



# Global Antimicrobial Stewardship with a Focus on Low- and Middle-Income Countries: A position statement for the international society for infectious diseases

Jacob Pierce<sup>a,\*</sup>, Anucha Apisarntharak<sup>b</sup>, Natalie Schellack<sup>c</sup>, Wanda Cornistein<sup>d</sup>, Amal Al Maani<sup>e</sup>, Syamhanin Adnan<sup>f</sup>, Michael P. Stevens<sup>a</sup>

<sup>a</sup> Virginia Commonwealth University School of Medicine, Department of Internal Medicine, Division of Infectious Diseases, 1000 E Marshall St. Richmond, VA, USA, 23298

<sup>b</sup> Thammasart University Hospital, 8 95 Phahonyothin Rd, Khlong Nueng, Khlong Luang District, Pathum Thani 12120

<sup>c</sup> Sefako-Makgatho Health Sciences University, School of Pharmacy, Pretoria. Motlegi St, Ga-Rankuwa Zone 1, Ga-Rankuwa, 0208, South Africa

<sup>d</sup> Hospital Universitario Austral Av. Juan Domingo Perón 1500, Pilar Centro, Buenos Aires, Argentina

<sup>e</sup> Directorate General for Disease Surveillance & Control, MOH. P.O Box: 393, PC 100 Muscat, Oman

<sup>f</sup> Hospital Sungai Buloh (Infectious Disease center) Jalan Hospital, 47000 Sungai Buloh, Selangor, Malaysia

## ARTICLE INFO

### Article history:

Received 27 May 2020

Accepted 28 May 2020

### Keywords:

Antimicrobial stewardship  
low- and middle-income countries  
antimicrobial resistance

## ABSTRACT

Antimicrobial resistance is a global public health crisis. Antimicrobial Stewardship involves adopting systematic measures to optimize antimicrobial use, decrease unnecessary antimicrobial exposure and to decrease the emergence and spread of resistance. Low- and middle-income countries (LMICs) face a disproportionate burden of antimicrobial resistance and also face challenges related to resource availability. Although challenges exist, the World Health Organization has created a practical toolkit for developing Antimicrobial Stewardship Programs (ASPs) that will be summarized in this article.

© 2020 The Authors. Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

### A key message of the 2019 toolkit:

“[Antimicrobial Stewardship] interventions should be implemented in a stepwise approach, build on existing structures and reporting, maximize teamwork, and encourage champions and clinical staff—including prescribers—to participate. Start small and keep it simple and doable.” (*Geneva: World Health Organization, 2019*).

The World Bank defines low- to middle-income countries (LMICs) based on gross national income per capita. Exact details on calculations and a list of LMICs can be seen on their website (<https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups>)

Per the World Bank in 2016 an aggregate of LMICs spent 5.42% of GDP (\$234 per person) on healthcare compared to 12.59% (\$5,179 per person) for high-income countries. This review will provide an overview of establishing an Antimicrobial Stewardship Program while acknowledging the unique challenges facing LMICs.

### Key Issues:

- Antimicrobial resistance is higher in low- and middle-income countries (LMICs)
- Antimicrobial stewardship programs (ASPs) can help decrease the emergence of antimicrobial resistance and improve the safe use of antimicrobials
- Addressing over the counter antimicrobial prescribing and water sanitation are integral to limiting antimicrobial resistance
- LMICs will have unique pathways for implementing ASPs
- ASPs must overcome communication issues (especially in countries with multiple languages)
- The World Health Organization's 'Antimicrobial Stewardship Programmes in Health-Care Facilities in Low- and Middle-Income Countries: A WHO Practical Toolkit' (*World Health Organization, 2019*) is a valuable resource for providers in LMICs.

## 1. Known Facts:

### 1.1. Introduction The Scope of the Problem

In 2016 the United Kingdom commissioned a report to define the problem of antimicrobial resistance (AMR). According to the

\* Corresponding author at: PO BOX 980509 Richmond, VA 23298 United States. Tel.: +804-828-2121.

E-mail address: [Jacob.Pierce@vcuhealth.org](mailto:Jacob.Pierce@vcuhealth.org) (J. Pierce).

report coordinated by economist Jim O'Neill, AMR is projected to cause 10 million deaths per year by 2050. Additionally, governments of all countries are projected to have escalating healthcare costs attributed to AMR. There is a projected 100 trillion USD global economic impact. The report stresses that resources dedicated to preventing AMR now will prevent far larger costs in the future (O'Neill, 2016). According to the Centers for Disease Control and Prevention (CDC) 2019 threat report, in the United States alone there are over 2.8 million AMR infections and 35,900 deaths from AMR per year (CDC, 2019). ASPs have been shown to decrease rates of AMR (Rahal et al., 1998; Raymond et al., 2001; Bantar et al., 2003; Cook et al., 2006; Busing et al., 2008). Additionally, there are numerous examples of ASP implementation providing cost savings, primarily by decreasing intravenous antimicrobial consumption (Amdany and Mcmillan, 2014; Boyles et al., 2017). Data in LMICs are limited. However, reviewing data from the early implementation of the global AMR surveillance system (GLASS) from 2017–2018 there is significant AMR in LMICs. In Malawi, among 401 *Klebsiella pneumoniae* isolates and 964 *Escherichia coli* isolates from blood cultures over 75% were resistant to ceftriaxone. In India, among 933 *Klebsiella pneumoniae* isolates over 75% were resistant to cefepime with nearly 50% resistant to carbapenems. Similarly concerning findings can be seen in Egypt, Nepal, Nigeria, Pakistan, Northern Macedonia, Tunisia, Uganda, and Zambia among others. For comparison, the United Kingdom reported less than 25% resistance to third generation cephalosporins for 5,303 isolates of *Klebsiella pneumoniae* and 30,218 *Escherichia coli* (World Health Organization, 2018). A review of data in South and Southeast Asia published in 2016 reported on the significant local burden of AMR. Most South (India and neighboring countries) and Southeast Asian countries estimated greater than 40% of *Acinetobacter baumannii* isolates were resistant to carbapenems (Hsu et al., 2017). Carbapenem-Resistant Enterobacteriaceae rates exceeding 10% in South Asia and lower but increasing rates in Southeast Asia were also reported (Hsu et al., 2017).

### 1.2. Water Sanitation

An especially important consideration in LMICs is water sanitation. According to the O'Neill report, universal access to sanitized water could decrease antimicrobial prescribing for diarrheal illness by 60%. In India, Indonesia, Nigeria and Brazil nearly 500 million courses of antimicrobials are prescribed for diarrheal illness per year. Diarrheal illness caused an estimated 1.2–1.3 million deaths per year in 2015 per the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD Diarrhoeal Diseases Collaborators 2015). Increased access to clean water can reduce morbidity and mortality from diarrheal illness. It has been estimated that improving sanitation by 50% could lead to 9.5 additional years of life expectancy (O'Neill, 2016). Initiatives such as the Clean India Mission provide examples of government sponsored efforts to improve water sanitation (O'Neill, 2016). Improved sanitation including hand hygiene have demonstrated benefit in decreasing transmission of hospital acquired infections in LMICs (Watson et al., 2019). A review from the International Society of Infectious Diseases is available that discusses hand hygiene in LMICs (Loftus et al., 2019).

### 1.3. Antimicrobial Use in Agriculture

Agriculture provides an additional target for ASP activities at the national level. In the United States up to 70% of antimicrobials are utilized in agriculture (O'Neill, 2016). There is some evidence correlating antimicrobial resistant infections in humans to use in agriculture (Chang et al., 2015). There are limited data on agricultural antimicrobial use in LMICs. The European Union has

banned use of antimicrobials for growth promotion in animals and studies from Denmark demonstrate no adverse effects on livestock (Aarestrup et al., 2010). By extension, the utilization of antimicrobials in aquaculture may put humans at risk for antimicrobial resistant pathogens. A study published in *EcoHealth* examined 94 aquaculture farms in Vietnam and reported an average of 3.3 kg of antibiotics for every ton of aquatic product, most of which were on the World Health Organizations (WHO) highly or critically important antimicrobials list. 26.9% of fish bought from local markets tested positive for antimicrobial residues (Pham et al., 2015). Additional data are needed to contextualize agricultural use of antimicrobials in LMICs and their role in AMR.

Consumption data for animals are scarce, come from variable sources, and are often measured in per kilogram consumption due to the high proportion of in-feed utilization. National programs to monitor antimicrobial distribution in animals should be essential, but such programs have not universally been adopted (Schellack, 2017). Some LMIC are already acting, however. China banned colistin for growth promotion in animal use in 2016, Malaysia followed in January 2019 and also plan to ban additional antibiotics as growth promoters in animal food. In South America, Argentina, Chile, and Columbia have banned various antimicrobials for growth promotion. Thailand and Vietnam have bans on antimicrobials for growth promotion although exceptions exist for disease prevention. Many other countries have proposed legislation or have developed national action plans to address this growing threat (FAIRR Initiative, 2019).

### 1.4. Antimicrobial Stewardship Programs are Safe and Effective

Part of the role of ASPs is to ensure guideline-directed empiric therapy (Geneva: World Health Organization, 2019). A 2016 meta-analysis in *Lancet Infectious Disease* examined 145 studies and demonstrated a 35% relative risk reduction in mortality when guideline-directed empiric antimicrobials were prescribed (Schuts et al., 2016). The same study demonstrated no statistically significant increase in mortality from intravenous to oral recommendation, narrowing of antimicrobial therapy, or restricting antimicrobials. Several studies have directly examined the role of ASP in LMICs. A 2019 scoping review of interventions to reduce antimicrobial prescribing in LMICs examined 102 studies across primary care, hospital, and pharmacy settings. The data were skewed towards urban hospital settings, and the quality of data were noted to be limited. Among a subset of 41 studies with the most complete study designs, 21 demonstrated a positive effect (decreased antimicrobial consumption) of various ASP interventions compared to only 4 demonstrating negative effects (the remainder revealed mixed or no effects). The most effective interventions were noted to be formal activities by an ASP (guidelines, targets with incentives/disincentives, provider education and prospective audit with feedback) (Wilkinson et al., 2019).

ASP activities can also be cost effective. A 2017 study in the *South African Medical Journal* examined the financial impact of an ASP over four years. They demonstrated a 2.8 million ZAR (approximately 193,000 USD at 2020 exchange rates) net savings primarily driven by decreased intravenous antimicrobial consumption (Boyles et al., 2017). Two studies have examined ASPs in Asia. A 2017 systematic review and meta-analysis examined 46 studies primarily focused on upper-middle- or high-income countries (Japan, Australia and Singapore were most represented), with 11 studies from LMICs (China- 6, Thailand - 4, Indonesia - 1). The study found a decrease in antimicrobial consumption and length of stay while demonstrating cost savings. There was no negative impact on mortality. The most commonly examined ASP interventions were PAF (17 studies) and antimicrobial restriction (8 studies) (Honda et al., 2017). A separate systematic review and

meta-analysis published in 2018 examined 77 studies with 43 from LMICs. The most common ASP interventions were PAF (29), education/training (23), and institutional guidelines (18). The majority of the studies demonstrated decreased antimicrobial consumption with cost savings ranging from 12–73%. A non-significant reduction in mortality was observed; a subgroup examining therapeutic drug monitoring (6 studies) did demonstrate significant reductions in mortality with a relative risk of 0.77, although this was largely driven by a single study. There was also a significant reduction in hospital-acquired infections, although this may have been confounded by infection prevention and control initiatives (Lee et al., 2018).

## 2. Suggested Practice

### 2.1. Establish ASP as a Priority (National Action plans)

In 2015, at the 68<sup>th</sup> World Health Assembly, a global action plan to address AMR was adopted focusing on 5 major objectives (Fig. 1). Members of the assembly stressed the importance of developing a national action plan focusing on these objectives while adapting to local situations (World Health Organization, Food and Agriculture Organization of the United Nations, and World Organisation for Animal Health 2016).

Within the past decade India, China, South Africa, Kenya, Argentina, Uruguay, Malaysia and Colombia among others have developed national action plans to further develop antimicrobial stewardship and limit AMR (Cox et al., 2017). The WHO provides a framework for the development of a national action plan, which WHO also notes is ideally the first step in developing local ASPs (Geneva: World Health Organization, 2019).

If the resources or government support is unavailable for the creation of a national action plan, there are alternative resources available to assist in creating country-specific antibiotic use and resistance data. The United States Center for Disease Dynamics, Economics and Policy (CDDEP) supports a program called the Global Antimicrobial Resistance Partnership (GARP) ([https://cddep.org/wp-content/uploads/2017/06/garp\\_factsheet-1.pdf](https://cddep.org/wp-content/uploads/2017/06/garp_factsheet-1.pdf)), which provides tools for LMIC to collect data on nation-wide trends in antibiotic use and AMR along with supporting stewardship activities (Cox et al., 2017). According to the CDDEP

website, countries such as Vietnam, India, Nepal, Kenya, Tanzania, Uganda, Mozambique, Pakistan, South Africa, Namibia, Nigeria, Seychelles, Bangladesh and Zimbabwe have partnered with the program. GARP is a valuable resource, especially if the program is already active in the country of interest. New countries are being added in phases. (<https://cddep.org/partners/global-antibiotic-resistance-partnership>).

Free resources are also available through non-government agencies such as ReAct (<https://www.reactgroup.org/toolbox>). ReAct is a web-based open access toolkit funded by the Swedish International Development Cooperation Agency and Uppsala University along with donation support. Their current strategic focus is in low resource settings and includes helping to develop national action plans. Their website also includes educational resources on AMR and discusses potential stewardship interventions in LMICs.

Country-level support and data are highly valuable in creating hospital-level efforts. If resources are available, a gap analysis can be performed to help determine regional needs. This involves surveying local institutions for current practices related to antimicrobial stewardship. As an example, this has successfully been performed in Thailand (Apisarntharak et al., 2019).

### 2.2. Medication Management

Currently, lack of access to antimicrobials may cause more deaths than antimicrobial resistant pathogens in LMICs. A 2016 report in the *Lancet* extrapolated data from 101 LMICs and estimated 445,000 deaths per year from pneumonia in children under 5 compared to 214,500 deaths per year from neonatal sepsis related to antibiotic resistant organisms (Laxminarayan et al., 2016).

Essential to ASP activity is having access to appropriate antimicrobial therapy as defined in WHO essential medicines (Geneva: World Health Organization, 2019). Broad spectrum antimicrobials designed to treat drug resistant organisms are not as widely available in LMICs (Laxminarayan et al., 2016). The WHO AWaRE classifications provide a framework for categorizing key antimicrobials (Fig. 2). Within this framework, RESERVE category antimicrobials are a key target for ASPs.

Although antimicrobial access is a major issue in LMICs, AMR is also significant. Point prevalence surveys (PPS) for collecting data



Fig. 1. World Health Organization (WHO) Global Action Plan Objectives (Geneva: World Health Organization, 2019).

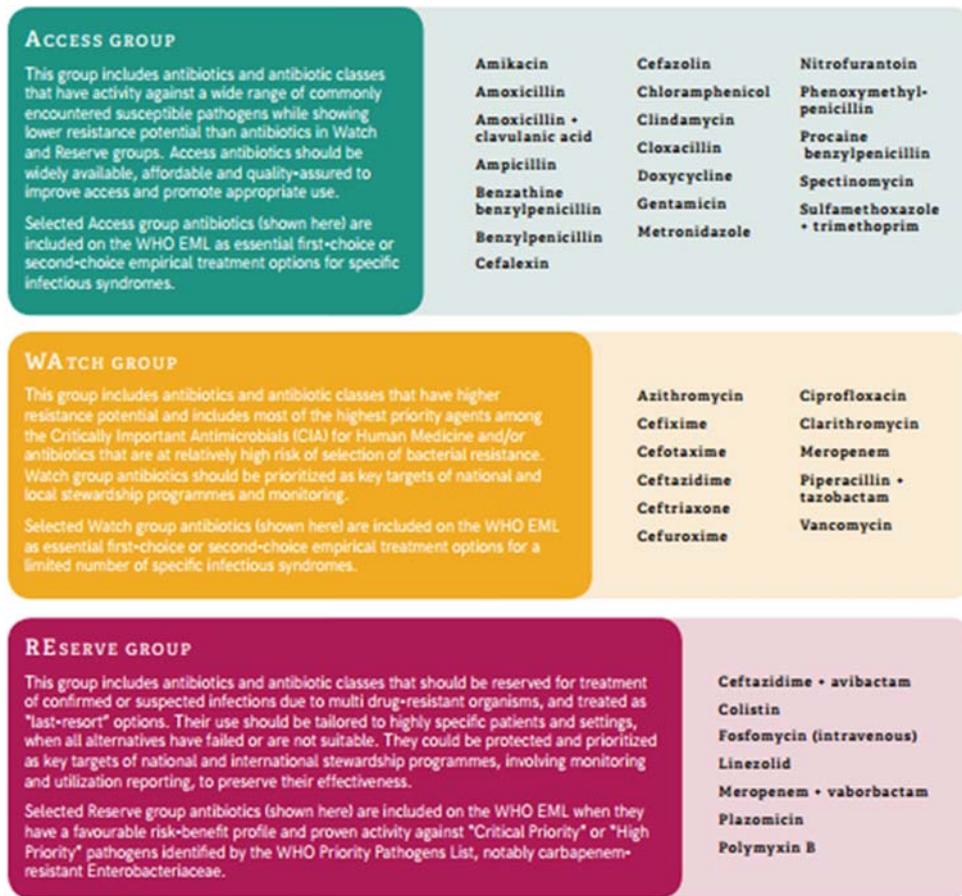


Fig. 2. World Health Organization AWaRE classification of antibiotics. Figure from World Health Organization Antimicrobial Stewardship Programmes in Health-Care facilities in low- and middle-income countries—A WHO Practical toolkit (Geneva: World Health Organization, 2019).

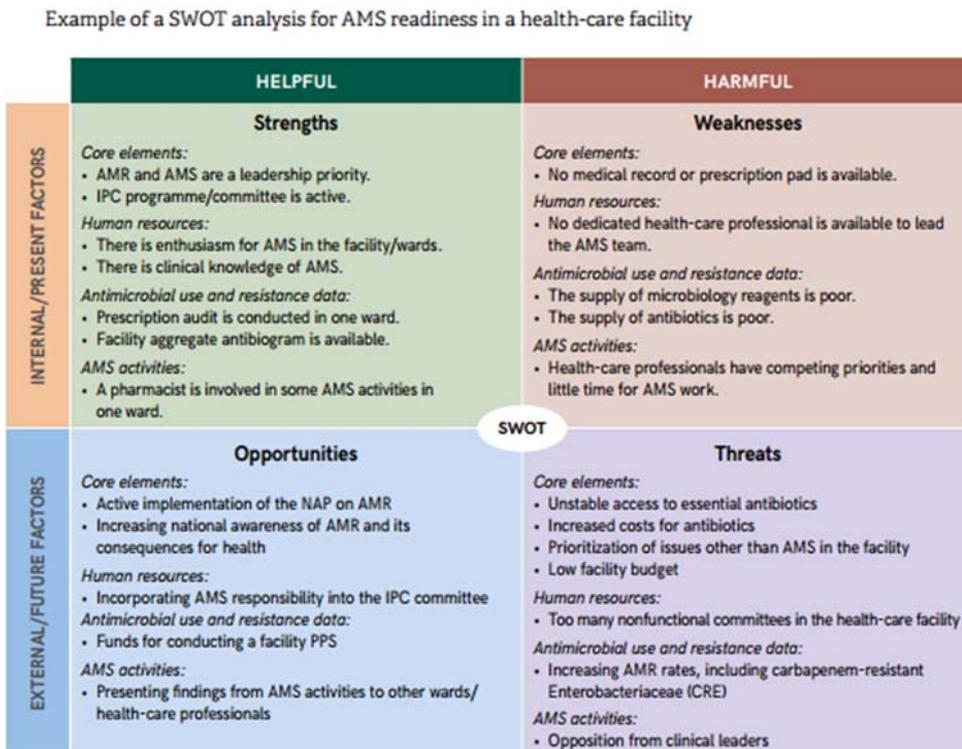


Fig. 3. World Health Organization SWOT analysis example. Figure from World Health Organization Antimicrobial Stewardship Programmes in Health-Care facilities in low- and middle-income countries—A WHO Practical toolkit (Geneva: World Health Organization, 2019).

on AMR or use from a few sites can provide a relatively quick assessment that is less resource intensive than more broad, continuous surveillance of use and resistance. Such surveys can be used to supplement existing surveillance in high-income countries but are particularly useful for providing a “snapshot” of resistance in LMICs without the infrastructure for continuous surveillance (IACG, 2018). Methodology can be found from the WHO at: <https://apps.who.int/iris/handle/10665/280063>.

Reducing suboptimal global antimicrobial consumption is critical for reducing the threat of antibiotic resistance, but reduction efforts must balance access limitations in LMICs and take into account both local and global resistance patterns (Klein et al., 2018).

### 2.3. Establishing an ASP Committee

The committee will ideally include an Infectious disease physician, clinical-pharmacist, clinical microbiologist or technologist (if a microbiology lab is present) and nurses (with infection control training if possible) (Geneva: World Health Organization, 2019). An expert panel from Asia also recommended the addition of an Information Technology expert (Apisarnthanarak et al., 2018). If some of these staff are not readily available, institutions may need to rely on antimicrobial stewardship champions. These can be physicians, pharmacists, or nurses with a special interest in antimicrobial stewardship. However, if a physician and/or pharmacist are not available to join the team, individuals should be identified from whom to seek advice when needed (Geneva: World Health Organization, 2019). The committee may also be established as a subcommittee of a pre-existing committee such as an Infection Prevention committee. In the latter instance, it is important that Antimicrobial Stewardship be a standing agenda item for reporting and discussion (Geneva: World Health Organization, 2019). Some hospitals lack infection prevention and control infrastructure. Separate resources exist that discuss implementing infection prevention and control programs in LMICs (Bardossy et al., 2016; Vilar-Compte et al., 2017).

### 2.4. Role of the ASP Committee

The role of the ASP committee is to optimize antimicrobial use along with promoting behavioral change in antimicrobial prescribing and dispensing. The aims of the committee should be to improve quality of care, reduce unnecessary antimicrobial exposure (with the goal of reducing the emergence of AMR) while also decreasing unnecessary health-care costs. A useful tool designed to focus priorities for the ASP team is a SWOT (Strengths, Weaknesses, Opportunities, and Threats) analysis. ASP committees can implement a SWOT analysis to help focus priorities (Fig. 3).

One role of the ASP committee should be developing a plan for data collection. Electronic collection is optimal but paper-based collection can also be utilized based on local resources. Data collection infrastructure is also essential to infection prevention and control programs (Vilar-Compte et al., 2017) and collaborative efforts could be considered in limited resource settings.

Sources of data collection can include pharmacy dispensing data or hospital antimicrobial purchasing data. Data collection should be standardized and the WHO defined daily dosing (DDD) is commonly employed. Instructions on this process can be found on the WHO website ([https://www.who.int/medicines/regulation/medicines-safety/toolkit\\_methodology/en/](https://www.who.int/medicines/regulation/medicines-safety/toolkit_methodology/en/)). Data can also be utilized to generate an antibiogram through coordination with microbiology (Geneva: World Health Organization, 2019). The Global Antimicrobial Resistance Surveillance System (GLASS) (<https://www.who.int/glass/en/>) is a global antimicrobial resistance surveillance tool developed by the WHO in 2015 designed to

distribute data on global AMR. This can be a valuable resource for assessing local AMR trends. Data is currently available for 2017–2018. As of July 2017, 69 countries were enrolled and 48 provided AMR data.

In the South African context, especially in the public sector, it is difficult to replicate resource abundant stewardship models that are mostly driven by medical microbiology teams, infectious disease (ID) specialists and epidemiologists. Consequently, it is critical in the South African context to utilize the existing resources of pharmacists, registered nurses (RNs) and other members of the health care team, who are well placed to coordinate anti-infective management and improve patient outcomes.

### 2.5. ASP Interventions

After data are collected basic ASP interventions can be employed. The ASP committee can identify targets for interventions. Examples provided in the WHO toolkit include ensuring written indications for antimicrobial prescribing, reviewing treatments for patients prescribed three or more broad-spectrum antibiotics or surgical prophylaxis prescribed beyond 24 hours (Geneva: World Health Organization, 2019). Appropriate surgical prophylaxis has been proven to be an effective measure to prevent hospital acquired infections in LMICs and could serve as a joint goal for both ASP and infection prevention and control programs (Bardossy et al., 2016).

Once targets are identified, guidelines can be established and providers can be educated, which are both proven effective measures to decrease inappropriate antimicrobial prescribing in LMICs (Cox et al., 2017).

Guidelines should be developed by the local institution to facilitate optimal antimicrobial use. Depending on available resources these can be enhanced and expanded over time. An example would be producing a guideline on appropriate empiric antimicrobials for a condition such as urinary tract infection or pneumonia or suggested regimens for surgical prophylaxis. Mobile phone-based applications can be a valuable tool for information dissemination if local information technology support is available. According to the International Telecommunication Union, in 2019 there were over 6.6 billion mobile cellular subscriptions in the developing world compared to 1.6 billion in the developed world and 46.7% of households in the developing world have access to the internet (ITU, 2019). A 2016 *Lancet* study examined the effect of text messaging reminders among 107 rural healthcare facilities in Kenya and demonstrated a statistically significant 23.7% increase in adherence to malaria treatment guidelines (Zurovac et al., 2011). The Commonwealth Partnerships for Antimicrobial Stewardship Programme is a non-profit organization funded by the United Kingdom Department of Health and offers a free web-based or mobile application that includes the AWaRE list of WHO essential medicine list of antibacterials, along with national prescribing guidelines for Ghana, Tanzania, Uganda, and Zambia (<https://viewer.microguide.global/CPA/CWPAMS>).

If more resources are available advanced ASP interventions may be employed. Examples include prospective audit and feedback, which involves reviewing antimicrobial orders and providing feedback to providers regarding appropriate prescribing. Restriction of antimicrobials can also be employed. This entails creating a list of antimicrobials that cannot be ordered (such as those on the WHO AWaRE reserve list) without approval from a designated person or group (such as an ID specialist or the ASP team) (Geneva: World Health Organization, 2019). Adherence to guidelines can also be one of the approaches in evaluating the success of an ASP initiative.

A systematic review evaluating ASP interventions in LMICs was published in the *Bulletin of the World Health Organization* in 2018 that examined 27 studies (primarily from middle-income countries). The most common intervention was utilization of procalcitonin (8 randomized controlled trials). Four studies examined audit and feedback; three demonstrated decreased antimicrobial consumption, one demonstrated decreased length of stay and one reported no change in length of stay. Several studies examined antimicrobial restriction bundled with other interventions with mixed results. The authors acknowledge low quality methodology among the included studies (van Dijck et al., 2018). It should be noted that there is limited data for procalcitonin for tropical diseases including malaria or non-standard bacterial infections that are more common in certain regions (such as tuberculosis) (Lee et al., 2020).

## 2.6. Measure Outcomes

In order to measure outcomes specific goals should be set. The SMART (specific, measurable, achievable, relevant, time-bound) framework is a good method to help in setting goals (Geneva: World Health Organization, 2019). A specific timeframe should be set in order to achieve goals (e.g. before the next ASP meeting, et cetera) (Geneva: World Health Organization, 2019). Goals can also be department specific. The Plan-Do-Study-Act (PDSA) framework is a useful tool for tracking progress and measuring outcomes of specific interventions (<http://www.ihl.org/resources/Pages/Tools/PlanDoStudyActWorksheet.aspx>). Basic measures such as antimicrobial consumption should be tracked as mentioned previously. More advanced measures can include length of stay, readmission rates, rates of AMR, mortality, et cetera (Apisarnthanarak et al., 2018).

Although outcome measures are easily identifiable, access to data is a major barrier, particularly in LMICs. As an example, a study of 45 hospitals in Thailand reported 49% had access to antimicrobial consumption data and 64% regularly published an antibiogram (Apisarnthanarak et al., 2019). A visual aid for establishing an ASP can be seen in Fig. 4.

## 3. Controversial Issues: Challenges in LMICs

### 3.1. Over-the-counter Antimicrobial Availability and Public Expectations

LMICs, including sub-Saharan Africa, have higher infectious disease rates than other developed countries. Additionally, there is extensive self-purchasing of antibiotics in LMICs and much of the global increase in antibiotic consumption in recent years has been in LMICs. The general public may come to expect the availability of non-prescription antibiotics, but these can pose a barrier to antimicrobial stewardship. AMR has been associated with non-prescription availability of antimicrobials (Bartoloni et al., 1998; Larsson et al., 2000; Dromigny et al., 2005; Apisarnthanarak and Mundy, 2008). Poor knowledge on the optimal use of antibiotics among the public could be one of the contributing factors of misuse of antibiotics by the community in LMICs (Roos et al., 2019).

Cost-effective measures LMICs can employ to combat AMR include public health campaigns designed to inform of the dangers of AMR and decrease unnecessary over the counter (OTC) antimicrobial use. Improved labeling for OTC medications may lead to decreased antimicrobial utilization, especially for countries in Africa where nearly all antimicrobials are obtained over the counter (O'Neill, 2016).

### 3.2. Unique Challenges and Knowledge Gaps in Antimicrobial Prescribing Among Providers

Prescribers in LMICs agree that AMR is a growing problem, although few acknowledge that their own practice contributes to this issue (García et al., 2011; Thriemer et al., 2013). Among 78 medical doctors and 106 medical students in Kisangani, Democratic Republic of Congo, more than 70% answered on a questionnaire they would prescribe antibiotics for an upper respiratory tract infection, for instance (Thriemer et al., 2013). Donkor and colleagues found that just under half of the



Fig. 4. Implementing an antimicrobial stewardship program.

students at tertiary level facilities in Ghana had poor knowledge about the suboptimal use of antibiotics (Donkor et al., 2012). Similarly, there were concerns about the level of knowledge of antibiotics and AMR among medical students in South Africa as well as appreciable differences in the knowledge and perception of ASPs among final year pharmacy students in South Africa (Wasserman et al., 2017). Many physicians and nurses in Ethiopia also lack knowledge about antimicrobials and AMR (Abera et al., 2014).

A key target for closing knowledge gaps is in medical school education. There is evidence that medical students would prefer additional education on appropriate antimicrobial prescribing while in medical school (Pulcini and Gyssens, 2013). The WHO Department of Health Workforce has produced a report on e-Learning that could be utilized for this purpose (World Health Organization, 2015). Direct education in the context of active patient interventions from ASPs to providers have proven to be some of the most effective education strategies (these include prospective audit and feedback along with antimicrobial restriction) (Pulcini and Gyssens, 2013).

### 3.3. Diagnostic Barriers: Microbiology Laboratory Access

Lack of microbiological laboratory support is a significant barrier in LMICs, and lack of laboratory diagnostic ability has been associated with increased mortality (Petti et al., 2006). A study of 251 children in Ghana demonstrated that approximately 40% of patients presumed to have severe malaria by symptoms actually had bacteremia (Evans et al., 2004). LMICs often have limited access to microbiology services and testing is often deferred to avoid associated costs (Petti et al., 2006).

Short term solutions may include partnering with larger institutions with microbiology laboratory capabilities, while long term solutions include prioritizing expanding microbiology laboratory infrastructure via a national action plan with dedicated funding. Global programs such as Strengthening Laboratory Medicine Toward Accreditation (SLMTA) and Stepwise Laboratory Improvement Process Towards Accreditation are working to increase access to microbiology laboratories in LMICs (Nkengasong et al., 2018). Other resources are available to aid in developing microbiology labs in LMICs (Barbé et al., 2016, 2017).

### 3.4. Access to Antimicrobials

Encouraging optimal use of antimicrobials through antimicrobial stewardship can help best utilize these limited resources. However, a disproportionate availability of WATCH or RESERVE antimicrobials compared to ACCESS antimicrobials may pose a barrier to effective stewardship in many countries (Frost et al., 2019). One goal of the WHO is to increase utilization of ACCESS group antibiotics from the AWaRE classification to greater than 60% of all antimicrobials (Geneva: World Health Organization, 2019). Essential to this goal is ensuring these ACCESS group antibiotics are available.

According to the 2011 WHO World Medicines Situation Report, 17.6% of the world's population live in low-income countries, but they account for only 1% of total pharmaceutical spending. In the same report, a seven-day course of ciprofloxacin among 20 LMICs was projected to cost more than 2 days wages in greater than 50% of the countries sampled. A cost greater than 1 day of wages is considered to be unaffordable (World Health Organization, 2011). This report suggests critical antimicrobials are financially inaccessible for a large proportion of the population in LMICs. However, there is

evidence that access to antimicrobials in LMICs may be increasing. Between 2000 to 2015 cephalosporin use increased by 399% in LMICs compared to an 18% decrease in high income countries (Frost et al., 2019). Increasing optimal access to antimicrobials should be part of a country's national action plan (Geneva: World Health Organization, 2019). However, key antimicrobial stewardship principles should be adopted with newly accessible antimicrobial agents in order to limit the emergence of AMR.

### 3.5. Insufficient Staffing

The optimal personnel profile of an ASP has been described above; however, major barriers to optimal personnel access exist, especially in LMICs. A 2012 global survey of 660 hospitals across 67 countries conducted by the European Society of Clinical Microbiology and Infectious Diseases revealed that only 12% of hospitals in Africa reporting the existence of an antimicrobial stewardship committee. Staff on these committees were primarily drawn from infection control personnel in Africa. Respondents from Africa and South and Central America noted the least average resource hours per week from an infectious disease-trained pharmacist or infectious disease physician. Lack of personnel or funding was the most commonly cited barrier to ASP activities among all surveyed institutions at 29% (Howard et al., 2014). In limited resource settings non-clinical pharmacists or nurses may need to play a larger role in ASPs (Brink et al., 2016). Other countries such as Oman have had success pooling limited resources into a single national antimicrobial stewardship team (Directorate General for Disease Surveillance and Control 2018).

### 3.6. ASPs and Pandemic Preparedness and Response Efforts

On January 30<sup>th</sup> 2020 the WHO declared Coronavirus Disease 2019 (COVID-19) a public health emergency of international concern (World Health Organization 2020). As of May 16 2020, COVID-19 has affected over 4.6 million people worldwide and has caused over 310,000 deaths (The Center for Systems Science and Engineering (CSSE) at JHU 2020).

Although infection prevention programs have a defined role in outbreak management, to date ASPs have not been involved in outbreak response efforts. There is emerging literature on the role of ASPs in pandemic response efforts, specifically in the context of COVID-19 (Stevens et al., 2020). ASPs can help identify patients with COVID-19, develop treatment protocols utilizing novel or repurposed medications and help manage limited medication supplies through existing structures such as prospective audit and feedback or antimicrobial restriction. ASPs are likely to have a key role in future outbreak response efforts.

## 4. Summary

Antimicrobial resistance is an established and growing threat and LMICs share a disproportionate burden related to limited resources. It is vital that governments and health organizations identify action to limit antimicrobial resistance as a top priority. Antimicrobial stewardship involves the systematic deployment of evidence-based interventions designed to optimize antimicrobial use and slow the emergence of antimicrobial resistance. Excellent resources exist (such as the World Health Organization Antimicrobial Stewardship Programmes in Health-Care facilities in low- and middle-income countries—A WHO Practical toolkit, 2019) that can help institutions develop and sustain ASPs and monitor outcomes.

## Competing interests

None declared

## Funding

None

## Ethical approval

Not required

## References

- Aarestrup FM, Vibeke F, Jacobsen E, Wegener HC. Changes in the use of antimicrobials and the effects on productivity of swine farms in Denmark. *Am J Vet Res.* 2010;71(7):726–33.
- Abera B, Kibret M, Mulu W. Knowledge and beliefs on antimicrobial resistance among physicians and nurses in hospitals in Amhara Region. Ethiopia. *BMC Pharmacol Toxicol.* 2014;15(1):1–7.
- Amdany HK, Mcmillan M. Metronidazole intravenous formulation use in in-patients in Kapkatet District Hospital. Kenya: a best practice implementation project. *JBI Database Syst Rev Implement Reports.* 2014;12(3):419–32.
- Apisarntharak A, Jantarathaneewat K, Weber DJ. Gap analysis on antimicrobial stewardship program in central Thailand. *Infect Control Hosp Epidemiol.* 2010;35(9):1077–9.
- Apisarntharak A, Kwa ALH, Chiu CH, Kumar S, Thu LTA, Tan BH, et al. Antimicrobial stewardship for acute-care hospitals: An Asian perspective. *Infect Control Hosp Epidemiol.* 2018;39(10):1237–45.
- Apisarntharak A, Mundy LM. Correlation of antibiotic use and antimicrobial resistance in Pratumthani, Thailand, 2000 to 2006. *Am J Infect Control.* 2008;36(9):681–2 [cited 2020 Jan 5].
- Bantar C, Sartori B, Vesco E, Heft C, Saul M, Salamone F, et al. A Hospitalwide Intervention Program to Optimize the Quality of Antibiotic Use: Impact on Prescribing Practice, Antibiotic Consumption, Cost Savings, and Bacterial Resistance. *Clin Infect Dis.* 2003;37(2):180–6.
- Barb e B, Verdonck K, Mukendi D, Lejon V, Lilo Kalo JR, Alirol E, et al. The Art of Writing and Implementing Standard Operating Procedures (SOPs) for Laboratories in Low-Resource Settings: Review of Guidelines and Best Practices. *PLoS Negl Trop Dis.* 2016;10(11):1–12.
- Barb e B, Yansouni CP, Affolabi D, Jacobs J. Implementation of quality management for clinical bacteriology in low-resource settings. *Clin Microbiol Infect.* 2017;23(7):426–33.
- Bardossy AC, Zervos J, Zervos M. Preventing Hospital-acquired Infections in Low-income and Middle-income Countries: Impact, Gaps, and Opportunities. *Infect Dis Clin North Am.* 2016;30(3):805–18. Available from: <https://doi.org/10.1016/j.idc.2016.04.006>.
- Bartoloni A, Cutts F, Leoni S, Austin CC, Mantella A, Guglielmetti P, et al. Patterns of antimicrobial use and antimicrobial resistance among healthy children in bolivia. *Trop Med Int Heal.* 1998;3(2):116–23.
- Boyles TH, Naicker V, Rawoot N, Raubenheimer PJ, Eick B, Mendelson M. Sustained reduction in antibiotic consumption in a south african public sector hospital: Four-year outcomes from the groote schuur hospital antibiotic stewardship programme. *South African Med J.* 2017;107(2):115–8.
- Brink A, Van den Bergh D, Mendelson M, Richards GA. Passing the baton to pharmacists and nurses: New models of antibiotic stewardship for South Africa?. *South African Med J.* 2016;106(10):947.
- Buising KL, Thursky KA, Robertson MB, Black JF, Street AC, Richards MJ, et al. Electronic antibiotic stewardship - Reduced consumption of broad-spectrum antibiotics using a computerized antimicrobial approval system in a hospital setting. *J Antimicrob Chemother.* 2008;62(3):608–16.
- CDC. Antibiotic resistance threats in the United States 2019. Atlanta: GA US Dep Heal Hum Serv.; 2019. p. 148.
- Chang Q, Wang W, Regev-Yochay G, Lipsitch M, Hanage WP. Antibiotics in agriculture and the risk to human health: How worried should we be?. *Evol Appl.* 2015;8(3):240–7.
- Roos Che, Aishah Nur, Bakar Abu, Muhamad, Haque M. Knowledge, attitude and practice among Malaysian medical students, doctors, other health professionals and common people regarding antibiotic use, prescribing and resistance: A systematic review. *Adv Hum Biol.* 2019;9(3):179–83.
- Cook PP, Catrou P, Gooch M, Holbert D. Effect of reduction in ciprofloxacin use on prevalence of methicillin-resistant *Staphylococcus aureus* rates within individual units of a tertiary care hospital. *J Hosp Infect.* 2006;64(4):348–51.
- Cox JA, Vlieghe E, Mendelson M, Wertheim H, Ndegwa L, Villegas MV, et al. Antibiotic stewardship in low- and middle-income countries: the same but different?. *Clin Microbiol Infect.* 2017;23(11):812–8 Available from: <https://doi.org/10.1016/j.cmi.2017.07.010>.
- van Dijk C, Vlieghe E, Cox JA. Antibiotic stewardship interventions in hospitals in low-and middle-income countries: A systematic review. *Bull World Health Organ.* 2018;96(4):266–80.
- Directorate General for Disease Surveillance and Control MO. Oman antimicrobial surveillance system (OMASS); the annual antimicrobial resistance report. 2018.
- Donkor ES, Tetteh-Quarcoo PB, Nartey P, Agyeman IO. Self-medication practices with antibiotics among tertiary level students in Accra. Ghana: A cross-sectional study. *Int J Environ Res Public Health.* 2012;9(10):3519–29.
- Dromigny JA, Nabeth P, Juergens-Behr A, Perrier-Gros-Claude JD. Risk factors for antibiotic-resistant *Escherichia coli* isolated from community-acquired urinary tract infections in Dakar. Senegal. *J Antimicrob Chemother.* 2005;56(1):236–9.
- Evans JA, Adusei A, Timmann C, May J, Mack D, Agbenyega T, et al. High mortality of infant bacteraemia clinically indistinguishable from severe malaria. *QJM - Mon J Assoc Physicians.* 2004;97(9):591–7.
- FAIRR Initiative. Improving antibiotics stewardship in livestock supply chains. Engagem Prog Rep [Internet]. 2019; Available from: <https://cdn.fairr.org/2019/05/19194214/FAIRR-antibiotics-engagement-update.pdf>.
- Frost I, Craig J, Joshi J, Faure K, Laxminarayan R. Access Barriers to Antibiotics. Washington: DC Cent Dis Dyn Econ Policy; 2019. p. 26.
- García C, Llamocca LP, García K, Jiménez A, Samalvides F, Gotuzzo E, et al. Knowledge, attitudes and practice survey about antimicrobial resistance and prescribing among physicians in a hospital setting in Lima, Peru. *BMC Clin Pharmacol.* 2011;11(1):18.
- GBD Diarrhoeal Diseases Collaborators. Articles Estimates of global, regional, and national morbidity, mortality, and aetiologies of diarrhoeal diseases: a systematic analysis for the Global Burden of Disease Study 2015. 2015; 909–48. Geneva: World Health Organization. Antimicrobial stewardship programmes in health-care facilities in low- and middle-income countries: a WHO practical toolkit. World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO.
- Honda H, Ohmagari N, Tokuda Y, Mattar C, Warren DK. Antimicrobial stewardship in inpatient settings in the Asia pacific region: A systematic review and meta-analysis. *Clin Infect Dis.* 2017;64(Suppl 2):S119–26.
- Howard P, Pulcini C, Levy Hara G, West RM, Gould IM, Harbarth S, et al. An international cross-sectional survey of antimicrobial stewardship programmes in hospitals. *J Antimicrob Chemother.* 2014;70(4):1245–55.
- Hsu L-Y, Apisarntharak A, Khan E, Suwantarit N, Ghafur A, Tambyah PA. Carbapenem-Resistant *Acinetobacter baumannii* and Enterobacteriaceae in South and Southeast Asia. *Clin Microbiol Rev.* 2017 Jan 19;30(1):1–22. Available from: <http://cmr.asm.org/lookup/doi/10.1128/CMR.00042-16>.
- IACG. Surveillance and monitoring for antimicrobial use and resistance IACG discussion paper 1. 2018; 2015(JUNE):120. Available from: <http://www.who.int/antimicrobial-resistance/global-action-plan/en/>.
- ITU. International Telecommunication Union Statistics [Internet]. 2019 [cited 2020 Apr 12]. Available from: <https://www.itu.int/en/ITU-D/Statistics/Pages/stat/default.aspx>.
- Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proc Natl Acad Sci [Internet].* 2018;201717295 Available from: <http://www.pnas.org/lookup/doi/10.1073/pnas.1717295115>.
- Larsson M, Kronvall G, Chuc NTK, Karlsson I, Lager F, Hanh HD, et al. Antibiotic medication and bacterial resistance to antibiotics: A survey of children in a Vietnamese community. *Trop Med Int Heal.* 2000;5(10):711–21.
- Laxminarayan R, Mouton RP, Pant S, Brower C, Rottgen JA, Klugman K, et al. Access to effective antimicrobials: A worldwide challenge. *Lancet.* 2016;387(10014):168–75.
- Lee C-C, Kwa ALH, Apisarntharak A, Feng J-Y, Gluck EH, Ito A, et al., Procalcitonin (PCT)-guided antibiotic stewardship in Asia-Pacific countries: adaptation based on an expert consensus meeting. *Clin Chem Lab Med.* 2020; 0(0).
- Lee CF, Cowling BJ, Feng S, Aso H, Wu P, Fukuda K, et al. Impact of antibiotic stewardship programmes in Asia: A systematic review and meta-analysis. *J Antimicrob Chemother.* 2018;73(4):844–51.
- Loftus MJ, Guitart C, Tartari E, Stewardson AJ, Amer F, Bellissimo-Rodrigues F, et al. Hand hygiene in low- and middle-income countries. *Int J Infect Dis.* 2019;86:25–30 Available from: <https://doi.org/10.1016/j.ijid.2019.06.002>.
- Nkengasong JN, Yao K, Onyebujoh P. Countries: Progress and Challenges. *Lancet.* 2018;391(10133):1873–5.
- O'Neill J. Tackling drug-resistant infections globally: Final report and recommendations. *Rev Antimicrob Resist.* 2016;84.
- Petti CA, Polage CR, Quinn TC, Ronald AR, Sande MA. Laboratory Medicine in Africa: A Barrier to Effective Health Care. *Clin Infect Dis.* 2006;42(3):377–82.
- Pham DK, Chu J, Do NT, Brose F, Degand G, Delahaut P, et al. Monitoring Antibiotic Use and Residue in Freshwater Aquaculture for Domestic Use in Vietnam. *Ecohealth.* 2015;12(3):480–9.
- Pulcini C, Gyssens IC. How to educate prescribers in antimicrobial stewardship practices. *Virulence.* 2013;4(2):192–202.
- Rahal JJ, Urban C, Horn D, Freeman K, Segal-Maurer S, Maurer J, et al. Class restriction of cephalosporin use to control total cephalosporin resistance in nosocomial *Klebsiella*. *J Am Med Assoc.* 1998;280(14):1233–7.
- Raymond DP, Pelletier SJ, Crabtree TD, Gleason TG, Hamm LL, Pruett TL, et al. Impact of a rotating empiric antibiotic schedule on infectious mortality in an intensive care unit. *Crit Care Med.* 2001;29(6):1101–8.
- Schuts EC, Hulscher MEJL, Mouton JW, Verduin CM, Stuart JWTC, Overdiek HWPM, et al. Current evidence on hospital antimicrobial stewardship objectives: A systematic review and meta-analysis. *Lancet Infect Dis.* 2016;16(7):847–56 Available from: [https://doi.org/10.1016/S1473-3099\(16\)00065-7](https://doi.org/10.1016/S1473-3099(16)00065-7).

- Stevens MP, Patel PK, Nori P. Involving antimicrobial stewardship programs in COVID-19 response efforts: All hands on deck. *Infect Control Hosp Epidemiol*. 2020;41(6):744–5.
- The Center for Systems Science and Engineering (CSSE) at JHU. COVID-19 Global Cases [Internet]. 2020 [cited 2020 Apr 4]. Available from: <https://coronavirus.jhu.edu/map.html>.
- Thriemer K, Katuala Y, Batoko B, Alworonga JP, Devlieger H, Van Geet C, et al. Antibiotic Prescribing in DR Congo: A Knowledge, Attitude and Practice Survey among Medical Doctors and Students. *PLoS One*. 2013;8(2):2–9.
- Vilar-Compte D, Camacho-Ortiz A, Ponce-de-León S. Infection Control in Limited Resources Countries: Challenges and Priorities. *Curr Infect Dis Rep*. 2017;19(5).
- Wasserman S, Potgieter S, Shoul E, Constant D, Stewart A, Mendelson M, et al. South African medical students' perceptions and knowledge about antibiotic resistance and appropriate prescribing: Are we providing adequate training to future prescribers?. *South African Med J*. 2017;107(5):405 Available from: <http://www.samj.org.za/index.php/samj/article/view/1189.4>.
- Watson J, D'Mello-Guyett L, Flynn E, Falconer J, Esteves-Mills J, Prual A, et al. Interventions to improve water supply and quality, sanitation and handwashing facilities in healthcare facilities, and their effect on healthcare-Associated infections in low-income and middle-income countries: A systematic review and supplementary scoping. *BMJ Glob Heal*. 2019;4(4):1–13.
- Wilkinson A, Ebata A, Macgregor H. Interventions to reduce antibiotic prescribing in LMICs: A scoping review of evidence from human and animal health systems. *Antibiotics*. 2019;8(1).
- World Health Organization, Food and Agriculture Organization of the United Nations, and World Organisation for Animal Health. Antimicrobial Resistance: A Manual for Developing National Action Plans, version 1. World Health Organization. 2016.
- World Health Organization. The World Medicines Situation 2011 - Complete Report. 2011; 3. Available from: [http://www.who.int/medicines/areas/policy/world\\_medicines\\_situation/en/](http://www.who.int/medicines/areas/policy/world_medicines_situation/en/).
- World Health Organization. eLearning for undergraduate health professional education: a systematic review informing a radical transformation of health workforce development. Imp Coll London [Internet]. 2015; 92. Available from: <https://www.who.int/hrh/documents/14126-eLearningReport.pdf>.
- World Health Organization. Global Antimicrobial Resistance Surveillance System (GLASS) Report. Geneva: World Health Organization [Internet]. 2018. Licence: CC BY-NC-SA 3.0 IGO.
- World Health Organization. WHO Events as they happen [Internet]. 2020 [cited 2020 Apr 4]. Available from: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen>.
- Zurovac D, Sudoi RK, Akhwale WS, Ndiritu M, Hamer DH, Rowe AK, et al. The effect of mobile phone text-message reminders on Kenyan health workers' adherence to malaria treatment guidelines: A cluster randomised trial. *Lancet*. 2011;378(9793):795–803 Available from: [https://doi.org/10.1016/S0140-6736\(11\)6078.3-6](https://doi.org/10.1016/S0140-6736(11)6078.3-6).