



Review

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

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ARTICLE INFO

Article history:

Received 17 April 2017

Received in revised form

6 July 2017

Accepted 6 July 2017

Available online 14 July 2017

Editor: Dr C. Pulcini

Keywords:

Antibiotic resistance

Antibiotic stewardship

Guidelines

Intervention

Low- and middle-income countries

Surveillance

ABSTRACT

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

Aims: We highlight challenges for ABS initiatives in LMICs, give an outline of (inter)national recommendations and demonstrate examples of effective, contextualized stewardship interventions.

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

Content: Evidence on effective and feasible stewardship interventions in LMICs is limited, and challenges for implementation of interventions are numerous. Nevertheless, several initiatives at the international and local levels in Latin America, Africa and Asia have shown that ABS effective interventions are feasible in LMICs, although contextualization is essential.

Implications: Specific guidance for setting up antimicrobial stewardship programs in LMICs should be developed. Strategic points might need to be progressively addressed in LMICs, such as (a) ensuring availability of diagnostic testing, (b) providing dedicated education in ABR both for healthcare workers and the general public, (c) creating or strengthening (inter)national agencies towards better regulations and audit on production, distribution and dispensing of drugs, (d) strengthening healthcare facilities, (e) exploring a broader synergism between policy makers, academia, professional bodies and civil society and (f) designing and studying easy and scalable ABS interventions for both hospital and community settings. **J.A. Cox, Clin Microbiol Infect 2017;23:812**

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Background

Antibiotic resistance (ABR) is a quickly worsening problem worldwide. Data suggest very high rates of ABR in several low- and

middle-income countries (LMICs), although representative data remain scarce for some regions [1]. Overuse and misuse of antibiotics, poor sanitation, low vaccination rates and poor infection prevention and control practices all contribute to the high rate of drug-resistant infections in LMICs [2].

In 2015, the World Health Organization (WHO) released a global action plan (GAP) on ABR. Antibiotic stewardship (ABS), i.e. the appropriate use of antibiotics in humans and animals to maximize

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both their current effects and their chances of being available for future generations, is one of the cornerstones of the GAP [3]. ABS interventions are aimed at various actors: prescribers, patients, drug providers, policy makers and the general public. Most evidence is available on the effectiveness of ABS interventions at the hospital level. ABS in hospitals has shown a positive impact, with reduced length of stay, shorter treatment duration without an increase in mortality and a reduction in colonization and infection with resistant bacteria [4,5]. In contrast, solid and generalizable data on cost and cost-effectiveness of hospital stewardship programs are lacking [4,6]. Fewer studies have been done on interventions targeting outpatient prescribers, but these have also proven to decrease antibiotic prescriptions and resistance rates [7–9]. The least evidence is available on the effect and cost-effectiveness of public awareness campaigns, with a limited number of studies showing improved consumer awareness and reduced prescriptions after their (targeted) implementation [10]. However, most studies on ABS have been performed in high-income settings in Europe, the United States and Australia. A systematic review on the effectiveness of ABS in hospitals in LMICs is in preparation [11].

Additionally, it is important to realize that delayed or no access to antibiotics still kills more people than antibiotic-resistant bacteria [12]. Therefore, ABS at a global scale is not only about reducing inappropriate use but also about assuring access to effective treatment when necessary.

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

We searched PubMed for articles on ABS interventions in humans in LMICs. The search terms used were ‘antibiotic stewardship,’ ‘antimicrobial stewardship,’ ‘Africa,’ ‘Asia,’ ‘South America,’ ‘resource-limited setting,’ ‘low-income country’ and ‘middle-income country,’ or their pertinent translation in Spanish. We limited the search to guidelines and original studies published within the last 5 years, written in English or Spanish, and performed in LMICs (according to their annual gross national income per capita in 2015) (<https://datahelpdesk.worldbank.org/knowledgebase/articles/906519>). Relevant websites (e.g. of the WHO, the Pan American Health Organization (PAHO), ReAct) and experts were consulted for additional sources.

Stewardship: challenges in LMICs

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

Diagnostic challenges

LMICs face a high burden of infectious diseases [14]. High rates of HIV, malnutrition and malaria may render patients more susceptible to invasive bacterial infections. At the same time, the availability of clinical microbiology laboratories is limited, even in hospitals [15]. Laboratories should meet high requirements in terms of infrastructure (e.g. electricity, water supply, waste management), materials, human resources (e.g. well-trained staff), standard operating

procedures (e.g. guidelines for specimen collection) and quality control systems [16,17]. Correct identification of pathogens and susceptibility testing is complex as a result of the number of antibiotics that could be potentially tested, the various methods and media required, and the interpretations of results and confirming unlikely resistance profiles. When laboratories are available, there is often a high threshold for testing because of financial constraints (both for health system and patients), lack of habit to obtain cultures, lack of experienced microbiologists and a long turnaround time for results [18–20]. Therefore, representative data on the prevalence of ABR in the case of invasive bacterial diseases and other infections are scarce; in most settings, samples from only extensively pretreated patients are submitted for analysis to referral centres. This paucity of diagnostics and representative surveillance data makes ABS in LMICs particularly difficult: prescribers frequently lack essential information to guide their clinical decision making; context-specific treatment guidelines are difficult to write; and policy makers are unable to make well-informed decisions because the magnitude of the actual problems remains unclear. Robust, point-of-care diagnostic tests which can guide clinical decision making could solve some of the barriers [21]. However, their use may be limited when, for example, costs are high, shelf life is short or disease epidemiology changes.

Knowledge and awareness

Up-to-date knowledge on optimal antibiotic use was found to be low among physicians and final year medical students in several LMICs [22–24]. In addition, ABR was recognized as an important topic by health professionals in general but was not often considered as a problem in their own practice [23,24]. In many LMICs, antibiotics are prescribed and/or provided by a wide variety of persons: healthcare workers with different training backgrounds (including nurses, dentists, pharmacists, dispensers and midwives) but also street vendors [25,26]. To ensure proper understanding and awareness, ABR should be a core component of undergraduate and in-service education of healthcare workers, and a requirement for graduation [3,27]. Access to objective information regarding the risks of antibiotic misuse is a challenge for both prescribers and patients [23]. The development of guidelines, usually an important source of information, is impaired in LMICs because of limited availability of locally applicable high-level evidence and little experience with evidence-based guideline development [28]. Even when available, guideline use is hampered because they may not be tailored to the target audience, contain conflicting recommendations or be restrictively disseminated [29].

Access to quality-assured antibiotics

Many LMICs face the challenge of both limited access to essential antibiotics and poorly regulated (over)access to antibiotics. On the one hand, the scarcity of public healthcare facilities in certain rural or remote areas, the high costs of drugs, the absence of sustainable financing systems (e.g. healthcare insurance) and the lack of a reliable drug supply system limit the access to a wide variety of much-needed antibiotics, both older agents with a narrow spectrum (e.g. penicillin, cloxacillin) and expensive broad-spectrum antibiotics such as glycopeptides, carbapenems or polymyxins [12,30,31]. On the other hand, there is widespread use of nonprescribed antibiotics that can be purchased over the counter [26]. Access to antibiotics without prescription through the internet is another potential threat (<http://boliviapills.info/page/60/>).

Perverse financial incentives for prescribers and drug providers, legal concerns and patient demands are additional drivers of antibiotic overuse [18,32–34]. The large and growing private sector

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