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

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► To cite this version:

Gianpiero Tebano, Grace Li, Bojana Beovic, Julia Bielicki, Adrian Brink, et al.. Essential and forgotten antibiotics: An inventory in low- and middle-income countries. *International Journal of Antimicrobial Agents*, 2019, 54 (3), pp.273-282. 10.1016/j.ijantimicag.2019.06.017 . hal-02460591

HAL Id: hal-02460591

<https://hal.univ-lorraine.fr/hal-02460591>

Submitted on 20 Jul 2022

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49

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51

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67 **Running head:** Essential and Forgotten antibiotics in LMICs

68

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85

86 **ABSTRACT**

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

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

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

97 **Results:** We surveyed 28 LMICs (Africa: 11, Asia: 11, America:6). Nine EML 'Access' antibiotics
98 (amoxicillin, ampicillin, benzylpenicillin, ceftriaxone, clarithromycin, ciprofloxacin, doxycycline,
99 gentamicin and metronidazole) were approved in all countries, 26/26 in more than two thirds. Among
100 'Forgotten' antibiotics only 1/15 was approved in more than two thirds of countries. The median
101 number of approved antibiotics per country was 30 [interquartile range: 23-35]. 6/14 paediatric
102 formulations (amoxicillin, amoxicillin-clavulanic acid, oral antistaphylococcal penicillin,
103 cotrimoxazole, erythromycin and metronidazole) were approved in more than two thirds of countries.
104 **Conclusions:** EML 'Access' antibiotics and the most frequently used formulations for paediatrics were
105 approved in the vast majority of the 28 surveyed LMICs. This was not the case for many 'Forgotten'
106 antibiotics, despite their important role, particularly in areas with high prevalence of multidrug-
107 resistant bacteria.

108

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

111

1. BACKGROUND

112

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

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

121

122 The World Health Organization (WHO) Essential Medicines List (EML) was developed in order to
123 provide guidance to country health systems for selecting priority drugs to be provided to the
124 population [6,7]. The WHO-EML was updated in 2017 (20th edition for adult, 6th edition for children)
125 [8,9], with re-categorisation of antibiotic agents into groups labelled ‘Access’, ‘Watch’ and ‘Reserve’,
126 to highlight both the need for measures guaranteeing access to these essential antibiotics, and for
127 stewardship programmes to promote responsible use. ‘Access’ antibiotics are those most frequently
128 used to treat common bacterial infections, hence those which should be available everywhere.

129

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

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

140

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

2. METHODS

146

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

149

150 **2.1 Definitions**

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

156

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

161

162 **2.2 Antibiotic selection**

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

169

170 A total of 41 antibiotics were selected (Table 1), while 13 antibiotics were rejected (Appendix C).

171 Selected antibiotics included: a) 24 WHO-EML 'Access' antibiotics; b) 15 'Forgotten' antibiotics; c)
172 imipenem and erythromycin (which are listed as alternatives to meropenem and clarithromycin

173 respectively in the EML). Eight of the WHO-EML ‘Access’ antibiotics (Table 1) were also originally
174 included in the ‘Forgotten’ antibiotics list [11,12]. These antibiotics, as well as erythromycin and
175 imipenem, are included among WHO-EML ‘Access’ antibiotics in the further paragraphs and figures.
176 Among the antibiotics included in the study, 14 had formulations specifically intended for paediatric
177 use [13].

178

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

181

182 **2.3 Survey deployment and double checking of results**

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

189

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

195

196 **2.4 Data analysis**

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

199

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

202

3. RESULTS

203

204 **3.1 Study participants**

205 The invitation to participate was sent to 40 national contacts and 28 (70%) accepted to participate: 11
206 (39%) from Africa, 11 (39%) from Asia, 6 (22%) from America (Table 2). Five (18%) countries were
207 classified as low income countries (LIC, gross national income - GNI - per capita: \$1,005 or less), 10
208 (36%) as low middle-income countries (LoMIC, GNI per capita: \$1,006 to \$3,955), and 13 (46%) as
209 upper middle-income countries (UpMIC, GNI per capita: \$3,956 to \$12,235) [14]. The respondents
210 are listed in the Acknowledgement section and their complete affiliations are detailed in the Appendix
211 D.

212

213 **3.2 Approval of antibiotics**

214 Figure 1 shows the number of countries having approved each of the WHO-EML 'Access' antibiotics
215 and 'Forgotten' antibiotics.

216

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

222

223 Figure 2 shows the number of antibiotics approved per country. The median number was: 30
224 [interquartile range 23-35] overall; 24 [23-27] in Africa; 31 [28-36] in America; 34 [23-37] in Asia; 24
225 [23-30] in LIC; 25 [21-36] in LoMIC; 31 [30-36] in UpMIC. Medians were not significantly different
226 among continents and different income groups (data not shown).

227

228

229 **3.3 Approval of antibiotics specifically intended for paediatric use**

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

232

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

236

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

239

240 The median number was: 8 [interquartile range 7-9] overall; 8 [7-10] in Africa; 7 [5-8] in America; 8
241 [7-11] in Asia; 7 [7-11] in LIC; 8 [8-10] in LoMIC; 7 [5-8] in UpMIC. Information about paediatric
242 formulations was not available for Vietnam.

243

244 **3.4 Double checking of results**

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

4. DISCUSSION

250

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

259

260 This study assessed if a given systemic antibiotic was approved for human use in a given country. We
261 did not aim to collect information about effective availability at different levels of each country’s
262 health care system. The appraisal of drug availability is challenging for several reasons: health care
263 systems in LMICs are known to have complex organisations, with different levels of health care
264 provision (e.g. reference hospitals, district hospitals, peripheral primary health care facilities), having
265 different aims and therefore providing different assortments of medications [15,16]; private for-profit
266 health care providers are variably present and do not necessarily follow the policies implemented in
267 the public system [17]; the circulation of drugs in the informal sector may be significant and difficult
268 to assess [18]; other relevant actors in the non-profit sector may adhere to independent drug policies
269 and provide their own supply channels [19–21]; drug shortages and troubles in supply chain may
270 affect effective access, particularly in remote and poorest areas [22]. Availability therefore needs to be
271 assessed on a country-by-country basis. For example, a report by the Ministry of Health and Social
272 Welfare of Tanzania showed that there are more than 25 stakeholders involved in the procurement of
273 medicines in that country [19]. This complex scenario revealed that investigations of drug approval is
274 an important first step, since the approval by the local drug authority is needed to further enable a
275 reliable and regulated access to a given antibiotic in a particular country.

276

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

285

286 The situation is significantly different for ‘Forgotten’ antibiotics. Our study explored the approval of
287 23 ‘Forgotten’ antibiotics; 8 were included also among the WHO-EML ‘Access’ antibiotics and were
288 approved in the large majority of countries (Figure 1); on the other hand, the remaining 15 ‘Forgotten’
289 antibiotics were approved only in a minority of countries (Figure 1). ‘Forgotten’ antibiotics can have a
290 role in daily practice in different clinical situations: enabling reduction in the use of other broader
291 spectrum and sometimes less effective antimicrobials (e.g. antistaphylococcal penicillins, oral
292 fosfomicin, pivmecillinam); offering the opportunity to treat MDR pathogens (e.g. aztreonam, IV
293 fosfomicin, polymyxins, temocillin and many others); acting as niche agent for specific pathogens
294 (e.g. ampicillin-sulbactam for *Acinetobacter baumannii*, spectinomycin for *Neisseria gonorrhoeae*,
295 tobramycin for *Pseudomonas aeruginosa*) (Appendix A) [4,11,24]. This can be of added value in
296 LMICs, where prevalence of MDR bacteria is often very high, calling for both effective treatments
297 and antibiotic stewardship efforts [25–27]. The availability of these mainly out-of-patent products is
298 threatened by a vicious circle including low economic incentives; limited market size; low level of
299 scientific evidence (particularly on pharmacokinetics/pharmacodynamics and clinical efficacy); low
300 use by physicians; and absence of inclusion in guidelines [4,11,24].

301

302 The last version of the WHO-EML marked a step forward since 3 of these ‘Forgotten’ antibiotics
303 (ertapenem, teicoplanin and ticarcillin-clavulanic acid) were included in the newly designed ‘Watch’
304 category and 5 (aztreonam, cefepime, colistin and polymyxin B, IV fosfomicin) in the ‘Reserve’

305 group [6]. This is a significant change compared to the previous WHO-EML list [23] and could help
306 improve the availability of these molecules for selected conditions.

307

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

313

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

322

323 There is still a long way to go. Coordinated efforts with multi-stakeholder approaches will be needed
324 to improve antimicrobial availability in LMICs. Areas include: continuous monitoring of the
325 availability of all antibiotics included in the WHO-EML; consideration of the possible role of
326 'Forgotten' antibiotics in these settings; access gap analysis; strengthening of health systems;
327 promotion of universal health coverage; promotion of alternative economic models to delink payments
328 for antimicrobials from the volumes sold; and the evaluation of the potential role and feasibility of a
329 Global Antibiotic Access and Conservation Fund [1,4,28,29].

330

331 This study has some limitations. Only one respondent was contacted for each country, thus the
332 reliability of some of the collected data could be questioned. However, respondents provided one or

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

346

347 In conclusion, most of the WHO-EML 'Access' antibiotics are approved in the 28 surveyed LMICs,
348 including the most relevant paediatric formulations. On the contrary, many 'Forgotten' antibiotics are
349 not approved in these countries, despite their important role in some specific clinical conditions,
350 particularly in areas with high prevalence of MDR bacteria. The WHO-EML therefore seems to have a
351 very positive impact regarding approval of antibiotics at national level. Further studies are needed to
352 verify in each LMIC if approved antibiotics are effectively available in daily clinical practice, with
353 reliable supply chain, affordable prices, and acceptable formulations, at different levels of the health
354 care system.

355 **Acknowledgements**

356 Partial results were presented as a poster (n° 2935) at the 2018 ECCMID in Madrid.

357 The authors would like to thank all national contacts who participated in the survey: Fidan Huseynova

358 (Azerbaijan), Abu Hena Mostafa Kamal (Bangladesh), Cossi Angelo Attinsounon (Benin), Joyce

359 Kgatlwane (Botswana), Paul Turner (Cambodia), Mei Zeng (China), Carlos Robledo (Colombia),

360 Daniel Kwame Afriyie and Emmanuel Sarkodie (Ghana), Mojdeh Hakemi-Vala (Iran), Vilada

361 Chansamouth (Lao), Buddha Basnyat (Nepal), Silvio Vega (Panama), Elena Candia Florentín

362 (Paraguay), Luis Cuellar (Peru), Awa Ndir (Senegal), Amu Adefolarin Ayodeji (Swaziland), Stanley

363 Mwita (Tanzania), Visanu Thamlikitku (Thailand)

364 Eric Vreede and Flavio Brandao De Araujo (Timor-Leste), Vu Dinh Phu (Vietnam), Aubrey

365 Chichonyi Kalungia (Zambia), Blessmore Vimbai Chaibva (Zimbabwe).

366

367 **Declarations**

368 **Funding:** No funding

369 **Competing Interests:** The authors have no conflict of interest to disclose related with the topic.

370 **Ethical Approval:** Not required

371

372

373 **REFERENCES**

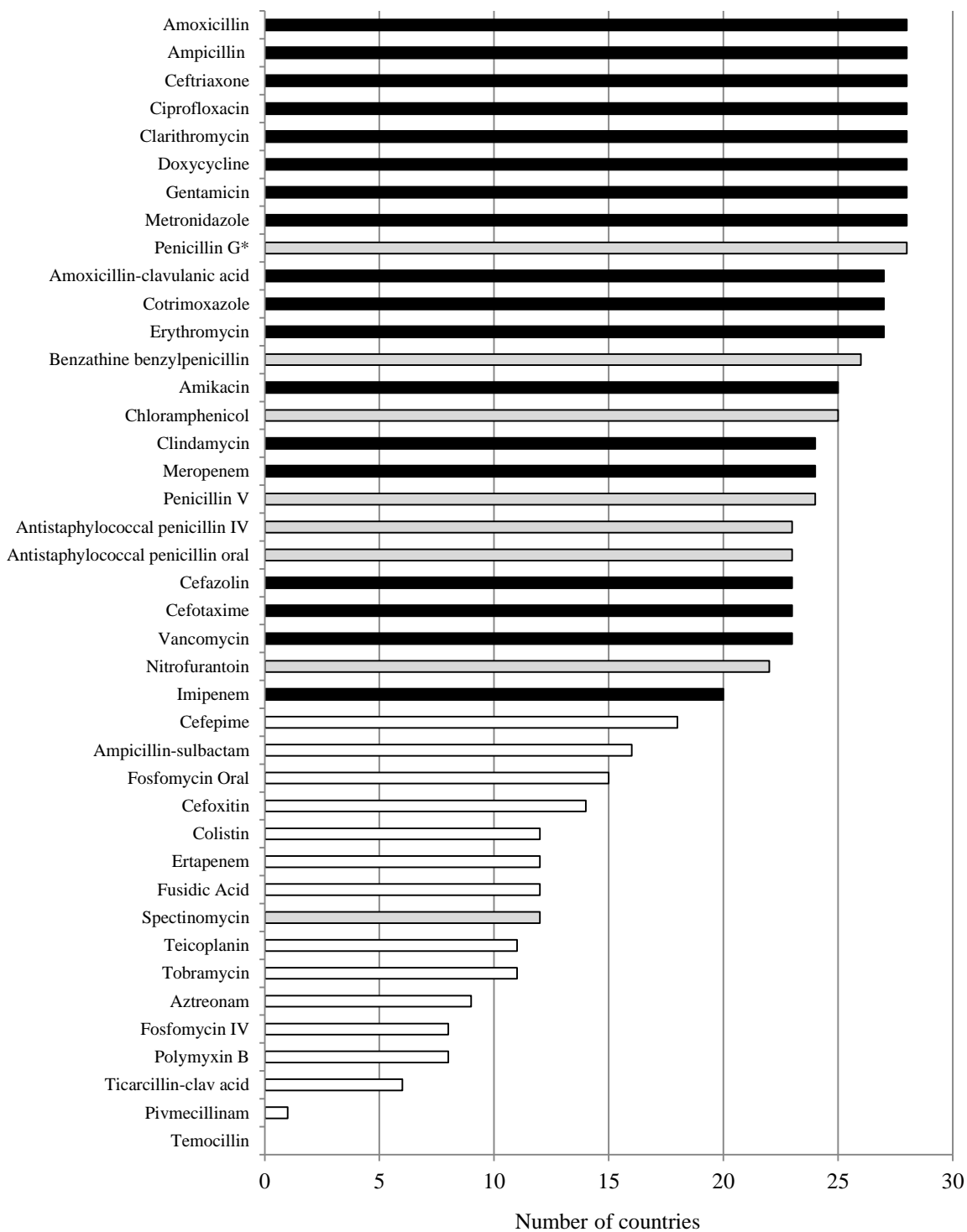
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Figure 1. WHO-EML ‘Access’ antibiotics and ‘Forgotten’ antibiotics approved in the 28 surveyed countries



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)

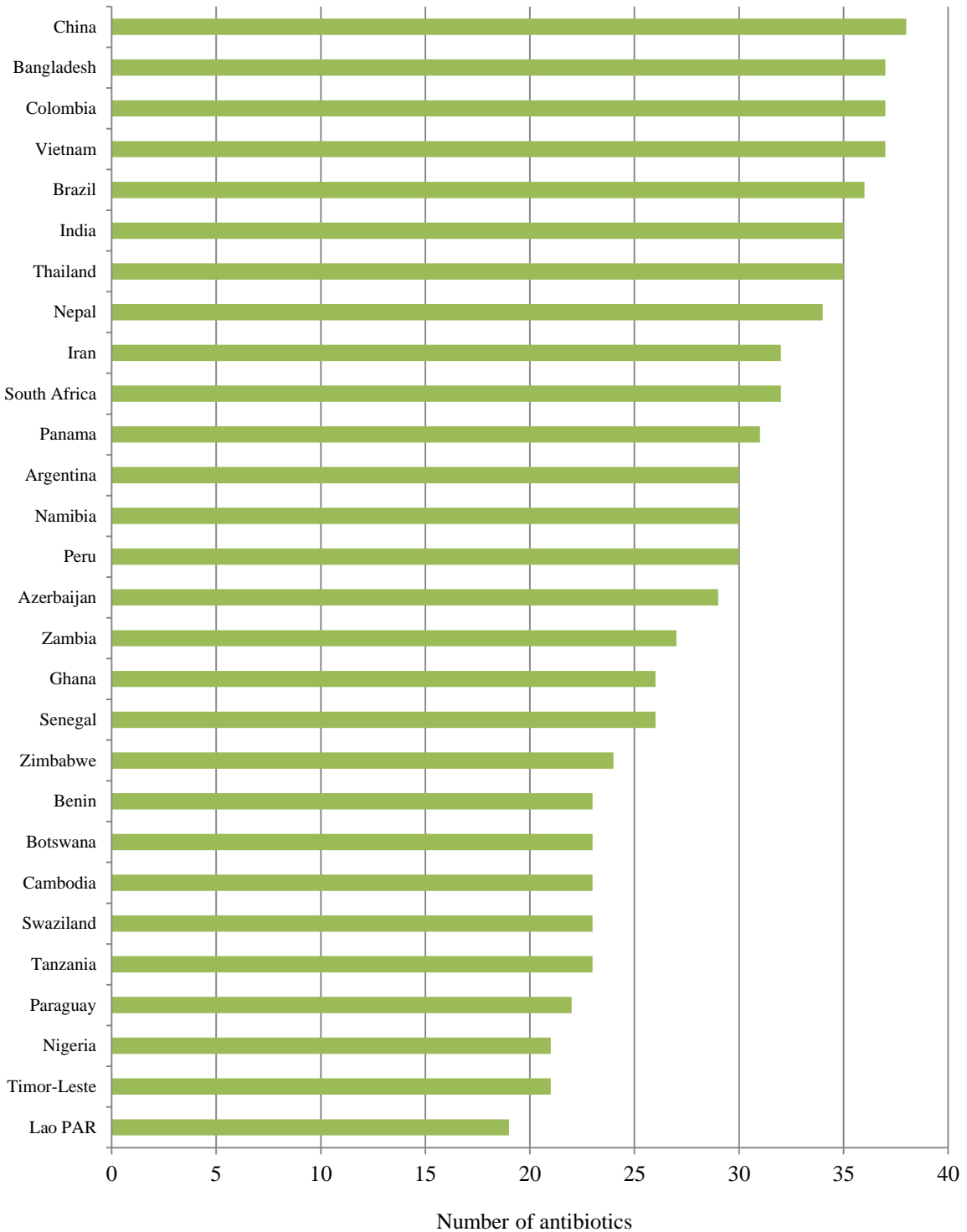
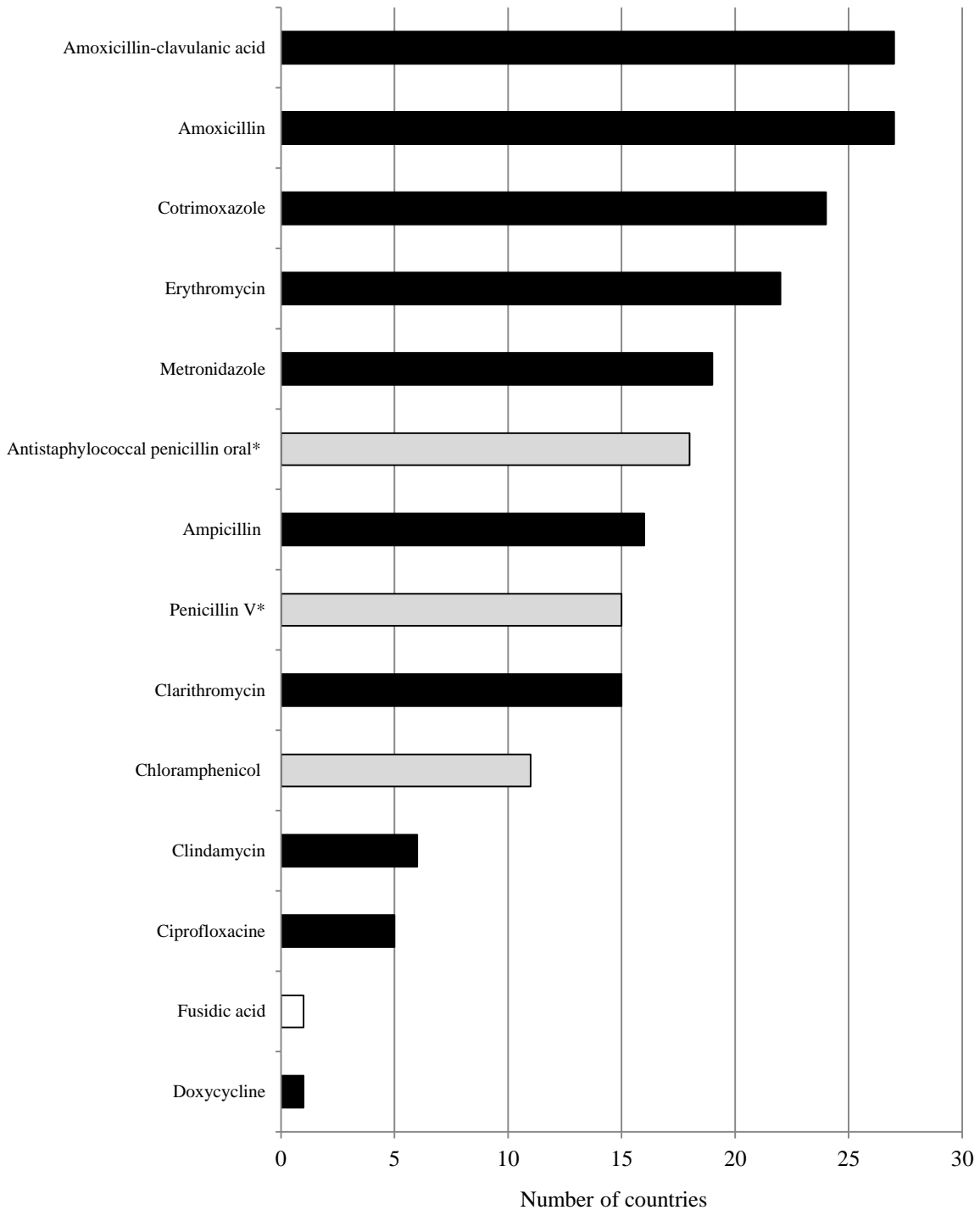


Figure 3. Approval of antibiotics specifically intended for paediatric use in the 28 surveyed countries



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)

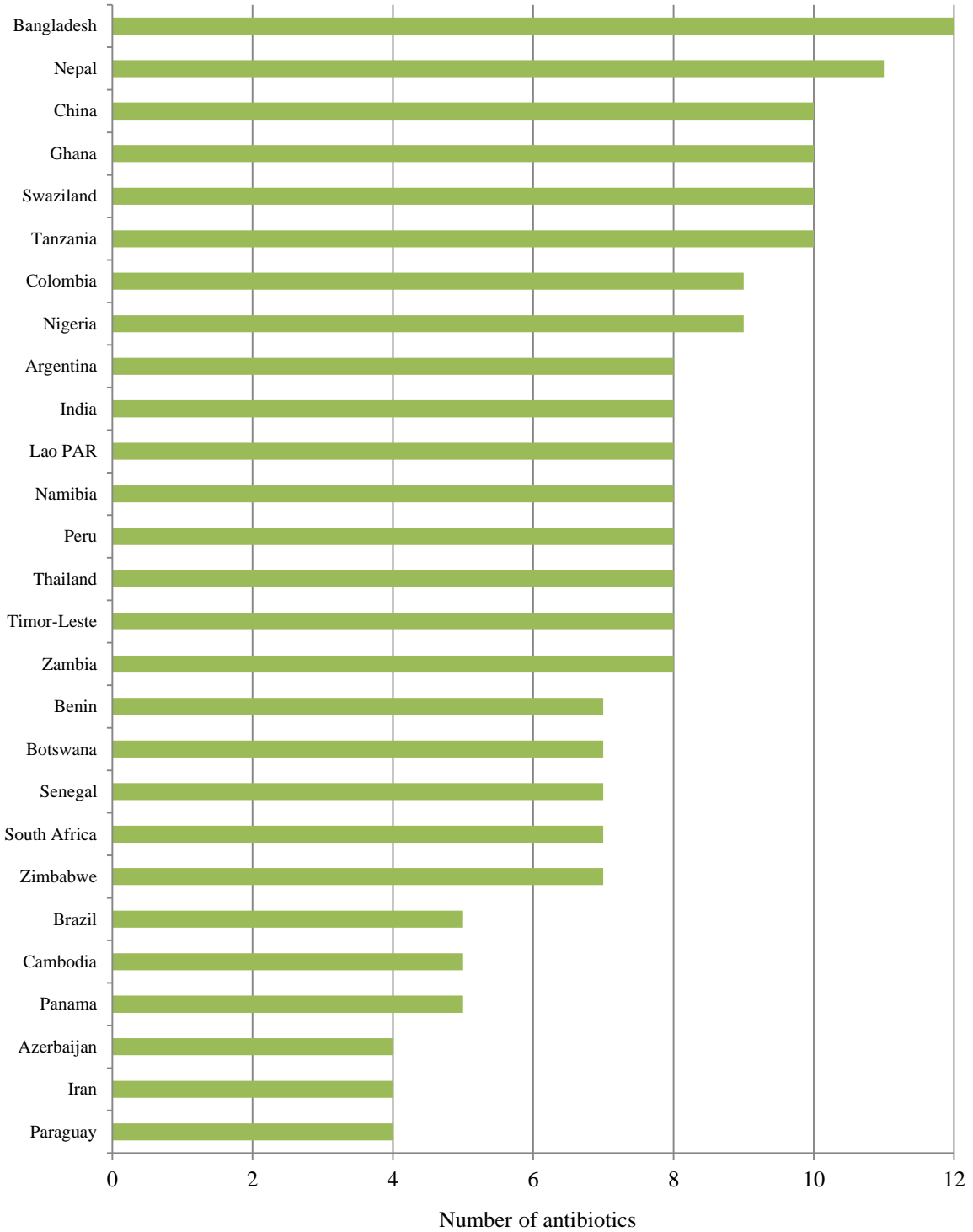


Table 1. List of the 41 included antibiotics

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
Fosfomicin IV			X			X
Fosfomicin 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

1 **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

2

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

4 • UpMIC: upper middle-income countries (GNI per capita: \$3,956 to \$12,235)

5 • LoMIC: low middle-income countries (GNI per capita: \$1,006 to \$3,955)

6 • LIC: low income countries (GNI per capita: \$1,005 or less)

7 2. HDI: Human development index. This is a composite indicator including a health dimension (life

8 expectancy at birth), an education dimension (mean of years of schooling for adults aged 25 years and more

9 and expected years of schooling for children of school entering age) and a standard of living dimension

10 (gross national income per capita). The rank in the table refers to 188 screened countries (the higher the

11 better). The HDI is endorsed by the United Nations Development Programme [30,31].