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The threat of Antimicrobial Resistance in Developing Countries: Causes and Control Strategies

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ABSTRACT

The causes of antimicrobial resistance (AMR) in developing countries are complex and may be rooted in practices of health care professionals and patients' behavior towards the use of antimicrobials as well as supply chains of antimicrobials in the population. Some of these factors may include inappropriate prescription practices, inadequate patient education, limited diagnostic facilities, unauthorized sale of antimicrobials, lack of appropriate functioning drug regulatory mechanisms, and non-human use of antimicrobials such as in animal production. Considering that these factors in developing countries may vary from those in developed countries, intervention efforts in developing countries need to address the context and focus on the root causes specific to this part of the world. Here, we describe these health-seeking behaviors that lead to the threat of AMR and healthcare practices that drive the development of AMR in developing countries and we discuss alternatives for disease prevention as well as other treatment options worth exploring.

Keywords: Antimicrobial resistance, Causes and Control Strategies

INTRODUCTION

The threat of antimicrobial resistance (AMR) is growing at an alarming rate and the situation is perhaps aggravated in developing countries due to gross abuse in the use of antimicrobials [1-17]. It is well known that any use of antimicrobials however appropriate and justified, contributes to the development of resistance, but widespread unnecessary and excessive use makes the situation worse [18]. Misuse of antimicrobials is facilitated in developing countries by their availability over the counter, without prescription and through unregulated supply chains [19]. Non-co mpliance in the use of antimicrobials has many repercussions upon resistance and poverty is a major root factor of antimicrobial misuse in developing countries [20]. On the other hand, even among the rich, some patients miss doses either by mistake or deliberate, especially in cases where signs and symptoms begin to subside after an initial favorable therapeutic response [21]. In other situations, such as in the event of an acute side effect, patients abandon their treatment, only to return to the hospital with a recurring infection by a more virulent and resistant strain of the microbe [22]. These actions result in the exposure of surviving pathogens to sub-therapeutic concentrations of antimicrobials thus increasing the chances of acquiring resistance. Self-medication is a common practice in developing countries where patients often get antimicrobials without prescription and through unregulated supply chains [23]. To make the situation even worst, some patients seek their first-line of treatment from traditional healers who provide them with herbal combinations for the treatment of infections. These substances of unknown composition and potency may enhance pathogen fitness and contribute to the development of

resistance. Antimicrobial resistance often occurs through the inhibition of specific antimicrobial pathways such as cell wall synthesis, nucleic acid synthesis, ribosome function, protein synthesis, folate metabolism, and cell membrane function [24-25].

Responding to the threat of Antimicrobial Resistance

While AMR has long been recognized as a threat to human health, in recent years many countries have focused on reducing healthcare-acquired infections such as methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* infection (CDI). This has led to a significant reduction in the incidence of both MRSA and CDI within hospitals in the UK and a major decline in prescribing of cephalosporins and fluoroquinolones. Arguably, this success has shifted attention away from AMR, allowing it to escalate. Despite concerted efforts from 1998 onwards, through a series of World Health Assembly (WHA) resolutions and the 2001 WHO global strategy for containment of AMR, the need to accelerate progress on AMR has been widely acknowledged by the WHO, the USA and the European commission. Though important for the UK, this action alone could not drive the collaborative response and commitment that was required from governments across the world. This demanded a strategic approach: maximizing political influence, engaging with the public and working to develop the scientific evidence-base to deliver new antimicrobials [26]. While there was global recognition of the importance of AMR, including a number of separate national initiatives, in the period immediately after publication of the CMO's report in 2011 there was no clear mechanism for collaborative international efforts. Driven by the UK and Sweden, a resolution on AMR was drafted and ratified at the 67th WHA in 2014. This gave the WHO a mandate to develop a global action plan, legitimizing action on behalf of member states. The draft action plan acknowledges that member states will have different priorities in relation to AMR so it has been devised as a series of building blocks [27]. Member states are encouraged to develop action plans that focus interventions on where nationally they are most needed.

Causes of antimicrobial resistance

To better appreciate the causes of AMR, we need to understand the various sequential steps involved for a drug to get to a patient and the eventual use, which include; production, distribution, prescription, dispensing, and finally consumption of the drug by the patient or use in animal production [22]. Consequently, any imprudent practice along this flow may result in the emergence of resistance.

1. Drug dispensers and drug quality

The lack of appropriate regulations in the sales of antimicrobials is also a driving factor in the access and misuse of antimicrobials. In most developing countries, antimicrobials can be purchased without medical prescription [28] and are usually dispensed on the streets by untrained persons. These drug vendors will sell medications just to make a sale and accommodate patients' ability to pay [29]. Even pharmacies operating without a license, appear to be more accessible to the public as they have shorter waiting time, do not charge consultation fees and above all are willing to negotiate treatment options to adjust to the financial ability of the patients [30]. Retail pharmacies in developing countries especially in Africa have emerged as the primary level of outpatient care rendering unauthorized services from consultation, diagnosis, prescription and dispensing of medication [30-31]. It has also been shown that many antimicrobials dispensed in Africa are of questionable pharmacological quality [32]. Adverse climatic conditions such as high ambient temperatures and humidity may affect the overall quality of the antimicrobials during storage [29]. Poor storage also increases the risk of degradation of the drug. Degraded medicines contain less than stated dose, implying that patients consume less than optimal dose of the drug. There is also a problem of outright counterfeit, in which the drug may contain little or no active substance of the antimicrobial or the wrong substance [33].

2. Health professionals

Health care providers play an essential role in the treatment and prevention of diseases, but may jeopardize this if their practices are not evidence-based. For example, the prescription practices of antimicrobials vary among physicians in most countries. In some cases, the antimicrobial prescriptions are inappropriate (i.e., wrong drug, wrong doses, or antimicrobial not necessary at all) [34]. Due to the high patient-doctor ratio in most developing countries, doctors are overwhelmed and there is often inadequate time for meaningful education and communication with the patient on drug adherence guidelines and consequences of poor or non-adherence to these guidelines. Treatment sometimes consists of administering broad-spectrum antibiotics without a definitive diagnosis and indication for antimicrobial treatment. In a Lebanese study, it was shown that in 52% of cases, the

prescription dose was inappropriate while 63.7% of physicians prescribed antibiotics with wrong duration of treatment [35]. Due to lack of effective and reliable surveillance systems and poor dissemination of research information, health professionals in developing countries sometimes lack up to date information on the AMR pattern within their populations.

3. Patients

As mentioned earlier, compliance is a major contributor to the development of AMR [36]. Patients miss doses, either by mistake or deliberate. Because patients are aware of the adverse impact of drinking alcohol while on antibiotics, some patients may skip doses when invited for a party in favor for the consumption of alcohol (unpublished data). These practices result in exposure of surviving microbes to sub-therapeutic concentrations of the drug and, consequently increases the chances of developing resistance [37]. Because of poverty, many sick individuals in developing countries of Africa often seek their first-line of treatment from traditional healers who provide them with herbal mixtures of unknown efficacy for the treatment of infections. Some combine antibiotics with their herbal mixtures simultaneously while others take antimicrobials and supplement them with herbal mixtures purportedly to improve efficacy [28]. These compounds of unknown potency may enhance pathogen fitness.

4. Non-human use of antimicrobials

Antimicrobials are used to prevent (prophylaxis in high-risk animals) and treat diseases in animals, as well as used as growth promoters in animal breeding [38-39]. Additionally, they are used as additives in plant agriculture (fruits, vegetables, and orchid, etc.), especially in the spraying of fruit trees for disease prophylaxis and the application of antibiotic-containing manure on farmland and in industrial processes [40]. The use of antimicrobial agents in animals and more importantly food-producing animals has important consequences for both human and animal health as it can lead to the development of resistant bacteria. These resistant bacteria (with resistance genes) in animals can be transferred to humans through the consumption of food or through direct contact with food-producing animals or through environmental spread (e.g. human sewage and runoff water from agricultural sites). The use of antimicrobial drugs in health care, agriculture or industrial settings, exerts a selection pressure which can favor the survival of resistant strains (or genes) over susceptible ones, leading to a relative increase in resistant bacteria within microbial communities [41]. It is now known that increased AMR in bacteria affecting humans and animals is primarily influenced by an increase in the use of antimicrobials for a variety of purposes, including therapeutic and non-therapeutic purposes in animal production (Food and Agriculture Organization. A strong association between agricultural use of antimicrobials and the development of resistance has been suggested [42], and it has been shown that the bulk of antimicrobials used worldwide are not consumed by humans but rather are given to animals for the purposes of food production [43]. A study in Kenya revealed a high level of antimicrobial drug residues in meat meant for consumption [43]. These findings further demonstrate that food animals are a major reservoir of drug resistant bacteria and present a major risk for dissemination and transmission of antimicrobial resistant bacteria in Africa as well as many developing countries. A large proportion of the population in developing countries live in close proximity with animals, thus increasing the chances of transmission of resistant microorganisms from animals to humans through animal handling [44-45]. In a recent study in rural Bangladesh animal healthcare providers responded they more often sought animal health care from pharmacies and village doctors, citing the latter two as less costly and more successful based on past performance [46]. In the absence of an effective animal healthcare system, villagers depend on informal healthcare providers for treatment of their animals. This may lead to suboptimal use of antimicrobials in such settings with unhygienic animal husbandry practices. In terms of aquaculture, heavy use of prophylactic antibiotics in aquaculture has been reported in developing countries and is a growing problem for human and animal health and for the environment [47]. Overall, limiting the routine use of in-feed antibiotics will improve human and animal health, by reducing the development and spread of antibiotic-resistant bacteria. Therefore, judicious use of antibiotics in healthcare and agricultural settings is essential to slow the emergence of resistance and extend the useful lifetime of effective antibiotics that are in existence today. In other to minimize the risk of AMR due to non-human use of antimicrobials especially in animal production, information resources in developing countries need to be strengthened to support health professionals, patients, animal keepers and the public, so that the society can have a better understanding of the value and importance of antimicrobials, especially antibiotics.

5. Limited laboratory antimicrobial susceptibility testing

The availability of routine antimicrobial susceptibility testing to provide information on resistance trends, including emerging resistance is very essential for routine clinical practice and for the development of effective policies against AMR. Antimicrobial susceptibility testing is not often performed in most rural laboratories due to lack of capacity [48].

6. Inadequate surveillance

In the absence of patient-specific antimicrobial susceptibility testing, community-based antimicrobial surveillance data may be very useful to health care professionals in particular communities or regions to treat infections with specific susceptible antimicrobials. Such surveillance needs to be conducted regularly and continuously because resistance rates can vary in one region of a country over time [22].

Antimicrobial resistance control strategies

The problem of AMR is aggravated by the fact that most world pharmaceutical companies consider research for new antimicrobials as being of "low profit" and some speculate that resistance will eventually develop for new antimicrobials anyway. Consequently, they prefer to invest in the development of drugs for chronic diseases (diabetes, hypertension) as well as those used to improve lifestyle (e.g., Cialis, Viagra, etc.) [49]. Therefore, the long-term solution should be focused on methods to prevent the emergence of resistance or the spread of resistant organisms from one person to another.

1.Hygiene and sanitation

Apart from the irrational use of antimicrobials, unique environmental conditions such as crowding and poor sanitation also contribute in the circulation and spread of resistant microorganisms. Transmission of resistant pathogens is facilitated by person-person contact, through contaminated water, food or by vectors. Improving basic hygiene and sanitation will reduce the spread of resistant organisms [50]. Improving infection prevention and control in hospitals will reduce the nosocomial spread of bacteria with acquired resistance such as *Staphylococcus aureus* amongst others.

2. Vaccination

While antimicrobials are used for treatment, vaccines are a primary mode of prevention of infectious diseases. Prior vaccination may reduce severity of disease, provide protection against shedding of pathogens and even raise the threshold load of pathogens required for infection [51-53]. Also, indirect population protection of some vaccines as a result of herd immunity in unvaccinated individuals represents additional advantage of vaccination. In most regions of the world, a number of diseases such as smallpox, measles, mumps rubella, diphtheria, hepatitis A, pertussis, and polio have been prevented by vaccination [54].

3. Alternative therapies

The increase in microbial resistance to traditional antimicrobials and the reluctance of pharmaceutical companies to invest in research and development of novel antimicrobial agents necessitate the exploration of alternative therapies. Future focus of medical therapeutics and research is to look beyond antibiotics [49], and search for alternatives which can regulate the microbial virulence as well as growth inhibition. There are currently a couple of other alternatives approaches at different levels of research and development.

1. The use of Bacteriophages is emerging as an alternative treatment option for bacteria infections [55]. Many authors have suggested that bacteriophage therapy is a necessary alternative to conventional antibiotics [56-57]. Bacteriophages are bacterial viruses with the capacity to invade bacterial cells and induce lysis of the bacteria (lytic cycle). In the present era of multidrug resistant bacteria and reluctance in the development of new antibiotics by pharmaceutical companies, the need to aggressively explore the possibility of phage therapy is unprecedented [58].

2.Quorum Sensing inhibitors represents an important antimicrobial target that may prevent, suppress, and/or treat infectious diseases. The mechanistic details (including auto-inducers) of Quorum Sensing are different between Gram-negative and Gram-positive bacteria. Gram-negative bacteria utilize N-acyl L-homoserine lactones (AHLs), which are homoserine lactone (HSL) rings with an additional fatty acid side chain while Gram positive bacteria uses oligopeptides [59-61]. While antibiotics kill or slow down the growth of bacteria, quorum sensing inhibitors or quorum quenchers simply attenuate bacterial virulence. A large body of work on Quorum Sensing has been carried out in deadly pathogens like *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Vibrio fischeri*, *Vibrio. harveyi*, *Escherichia coli* and *Vibrio. cholerae* etc. A number of these studies have succeeded

in exploiting the bacterial Quorum Sensing system as potential target for treatment of bacterial infections. The inhibition of Quorum Sensing system is believed to be advantageous over conventional antibiotics, because only the communication mechanism between the bacteria is disrupted without killing the individual cells. Hence, this strategy should generate a lower selective pressure and reduce the rate at which AMR develops during the treatment [61].

3. Probiotics, otherwise referred to as fecal transplant therapy (FTT) is a treatment option that has been employed for decades, albeit with mixed results. FTT is the act of using fecal material from pathogen-free healthy donors to repopulate the microbiota of a recipient. Probiotics are considered to be able to destroy pathogenic microorganisms by producing antimicrobial compounds such as bacteriocins and organic acids, improve gastrointestinal microbial environment by adherence to intestinal mucosa thereby preventing attachment of pathogens and competing with pathogens for nutrients, stimulate the intestinal immune responses and improve the digestion and absorption of nutrients.

The role of stakeholders in the control of antimicrobial resistance

The control of AMR cannot be the sole responsibility of medical professionals and scientists. Although continuing education is essential to enable health care providers learn the need in rational prescription practices and the importance of evidence-based prescription [62], the general population and other stakeholders have a central role to play [63]. The government of every country should consider AMR as a public health priority issue. Policies and regulations should be put in place to enforce the prudent access and use of antimicrobials. The population needs to be educated on the threat of AMR and therefore media professionals need to get adequate training on how to convey medical and scientific information in lay language through multiple channels to inform the populations on practices that promote the emergence of AMR organisms [62]. The benefits of an education program for journalists have been successful for the fight against HIV/AIDS in many developing countries and a similar approach for AMR will likely result to an added benefit [64].

The role of government regulatory agencies

With the new and emergent issue regarding the development of AMR, government agencies globally have engaged in new action plans in order to combat the AMR issue [63-65]. However, actions toward this have been severely lacking in developing countries especially those in Africa where high-quality regulatory agencies are lacking. In May 2015, the WHO endorsed a global action plan to tackle AMR [65]. In September 2014, the US government released a 'National Strategy for Combating Antibiotic-Resistant Bacteria' that included an executive order signed by the US president. The action plan provided several goals and a roadmap to guide the Nation in rising to this challenge. In 2013, the United Kingdom released the 'UK Five Year Antimicrobial Resistance Strategy (2013 to 2018)' that sets out actions to address the key challenges to AMR. Similarly, in 2015, the government of Canada also released the Federal Action Plan on antimicrobial resistance and use in Canada (Building on the federal framework for action). While many developed countries have developed such AMR action plans either nationally or at the regional level such as the European Union and Asia-Pacific region, this is still lacking in many developing countries especially in Africa [65]. A few African countries have been identified as being involved in the Global Antibiotic Resistance Partnership (GARP), established in 2009 to create a platform for developing actionable policy proposals on antibiotic resistance in low-income and middle-income countries. However, national GARP working groups are established only in India, Kenya, South Africa, Vietnam, Mozambique, Nepal, Tanzania and Uganda. Moreover, a close look at the national action plans showed that only one African country (Ethiopia), was identified by the WHO as having a national AMR action plan [27]. What most developing countries especially those in Africa lack is not the legislation prohibiting the manufacture and distribution of sub-standard drugs but resources to enforce these policies and to impose penalties to defaulters. There is also lack of resources to identify counterfeit drugs or verify the quality of locally manufactured or imported drugs [65]. In addition, governments need to address the sale of antimicrobials without prescription and illegalize the dispensing of drugs by unauthorized and unqualified persons. There is also need for the population to be sensitized on the public health risks of AMR. A recent WHO survey revealed that while much activity is underway and many governments are committed to addressing the AMR problem, there are major gaps in actions needed across all 6 WHO regions to prevent the misuse of antibiotics and reduce spread of AMR [65]. Despite these challenges some progress is currently being made in setting up drug regulatory agencies in Africa. The effort is supported by the New Partnership for Africa's Development (NEPAD) of the African Union and the WHO. Through the creation of the African Medicines Regulatory

Harmonization (AMRH), it is envisioned that safe, good quality, efficacious and reasonably priced medicines will be available in Africa. Recently, the African Society for Laboratory Medicine (ASLM) has engaged in activities to share research, debate, and generate solutions to build a strong African laboratory infrastructure to help combat common global health threats, like AMR as well as HIV/AIDS, and other medical conditions. Therefore, a multi-disciplinary approach involving a wide range of partners is therefore needed to limit the risk of AMR and minimize its impact on human and animal health especially in developing countries.

CONCLUSION

The irrational use of antimicrobials is certainly a complex and multifactorial problem in developing countries and a proper understanding of the problem is necessary for effective control policies. Without effective antimicrobials, diverse medical procedures such as surgery, the care of premature infants, cancer chemotherapy, care of the critically ill, invasive diagnostic and treatment procedures, and transplantation medicine will be severely hampered with a corresponding increase in morbidity and mortality from secondary microbial infections. The challenge of global antimicrobial resistance is comparable to climate change and global warming. Therefore, as we seek to protect the climate for the future generation, it is our responsibility not to pass over to the next generation, microbial population that is resistant to antimicrobial agents that they are supposed to treat as the consequence is likely to be very dangerous.

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