten' antibiotics. This study explored the approval of 23 'forgotten' antibiotics;



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

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

eight were included in the WHO-EML 'access' antibiotics and were approved in the large majority of countries (Fig. 1); on the other hand, the remaining 15 'forgotten' antibiotics were only approved in a minority of countries (Fig. 1). 'Forgotten' antibiotics can have a role in daily practice in different clinical situations, such as enabling reduction in the use of other broader-spectrum and sometimes less effective antimicrobials (e.g. antistaphylococcal penicillins, oral fosfomycin and pivmecillinam), offering the opportunity to treat MDR pathogens (e.g. aztreonam, intravenous fosfomycin, polymyxins, temocillin etc.), and acting as a 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 the 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 WHO-EML marked a step forwards as three of these 'forgotten' antibiotics (ertapenem, teicoplanin and ticarcillin-clavulanic acid) were included in the newly designed

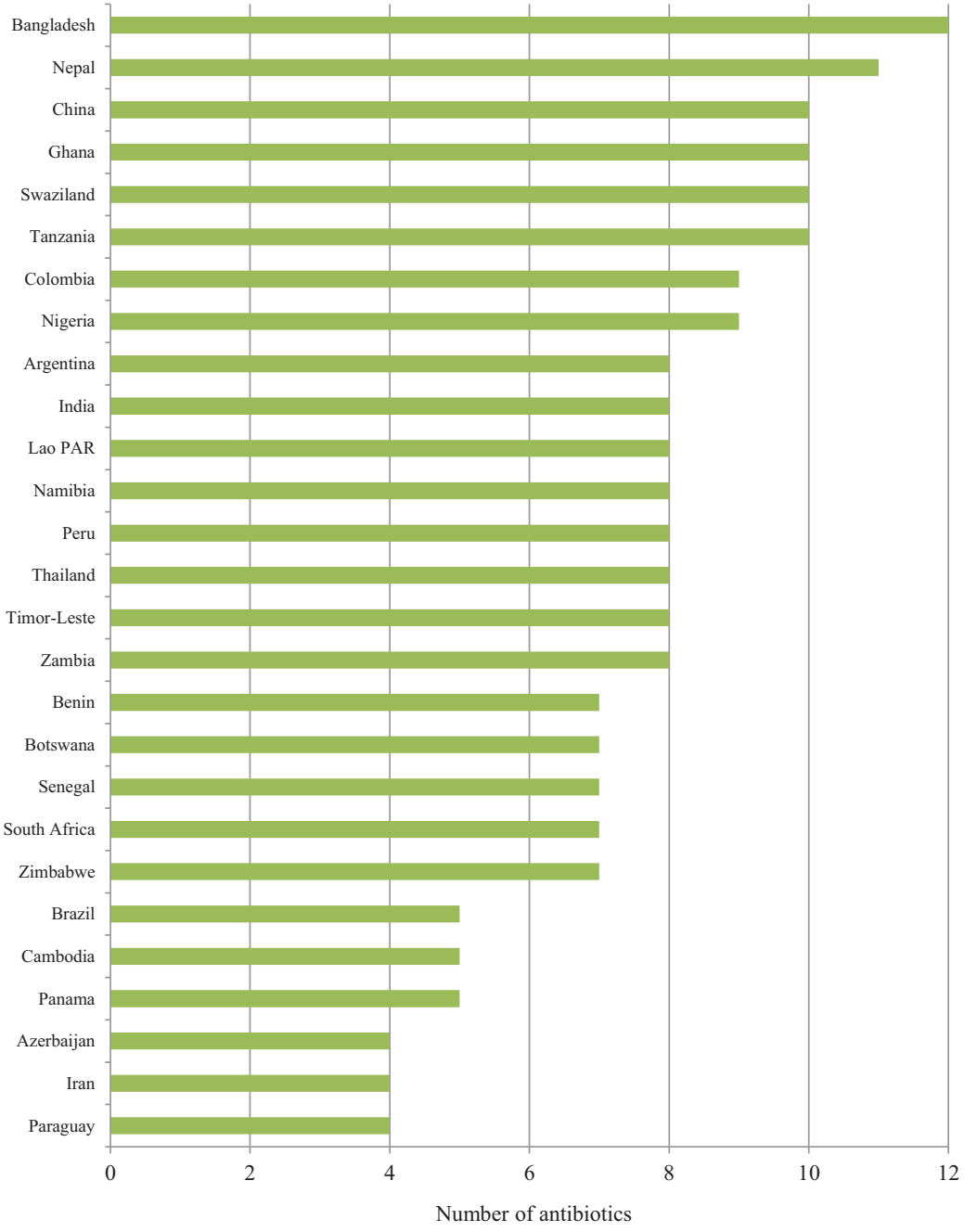


Fig. 4. Number of formulations intended specifically for paediatric use approved by country (out of 12 antibiotics).

'watch' category, and five (aztreonam, cefepime, colistin, polymyxin B and intravenous fosfomycin) were included in the 'reserve' category [6]. This is a significant change compared with the previous WHO-EML [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, approved more antibiotics than African countries and lower-income countries. These data suggest that countries with higher incomes could guarantee access to more antibiotics, even if these differences were not significant, probably due to the relatively small number of countries studied.

Concerning formulations intended specifically for paediatric use (Figs 3 and 4), the antibiotics used more frequently 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 of proper access to medicines on children's health [5] and the paucity of data about the availability of paediatric drugs, this aspect is in urgent need of further research efforts, 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 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 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, so the reliability of some of the collected data could be questioned. However, respondents provided one or more official documents and/or websites as sources 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 whether different types of formulations (intended for children of different age groups) were approved. This study did not distinguish between the approval of an antibiotic by a drug regulatory agency and/or the national ministry of health and inclusion in the national EML, even if this difference could influence the effective drug availability. This study did not collect data on how many brands and/or generics are approved for each antibiotic, in order 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 compared with many approvals per medicine. Finally, this study screened a sample of 28 countries, and the results cannot be generalised to other countries. This sample nevertheless included countries from three continents, with good geographic distribution and huge variability in terms of healthcare, 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. WHO-EML therefore seems to have a very positive impact regarding approval of antibiotics at national level. Further studies are needed in each LMIC to verify if the approved antibiotics are effectively available in daily clinical practice, with reliable supply chains, affordable prices and acceptable formulations, at different levels of the healthcare system.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2019.06.017.

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