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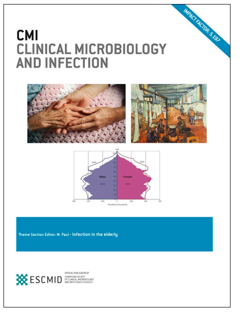

Antibiotic stewardship in low-and middle-income countries: '*same, but different'*?

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Running title

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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 corner stones of the World Health Organization's global action plan for ABR. Many LMICs are in the process of developing stewardship policies and programs.

Aims

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

Sources

We searched PubMed for articles on ABS programs and 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 the challenges for implementation of interventions are numerous. Nevertheless, several initiatives at international and local level in Latin-America, Africa and Asia have shown that ABS effective interventions are also feasible in LMICs, although contextualisation is essential and particular challenges should be taken into account.

Implications

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

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

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). Over- 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 both their current effects and their chances of being available for future generations, is one of the corner stones of the GAP(3). Antibiotic stewardship interventions are aimed at various actors: prescribers, patients, drug providers, policy makers and 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(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, the large majority of studies on ABS have been performed in high-income settings in Europe, the United States (U.S.) and Australia. A systematic review on the effectiveness of ABS in hospitals in LMICs is currently 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 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, contextualised stewardship interventions. This paper focuses on ABS in humans in LMICs. Some of the issues raised are also applicable to the high-income country setting, but may be more significant in LMICs.

Search strategy

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 (*e.g*. programas de optimización de antimicrobianos, uso racional de antimicrobianos, uso prudente de antimicrobianos). We limited the search to guidelines and original studies published within the last five years, written in English or Spanish, and performed in LMICs (according to their annual gross national income per capita in 2015)(14). 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

Antibiotic stewardship is challenging in general and 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 highlights some of the most prominent challenges.

a. Diagnostic challenges

LMICs face a high burden of infectious diseases(15). 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(16). 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(17, 18). Correct identification of pathogens and susceptibility testing is complex due to 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(19-21). Therefore, representative data on the prevalence of ABR in the case of invasive bacterial diseases and other infections is scarce; in most settings, samples from only extensively pre-treated 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 as 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, as exemplified in Box 2(22). However, their use may be limited when for example costs are high, shelve-life is short or disease epidemiology changes.

b. 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(23-25). In addition, ABR was recognized as an important topic by health professionals in general, but not often considered as a problem in their own practice(24, 25). 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(26, 27). 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, 28). Access to objective information regarding the risks of antibiotic misuse is a challenge both for prescribers and patients(24). The development of guidelines, usually an important source of information, is impaired in LIMCs because of limited availability of locally applicable high-level evidence and little experience with evidence-based guideline development(29). Even when available, guideline use is hampered because they may not be tailored to the target audience, contain conflicting recommendations or are restrictively disseminated(30).

c. Access to quality-assured antibiotics

Many LMICs face the challenge of both limited access to essential antibiotics, and poorly regulated 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.* health care 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) as well as expensive broad-spectrum antibiotics such as glycopeptides, carbapenems or polymyxins(12, 31, 32). On the other hand, there is widespread use of non-prescribed antibiotics that can be purchased 'over-the-counter'(27). Access to antibiotics without prescription through the internet is another potential threat(33).

Perverse financial incentives for prescribers and drug providers, legal concerns and patient demands are additional drivers of antibiotic overuse(19, 34-36). The large and growing private sector poses a particular problem, as in many LMICs its control by regulatory bodies is even more challenging than for the public sector.

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

d. Health care facilities

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

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

The road ahead...

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

Containment of antibiotic resistance: International guidelines and recommendations

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

International and National approaches

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

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).

International antibiotic market and policy

Regarding the regulation of availability, quality and use of antibiotics at the national level, the GAP builds on existing initiatives concerning rational drug use and national medicines policy, including the use of essential medicine lists (EML)(59). However, dedicated interventions focusing on the positioning and availability of antibiotics have been limited so far. For instance, national EMLs in many LMICs have not yet included certain antibiotics such as carbapenems, glycopeptides, polymyxins, which is at odds with increasing ABR in many countries. On an international scale, pre-qualification to produce antibiotics remains largely lacking in contrast with the production of antimalarial and antiviral drugs. These discrepancies may be partially explained by the absence of national programs dedicated to bacterial infections, in contrast to *e.g.* malaria or tuberculosis, and subsequent limited ‘visibility’ of bacterial diseases for lobbying and advocacy groups. It is hoped that the recently issued WHO-based ‘*Global priority pathogens list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics’* may help to drive antibiotic development for bacteria with limited or no options for treatment(60). Moreover, initiatives like the Global Antibiotic Research and Development Partnership (GARDP) that intend to use partnership models instead of a market-driven pharmaceutical approach to develop new antibiotic treatments may be able to ensure responsible use and equitable access to antibiotics, also in LMICs(61)

Stewardship interventions at the facility level

Also at the individual facility level, an increasing number of ABS initiatives in LMICs have brought theory into practice. Box 2 displays a selection of exemplary and inspirational ABS interventions from different continents and facility types. When deciding on ABS interventions, certain activities could be identified as ‘low-hanging fruit’. The concept refers to the selection of the most obtainable targets with limited resources based on the impact and severity of the problem, the availability of (evidence-based) interventions and their possible impact (62). From this perspective, targeted interventions such as intravenous to oral conversion, optimization of surgical antibiotic prophylaxis and the introduction of dedicated antibiotic forms could be considered (Box 2). Improving antibiotic hang time –*i.e.* the time between the antibiotic prescription and its administration- is another relatively easy intervention which may improve individual patient outcomes(63). However, what are obtainable targets remains context-specific. In hospitals, emphasis has been traditionally placed on guideline development and education of staff. A recent survey among 340 doctors, microbiologists, pharmacists and nurses working in hospitals in 58 different LMICs found that the issuing of guidelines and education were perceived as the two most effective ABS intervention (unpublished data, J. Cox). However, to actually change and improve prescription behaviour, education should be sustained in time, which is a challenge in many LMICs. Online free-of-charge training modules have increasingly being developed *e.g.* in Latin America and South-Africa(64, 65). In addition, specific massive open online courses on ABS are globally available now. Although accessibility (internet, non-English speakers) may be an issue in some LMICs and their effectiveness and sustainability still needs to be established, this kind of learning offers great opportunities(66).

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 pipercillin/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).

Primary health care and community initiatives

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

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

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 trough 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).

Conclusion

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

Transparency declaration

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