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**Reference:**

Cox J. A., Vlieghe Erika, Mendelson M., Wertheim H., Ndegwa L., Villegas M. V., Gould I., Levy Hara G.- Antibiotic stewardship in low - and middle-income countries : the same but different?

Clinical microbiology and infection / European Society of Clinical Microbiology and Infectious Diseases; ESCMID - ISSN 1198-743X - Oxford, Elsevier sci ltd, 23:11(2017), p. 812-818

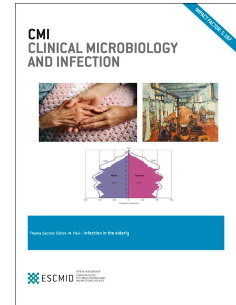
Full text (Publisher's DOI): <https://doi.org/10.1016/J.CMI.2017.07.010>

To cite this reference: <http://hdl.handle.net/10067/1474220151162165141>

# Accepted Manuscript

Antibiotic stewardship in low-and middle-income countries: 'same, but different'?

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PII: S1198-743X(17)30365-8

DOI: [10.1016/j.cmi.2017.07.010](https://doi.org/10.1016/j.cmi.2017.07.010)

Reference: CMI 1007

To appear in: *Clinical Microbiology and Infection*

Received Date: 17 April 2017

Revised Date: 6 July 2017

Accepted Date: 6 July 2017

Please cite this article as: Cox JA, Vlieghe E, Mendelson M, Wertheim H, Ndegwa L, Villegas MV, Gould I, Levy Hara G, Antibiotic stewardship in low-and middle-income countries: 'same, but different'?, *Clinical Microbiology and Infection* (2017), doi: 10.1016/j.cmi.2017.07.010.

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1 **Title page**

2 **Intended category**

3 Narrative review

4

5 **Title**

6 **Antibiotic stewardship in low-and middle-income countries: 'same, but different'?**

7

8 **Running title**

9 Antibiotic stewardship in low-and middle-income countries

10

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**37 Abstract****38 Background**

39 Antibiotic resistance (ABR) is a quickly worsening problem worldwide, also in low-and middle-income  
40 countries (LMICs). Appropriate antibiotic use in humans and animals, *i.e.* antibiotic stewardship (ABS), is  
41 one of the corner stones of the World Health Organization's global action plan for ABR. Many LMICs are  
42 in the process of developing stewardship policies and programs.

**43 Aims**

44 We highlight the challenges for ABS initiatives in LMICs, give an outline of the (inter)national  
45 recommendations and demonstrate examples of effective, contextualised stewardship interventions.

**46 Sources**

47 We searched PubMed for articles on ABS programs and interventions in humans in LMICs. Relevant  
48 websites and experts were consulted for additional sources.

**49 Content**

50 Evidence on effective and feasible stewardship interventions in LMICs is limited and the challenges for  
51 implementation of interventions are numerous. Nevertheless, several initiatives at international and  
52 local level in Latin-America, Africa and Asia have shown that ABS effective interventions are also feasible  
53 in LMICs, although contextualisation is essential and particular challenges should be taken into account.

**54 Implications**

55 Specific guidance for setting up antimicrobial stewardship programs in LMICs should be developed. Many  
56 strategic points might need to be progressively addressed in LMICs, such as (1) ensuring availability of  
57 diagnostic testing (2) dedicated education in ABR both for healthcare workers and the general public, (3)  
58 creating or strengthening (inter)national agencies towards better regulations and audit on production,  
59 distribution and dispensing of drugs, (4) strengthening health care facilities, (5) exploring a broader  
60 synergism between policy makers, academia, professional bodies and the civil society and (6) designing

61 and studying easy and scalable ABS interventions for both the hospital and the community setting.

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## 62 **Background**

63 Antibiotic resistance (ABR) is a quickly worsening problem worldwide. Data suggest very high rates of  
64 ABR in several low-and middle-income countries (LMICs), although representative data remain scarce for  
65 some regions(1). Over- and misuse of antibiotics, poor sanitation, low vaccination rates and poor  
66 infection prevention and control practices all contribute to the high rate of drug-resistant infections in  
67 LMICs(2).

68 In 2015, the World Health Organization (WHO) released a Global Action Plan (GAP) on ABR. Antibiotic  
69 stewardship (ABS), *i.e.* the appropriate use of antibiotics in humans and animals to maximize both their  
70 current effects and their chances of being available for future generations, is one of the corner stones of  
71 the GAP(3). Antibiotic stewardship interventions are aimed at various actors: prescribers, patients, drug  
72 providers, policy makers and general public. Most evidence is available on the effectiveness of ABS  
73 interventions at the hospital level. ABS in hospitals has shown a positive impact, with reduced length of  
74 stay, shorter treatment duration without an increase in mortality and a reduction in colonization and  
75 infection with resistant bacteria(4, 5). In contrast, solid and generalizable data on cost(effectiveness) of  
76 hospital stewardship programs are lacking(4, 6). Fewer studies have been done on interventions  
77 targeting outpatient prescribers, but these have also proven to decrease antibiotic prescriptions and  
78 resistance rates(7-9). The least evidence is available on the effect and cost-effectiveness of public  
79 awareness campaigns, with a limited number of studies showing improved consumer awareness and  
80 reduced prescriptions after their (targeted) implementation(10). However, the large majority of studies  
81 on ABS have been performed in high-income settings in Europe, the United States (U.S.) and Australia. A  
82 systematic review on the effectiveness of ABS in hospitals in LMICs is currently in preparation(11).  
83 Additionally, it is important to realize that delayed or no access to antibiotics still kills more people than  
84 antibiotic resistant bacteria(12). Therefore, ABS at global scale is not only about reducing inappropriate  
85 use, but also about assuring access to effective treatment when necessary.

86 It is acknowledged that global collaborative action is needed across all resource settings to tackle the  
87 problem of ABR. Many LMICs are in the process of developing stewardship policies and programs(13). In  
88 this narrative review, we highlight the challenges that ABS initiatives face in LMICs, give an outline of the  
89 (inter)national recommendations for ABS and demonstrate examples of effective, contextualised  
90 stewardship interventions. This paper focuses on ABS in humans in LMICs. Some of the issues raised are  
91 also applicable to the high-income country setting, but may be more significant in LMICs.

92

### 93 *Search strategy*

94 We searched PubMed for articles on ABS interventions in humans in LMICs. The search terms used were  
95 “antibiotic stewardship”, “antimicrobial stewardship”, “Africa”, “Asia”, “South-America”, “resource-  
96 limited setting”, “low-income country” and “middle-income country” or their pertinent translation in  
97 Spanish (*e.g.* programas de optimización de antimicrobianos, uso racional de antimicrobianos, uso  
98 prudente de antimicrobianos). We limited the search to guidelines and original studies published within  
99 the last five years, written in English or Spanish, and performed in LMICs (according to their annual gross  
100 national income per capita in 2015)(14). Relevant websites (*e.g.* of the WHO, the Pan American Health  
101 Organization (PAHO), ReAct) and experts were consulted for additional sources.

102

### 103 **Stewardship: challenges in LMICs**

104 Antibiotic stewardship is challenging in general and even more so when resources - human, laboratory,  
105 drugs, policies and formal programs - are limited. We will discuss several challenges that are of particular  
106 concern for LMICs. This listing may not be exhaustive, but highlights some of the most prominent  
107 challenges.

108

#### 109 *a. Diagnostic challenges*



110 LMICs face a high burden of infectious diseases(15). High rates of HIV, malnutrition and malaria may  
111 render patients more susceptible to invasive bacterial infections. At the same time, the availability of  
112 clinical microbiology laboratories is limited, even in hospitals(16). Laboratories should meet high  
113 requirements in terms of infrastructure (*e.g.* electricity, water supply, waste management), materials,  
114 human resources (*e.g.* well-trained staff), standard operating procedures (*e.g.* guidelines for specimen  
115 collection) and quality control systems(17, 18). Correct identification of pathogens and susceptibility  
116 testing is complex due to the number of antibiotics that could be potentially tested, the various methods  
117 and media required and the interpretations of results and confirming unlikely resistance profiles. When  
118 laboratories are available, there is often a high threshold for testing because of financial constraints  
119 (both for health system and patients), lack of habit to obtain cultures, lack of experienced  
120 microbiologists and a long turnaround time for results(19-21). Therefore, representative data on the  
121 prevalence of ABR in the case of invasive bacterial diseases and other infections is scarce; in most  
122 settings, samples from only extensively pre-treated patients are submitted for analysis to referral  
123 centres. This paucity of diagnostics and representative surveillance data makes ABS in LMICs particularly  
124 difficult: prescribers frequently lack essential information to guide their clinical decision making; context-  
125 specific treatment guidelines are difficult to write; and policy makers are unable to make well-informed  
126 decisions as the magnitude of the actual problems remains unclear. Robust, point-of-care diagnostic  
127 tests which can guide clinical decision making could solve some of the barriers, as exemplified in Box  
128 2(22). However, their use may be limited when for example costs are high, shelf-life is short or disease  
129 epidemiology changes.

130

131 *b. Knowledge and awareness*

132 Up-to-date knowledge on optimal antibiotic use was found to be low among physicians and final year  
133 medical students in several LMICs(23-25). In addition, ABR was recognized as an important topic by

134 health professionals in general, but not often considered as a problem in their own practice(24, 25). In  
135 many LMICs, antibiotics are prescribed and/or provided by a wide variety of persons: healthcare workers  
136 with different training backgrounds (including nurses, dentists, pharmacists, dispensers and midwives)  
137 but also street vendors(26, 27). To ensure proper understanding and awareness, ABR should be a core  
138 component of undergraduate and in-service education of healthcare workers, and a requirement for  
139 graduation(3, 28). Access to objective information regarding the risks of antibiotic misuse is a challenge  
140 both for prescribers and patients(24). The development of guidelines, usually an important source of  
141 information, is impaired in LMICs because of limited availability of locally applicable high-level evidence  
142 and little experience with evidence-based guideline development(29). Even when available, guideline  
143 use is hampered because they may not be tailored to the target audience, contain conflicting  
144 recommendations or are restrictively disseminated(30).

145

146 *c. Access to quality-assured antibiotics*

147 Many LMICs face the challenge of both limited access to essential antibiotics, and poorly regulated  
148 access to antibiotics. On the one hand, the scarcity of public healthcare facilities in certain rural or  
149 remote areas, the high costs of drugs, the absence of sustainable financing systems (*e.g.* health care  
150 insurance), and the lack of a reliable drug supply system limit the access to a wide variety of much-  
151 needed antibiotics, both older agents with a narrow spectrum (*e.g.* penicillin, cloxacillin) as well as  
152 expensive broad-spectrum antibiotics such as glycopeptides, carbapenems or polymyxins(12, 31, 32). On  
153 the other hand, there is widespread use of non-prescribed antibiotics that can be purchased 'over-the-  
154 counter'(27). Access to antibiotics without prescription through the internet is another potential  
155 threat(33).

156 Perverse financial incentives for prescribers and drug providers, legal concerns and patient demands are  
157 additional drivers of antibiotic overuse(19, 34-36). The large and growing private sector poses a

158 particular problem, as in many LMICs its control by regulatory bodies is even more challenging than for  
159 the public sector.

160 Of additional concern is the regulation of the quality, safety and efficacy of drugs. Therefore, the  
161 confidence in the quality of (generic) medicines is poor - both from the public and health care workers -  
162 and leads to the prescription of more expensive, non-generic products. Deliberately falsified and  
163 substandard drugs appear to be widespread(37, 38). Donations pose a particular problem in spite of the  
164 long-term existence of a WHO guidance in this matter(39). The origin, quality and supply chain of these  
165 products may be difficult to trace, and the influence of pharmaceutical companies is often not  
166 transparent nor regulated(40). Lastly, well-functioning national regulatory agencies for medical products  
167 such as the Food and Drug Administration in the U.S. or European Medicines Agency may be absent or  
168 poorly functioning in some LMICs. Administrative corruption might also be an influencing factor, not  
169 limited to LMICs(41).

170

171 *d. Health care facilities*

172 Healthcare facilities in LMICs face significant challenges concerning lack of basic infrastructure and  
173 equipment, large patient numbers and shortage of healthcare personnel with high turnover and poor job  
174 satisfaction(42, 43). These challenges may be even more extreme in rural and first-line health care  
175 facilities, where antibiotics are frequently prescribed empirically by lower level health care professionals.  
176 In high-income settings, hospital stewardship programs typically contain the following components: an  
177 antibiotic committee, the continuous monitoring of antibiotic resistance and antibiotic use and the  
178 implementation and evaluation of stewardship interventions, with treatment guidelines and the hospital  
179 formulary as essential tools. However, these components may not always be in place in LMICs given the  
180 aforementioned problems with human resources, infrastructure, funding and internal organisation(13).

181 Other models of care and service delivery - including task shifting to non-specialist pharmacists and  
182 nurses have shown good results(44).

183

#### 184 **The road ahead...**

185 The challenges for implementation of ABS interventions are many and the published evidence for the  
186 effectiveness of stewardship interventions in LMICs is limited. Nevertheless, over the last years, a  
187 number of initiatives have arisen, both at the (inter)national and the facility level. We have selected  
188 several examples from different geographical areas, describing a variety of interventions, in different  
189 settings and in different stages of development (Box 1-3).

190

#### 191 *Containment of antibiotic resistance: International guidelines and recommendations*

192 The WHO GAP for antimicrobial resistance sets out a road map of activities necessary to combat ABR(3).  
193 Moreover, recommendations and roadmaps for the containment of ABR have been drawn by policy  
194 makers (*e.g.* Public Health England), the scientific community and other international initiatives (*e.g.*  
195 Global Antimicrobial Resistance Partnership (GARP), ReAct)(12, 45-50). They have all indicated the  
196 importance of a comprehensive approach which includes better knowledge and awareness of ABR  
197 among healthcare workers and the general public, the need of surveillance and research, infection  
198 prevention and control measures including vaccination, antibiotic stewardship and the development of  
199 an economic case for sustainable investment in (new) antibiotics. This should be done within a global  
200 collaborative, One Health framework. The core ABS components that have been identified include local  
201 leadership, the continuous surveillance and analysis of ABR and consumption data, the global and  
202 national regulation of antibiotic distribution, quality and use, the development of affordable and scalable  
203 point-of-care diagnostic tools, improvement of human resources and the urgent need for education(3).

204

205 *International and National approaches*

206 To stimulate further implementation of the GAP at national level, WHO offers a framework for  
207 developing National Action Plans (NAP), and monitoring tools for the self-assessment of a country's  
208 progress(51). As illustrated with examples in Box 1, an increasing number of countries have set up NAPs  
209 and carried out initiatives at national scale. In addition, over the last years many Latin American  
210 countries have started to design their own NAP, tailored to their own reality, under guidance of the  
211 PAHO(52). As a non-governmental example, GARP is a project of the Center for Disease Dynamics,  
212 Economics & Policy (CDDEP, U.S.) which supports the creation of multi-sectoral national-level working  
213 groups in LMICs, with the mandate to understand and document antibiotic use and ABR in the human  
214 and animal population in the national context, and to then develop evidence-based interventions.  
215 Partner countries include Vietnam, India, Nepal, Kenya, Tanzania, Uganda, Mozambique. Pakistan and  
216 Bangladesh. More experienced partner countries act as mentors for newer members. A high level of  
217 contextualizing to the local setting and a close relationship between researchers and policy makers are  
218 key building blocks of the project(53). In addition, specific toolboxes and interactive websites have been  
219 developed by non-governmental and professional organisations such as ReAct, which offer open access  
220 to a broad range of information for containment of ABR(54).

221

222 **Box 1 NATIONAL INITIATIVES**

The Ministry of Health & Family Welfare of India appointed a Core Working Group in September 2016 to draft the National Action Plan (NAP) and the government of India released the NAP on Antimicrobial Resistance (AMR) 2017-2021 in April 2017. Six key areas have been identified as being strategic priorities: 1. improved awareness through effective communication, 2. strengthening knowledge and evidence through surveillance, 3. effective infection prevention and control, 4. optimizing the use of antimicrobial agents in health, animals and food, 5. investments in research

and innovations and 6. strengthening collaborations on antimicrobial resistance at international, national and subnational levels. The development and dissemination of the NAP involved policymakers from different sectors including animal husbandry, dairying and fisheries, biotechnology, food processing industries, pharmaceuticals, information and broadcasting and finance(55).

In August 2016 the Chinese National Health and Family Planning commission released the NAP to contain AMR 2016-2020. They defined the following 6 goals for 2020: 1. launch 1-2 new initiative antibacterial agents and 5-10 new diagnostic instruments and reagents, 2. ensure sales of antibiotics are only upon prescription in both human and animal sector, 3. optimize surveillance networks of antibacterial agent consumption and AMR in both healthcare and food-and animal sectors, 4. establish stewardship programs in secondary- and tertiary-level hospitals and control the increasing trend of the main AMR bacteria, 5. regulate the market of animal growth promoters and 6. develop and implement education for medical staff, veterinarians and animal producers, for primary and secondary schools and for the general public (56).

Following a situational analysis of antibiotic resistance (ABR) in humans and animals in collaboration with the Global Antimicrobial Resistance Partnership in 2011, the South African Antibiotic Stewardship Programme formed as the implementation and advocacy body for South Africa, combining in partnership with the Department of Health, which culminated in the signing of a commitment document by government, societies, regulatory bodies and councils to combat ABR with defined goals and timelines. The South African Antimicrobial Resistance National Strategy Framework 2014-2024 was published in October 2014, and followed by the Implementation plan 2014-2019. Two national stewardship training centres have been funded to upskill under-resourced provinces. The national strategic framework is being updated in 2017 to strengthen the animal and environmental health aspects of the strategy(57).

The Infection Prevention Network Kenya, the Infection Control African Network, the International Society of Chemotherapy and GARP-Kenya organised a 2-day workshop in 2013. Many National Health authorities were present, and in 2015 a national ABR focal point was appointed, followed by a multi-sectoral National Antimicrobial Stewardship Advisory Committee. Under this leadership and leveraging the Global Action Plan for AMR, the International Health Regulations and the action package for AMR in the Global Health Security Agenda, a National Policy on Prevention and Containment of AMR was released in May 2017(58).

The Colombian Nosocomial Resistance Study Group is a network of 32 public and private hospitals in 11 cities. Network activities include 6-monthly surveillance reports on resistance patterns to each hospital, antibiotic treatment suggestions, and the analysis of outbreaks. These customized recommendations allow for regular updates of the antibiotic guidelines and for over-time comparison. In addition, education and training is provided locally by the International Centre for Medical Research and Training(48).

223  
224  
225 *International antibiotic market and policy*  
226 Regarding the regulation of availability, quality and use of antibiotics at the national level, the GAP builds  
227 on existing initiatives concerning rational drug use and national medicines policy, including the use of  
228 essential medicine lists (EML)(59). However, dedicated interventions focusing on the positioning and  
229 availability of antibiotics have been limited so far. For instance, national EMLs in many LMICs have not  
230 yet included certain antibiotics such as carbapenems, glycopeptides, polymyxins, which is at odds with  
231 increasing ABR in many countries. On an international scale, pre-qualification to produce antibiotics  
232 remains largely lacking in contrast with the production of antimalarial and antiviral drugs. These  
233 discrepancies may be partially explained by the absence of national programs dedicated to bacterial

234 infections, in contrast to *e.g.* malaria or tuberculosis, and subsequent limited ‘visibility’ of bacterial  
235 diseases for lobbying and advocacy groups. It is hoped that the recently issued WHO-based ‘*Global*  
236 *priority pathogens list of antibiotic-resistant bacteria to guide research, discovery, and development of*  
237 *new antibiotics*’ may help to drive antibiotic development for bacteria with limited or no options for  
238 treatment(60). Moreover, initiatives like the Global Antibiotic Research and Development Partnership  
239 (GARDP) that intend to use partnership models instead of a market-driven pharmaceutical approach to  
240 develop new antibiotic treatments may be able to ensure responsible use and equitable access to  
241 antibiotics, also in LMICs(61)

242

243 *Stewardship interventions at the facility level*

244 Also at the individual facility level, an increasing number of ABS initiatives in LMICs have brought theory  
245 into practice. Box 2 displays a selection of exemplary and inspirational ABS interventions from different  
246 continents and facility types. When deciding on ABS interventions, certain activities could be identified  
247 as ‘low-hanging fruit’. The concept refers to the selection of the most obtainable targets with limited  
248 resources based on the impact and severity of the problem, the availability of (evidence-based)  
249 interventions and their possible impact (62). From this perspective, targeted interventions such as  
250 intravenous to oral conversion, optimization of surgical antibiotic prophylaxis and the introduction of  
251 dedicated antibiotic forms could be considered (Box 2). Improving antibiotic hang time –*i.e.* the time  
252 between the antibiotic prescription and its administration- is another relatively easy intervention which  
253 may improve individual patient outcomes(63). However, what are obtainable targets remains context-  
254 specific. In hospitals, emphasis has been traditionally placed on guideline development and education of  
255 staff. A recent survey among 340 doctors, microbiologists, pharmacists and nurses working in hospitals in  
256 58 different LMICs found that the issuing of guidelines and education were perceived as the two most  
257 effective ABS intervention (unpublished data, J. Cox). However, to actually change and improve



258 prescription behaviour, education should be sustained in time, which is a challenge in many LMICs.  
259 Online free-of-charge training modules have increasingly being developed e.g. in Latin America and  
260 South-Africa(64, 65). In addition, specific massive open online courses on ABS are globally available now.  
261 Although accessibility (internet, non-English speakers) may be an issue in some LMICs and their  
262 effectiveness and sustainability still needs to be established, this kind of learning offers great  
263 opportunities(66).

264

265 **Box 2 HOSPITAL-BASED INTERVENTIONS**

In 5 tertiary, emergency surgical hospitals in Egypt, a 2-day training curriculum for surgeons and anaesthesiologists was developed on surgical prophylaxis, in addition to on-the-job training for junior surgeons and residents during morning rounds, installation of posters with reminders and the nomination of a senior surgeon in 3 of 5 hospitals as a champion to audit prescriptions and provide personal feedback to the prescribers. This led to an improved optimal timing of prophylaxis in all and a shorter duration of prophylaxis in some hospitals(67).

In a public tertiary university hospital in South-Africa, an antibiotic prescription chart, antibiotic stewardship ward rounds with antibiotic stewardship (ABS) and infection-prevention and control specialists giving audit and feedback for individual (complex) patients and restricted use of certain antibiotics were introduced. This led to a sustainable drop in total antibiotic consumption, significant cost savings (215000 U.S. dollars over 4 years) and no significant changes in mortality or 30-day readmission rates(68).

In 47 private rural and urban hospitals in South Africa an audit-and feedback program was implemented in which pharmacists provided feedback to doctors on individual prescription of systemic antibiotics and to doctors, hospital management and the ABS committees on overall performance on 5 predefined outcomes. This lead to a 18% reduction in defined daily dosages per

100 patient days(69).
In an urban tertiary pediatric hospital in China, the issuing of the National Action Plan led to the development of antibiotic treatment guidelines by a newly established antibiotic committee, availability of the guidelines in pocket-sized formats and through the hospital intranet and restriction of certain antibiotics. In second instance, pharmacist-led audit and feedback to individual prescribers and the administration and punishment in case of non-compliance (financial penalties, revocation of the prescribing privilege and mandatory training) were installed. The proportion of antibiotic prescriptions and the expenditure on antibiotics declined significantly in both ambulatory and inpatient settings immediately after the second phase(70).
In a rural governmental hospital in Kenya a program for intravenous to oral switch of metronidazole was introduced in the medicine and surgical wards. A checklist was developed which was placed in the patients' treatment sheet, along with weekly education for clinicians on the importance of documentation, good antibiotic prescribing practice, IV to oral switch, timely procurement of pharmaceutical supplies and proper drug supply management and twice-weekly ward rounds with a pharmacist. This led to an improvement of documentation and an increase in oral metronidazole use(71).
In Caribbean Barbados, a formal ABS program started in September 2015 at the main referral hospital after a workshop held by the Pan American Health Organization, focusing on intensive care units. The program included restricted use of carbapenems, vancomycin and piperacillin/tazobactam, which together accounted for 60% of antibiotic cost. Training included the optimization for sampling and interpreting culture results. Preliminary data suggest a decrease in use and cost across the institution following the extensive education programs(72).

266

267 *Primary health care and community initiatives*

268 Although most antibiotic use occurs in the community, a limited number of studies on interventions in  
269 the primary health care setting (*i.e.* first line public health facilities including outpatients' clinics) have  
270 been published so far (Box 3).

271 Currently, a multi-country project comparing community-based antibiotic access and consumption  
272 practices across a range of LMICs in Asia and Africa is being carried out in order to inform and design  
273 community-based ABS intervention strategies (ABACUS, InDepth Network). This project will provide a  
274 standardized framework for appraising current antibiotic use patterns, demand and access, which may  
275 subsequently be used in other LMICs.

276

277 **Box 3 COMMUNITY INTERVENTIONS**

Antibiotics Smart Use was introduced in 2007 in 10 district hospitals and 87 primary health centres in rural Thailand. It involved local health care workers as well as policy-makers and researchers from provincial and national health agencies. A broad package of interventions was introduced, including education of prescribers and patients, managerial interventions *e.g.* the prescription of herbal medicine for non-bacterial infections, incentives *e.g.* the attendance of (inter)national study visits and policy *e.g.* changing the national policy of payment of health care providers. After the study, the program was scaled up within Thailand(73).

In 10 urban and rural primary health care centres in Vietnam patients with acute respiratory tract symptoms were randomly assigned to the intervention arm, consisting of the use of point-of-care (POC) C-reactive protein testing to guide treatment decisions versus standard care. The use of the POC led to less antibiotic use within 14 days after presentation: 64% versus 78% in the routine care group(22).

A non-inferiority trial was conducted, comparing 2 urban and 2 rural primary health care centres in Tanzania. In the intervention centres, a new algorithm for the treatment of childhood illnesses was introduced. The algorithm was first available on paper and afterwards through a smartphone

application. Face-to-face supervision was given at the introduction of the algorithm. The algorithm improved clinical outcome and reduced antibiotic prescription by 80%(74).

In 2010, both Mexico and Brazil implemented policies to enforce existing laws of restricting consumption of antibiotics only to patients presenting a prescription. Between 2007 and 2012, in Brazil the total antibiotic use increased by 49.3% and decreased in Mexico by 29%. In Brazil, the consumption of penicillins, sulfonamides and macrolides decreased after the intervention while in Mexico only for penicillins and sulfonamides significant changes were noted. High seasonal fluctuations in antibiotics consumption suggested inadequate use for viral acute respiratory tract infections. The authors concluded that the reinforcement of regulations should be monitored together with the development of more comprehensive measures to promote adequate use of antibiotics in both countries(75).

278

## 279 **Conclusion**

280 Evidence for the effectiveness of stewardship interventions in LMICs is limited and the challenges for  
281 implementation of interventions are numerous. However, several initiatives at international and local  
282 level have shown that ABS interventions are also feasible in LMICs, although contextualisation is much  
283 needed and the challenges should be considered. For this reason, specific guidance for setting up  
284 antimicrobial stewardship programs in LMICs should be developed. There are many strategic points  
285 which might be progressively addressed, such as (1) ensuring availability of diagnostic testing, (2)  
286 dedicated education in ABR both for healthcare workers (undergraduate and in-service) and the public,  
287 (3) creating or strengthening (inter)national agencies towards better regulations and audit on  
288 production, distribution and dispensing of drugs, (4) strengthening health care facilities (5) exploring a  
289 broader synergism between policy makers, academia, professional bodies and the civil society and (6)  
290 designing and studying easy and scalable ABS interventions for both the hospital and the community

291 setting. Some of the recent experiences described in this article suggest that this road is possible.

292

293 **Transparency declaration**

294 We state that none of the authors has a conflict of interest. No external funding was received for this

295 study.

ACCEPTED MANUSCRIPT

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