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Review

Menace of antimicrobial resistance in LMICs: Current surveillance practices and control measures to tackle hostility[☆]



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ABSTRACT

Antimicrobial Resistance (AMR) is significant challenge humanity faces today, with many patients losing their lives every year due to AMR. It is more widespread and has shown a higher prevalence in low- and middle-income countries (LMICs) due to lack of awareness and other associated reasons. WHO has suggested some crucial guidelines and specific strategies such as antimicrobial stewardship programs taken at the institutional level to combat AMR. Creating awareness at the grassroots level can help to reduce the AMR and promote safe and effective use of antimicrobials. Control strategies in curbing AMR also comprise hygiene and sanitation as microbes travel from contaminated surroundings to the human body surface. As resistance to multiple drugs increases, vaccines can play a significant role in curbing the menace of AMR. This article summarizes the current surveillance practices and applied control measures to tackle the hostility in these countries with particular reference to the role of antimicrobial stewardship programs and the responsibilities of regulatory authorities in managing the situation.

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Introduction

In the late 1800s, the discovery of infectious organisms sparked a quest for effective prophylactic and therapeutic regimens. However, it was not until the next century it was achieved, with the discovery of antibiotics, which became a turning point in medical history. A complete transition was observed in the infectious disease arena by discovering antibiotics, which saved countless lives [1]. However, poor hygiene, lack of education in the general population, especially in lower- and middle-income countries (LMICs), and rampant use of antibiotics in animal husbandry and agriculture, easy accessibility of antibiotics in LMICs as well as irrational use of antibiotics are all major contributors to the emergence of AMR as a global health concern [2]. One of the possible causes for the development of AMR is the highly optimistic approach taken after achieving unprecedented advancements in antimicrobial chemotherapy and belief that the humanity would conquer infectious diseases in the coming years. Another cause is that pharmaceutical companies prioritize manufacturing medications for chronic diseases such as hypertension, dyslipidemia, and other conditions that generate more revenues over infectious diseases. Thus the bacterial infections are becoming increasingly challenging to treat [3]. Conversely, in the current deluge of ever-evolving contagious diseases, we have reached up to the extent where many antimicrobials are now ineffective against several microorganisms. Therefore, a challenging aspect of clinical practice is to combat the infections due to these drug-resistant organisms [4].

MDR-TB is still a public health problem and a health security hazard. In 2019, 206,030 individuals with multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) were confirmed and notified globally, increasing 10% from 186,883 in 2018 [5]. Approximately 60,000 newborn infants die from antibiotic-resistant neonatal infections in India [6]. In India, 80% of strains of *Staphylococcus* are resistant to penicillin and ampicillin [7]. A report published by the World Health Organization (WHO) on the surveillance of antibiotic resistance at a global level highlighted that: *Escherichia coli* and *Staphylococcus aureus* is resistant to the 3rd generation cephalosporins and fluoroquinolones in many parts of the world [8]. Multidrug-resistant bacteria accounted for 45% of fatalities in South East Asia and Africa. Increased mortality was observed due to predominantly prevalent *Klebsiella pneumoniae* in the poor and developing countries, resistant to the third-generation cephalosporins. In Africa, this resistance was 77%, while in South East Asia and Mediterranean regions, it was 81% and 50%, respectively [9].

As evident through various studies, the primary cause of AMR in these countries is that the patients and their relatives were unaware of the resistance, which caused hurdles in the treatment, eventually failing the therapy [10,11]. Due to the lack of knowledge, the general public fails to accept any role in addressing the

AMR problem, particularly in developing countries. Various studies have been published on the prevalence of AMR infections in LMICs. However, very few studies are carried out on the current surveillance practices and applied control measures to tackle the hostility in LMICs countries with particular reference to the role of antimicrobial stewardship programs and responsibilities of regulatory authorities in managing the situation to tackle the AMR effectively.

This article aims at reviewing the AMR problems in LMICs countries, their impact in the community and hospital settings, understanding the current surveillance practices, applied control measures with particular reference to the role of antimicrobial stewardship programs and responsibilities of regulatory authorities in managing the situation.

Methods

The authors carried out searches on particular objectives with the help of search engines- Google Scholar, PubMed, and SCOPUS. The search items used were a compilation of keywords such as antimicrobials, developing countries, lower-middle-income countries, transmission, infectious diseases, resistance, surveillance, survey, control strategies, infection prevention and control, and antimicrobial stewardship. The material included in this narrative review is most recent, but earlier material as far as 1983 is included based on its requirement and relevance. Related journals and articles were selected and searched, and their references were explored for additional relevant published studies. Articles pertinent to the search, as mentioned earlier items were considered for this review. The issues and findings discussed in various articles related to AMR in LMICs are summarized below.

Problems of antimicrobial resistance

The 20th century in its later decades, saw a wave of novel antimicrobial compounds hitting the market, which served to save countless lives. New drugs, such as quinolones, cephalosporins, etc., were synthesized with more recent generations of these drugs with improved pharmacokinetic profiles introduced in the successive years [12,13]. It led to widespread misuse of antimicrobials, especially in LMICs countries where they are available without prescription and unauthorized supply chains [14]. According to WHO's data, nearly 80% of drugs prescribed in developing countries are carried by a person with no educational background in dispensing medications [15–18]. Several key factors have played a significant role in the progression of AMR (Fig. 1). One such reason for AMR is the entry of spurious and adulterated drugs having low therapeutic activity coming into the market. It adds to serious issues as the microorganisms tend to become resistant at low levels of drug concentration. These low drug concentration levels tend to therapeutic failures due to the development of resistance by the

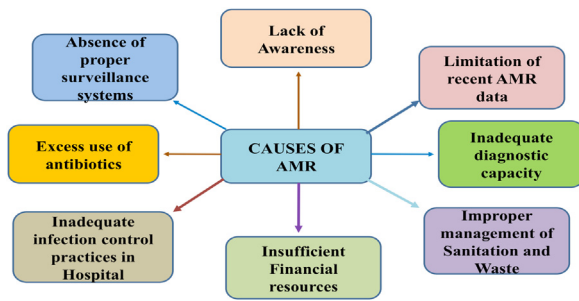


Fig. 1. Causes of AMR in resources-limited countries.

microorganisms against the antimicrobials [19]. A study conducted in Cameroon revealed that in a sample of 284 antimicrobial drugs from 132 vendors, 32%, 10% and 13% of chloroquine, quinine and sulfadoxine/pyrimethamine, respectively, were found to be fake [20]. In many LMICs, the regulatory authorities cannot establish stringent regulations restricting the “Over counter” sale of prescription medicines [21,22]. A study conducted in Tanzania revealed that despite the government policy for restriction on the sale of antimicrobials without prescription and dispensing of drugs should take place under the supervision of a registered pharmacist only, the inappropriate and over-consumption of drugs was found to be 80–85% [23–25]. The causes of AMR in LMICs are shown in Fig. 1.

In LMICs, infectious diseases have become the most significant challenge with high mortality rates [26,27]. In 1990, developing nations, which accounted for over 78% of the world’s population was responsible for 23% of fatalities in their countries due to infectious and parasitic illnesses [28]. The lack of access to effective medications, uncontrolled manufacturing and distribution of antibiotics, shortage of financial support, high-quality pharmaceuticals are a few of the primary poverty-driven factors leading to antimicrobial resistance in poor nations [29–31]. Poverty also hampers the patient’s compliance, which encourages the formation of antibiotic resistance in both short-term treatments of acute illnesses and long-term treatment of chronic diseases like TB [32]. Furthermore, it is observed that poverty-stricken people have no option but to seek out the fake doctors and medication vendors that provide substandard, spurious, and expired drugs or antimicrobials dosages with low therapeutic levels. Thus, self-medication is one of the core reasons people living in poverty lack access to medical care [33].

Health professionals in developing nations sometimes lack up-to-date knowledge on the AMR trend in their populations due to inadequate and accurate monitoring methods and poor distribution of research material. As a result, physicians depend on the resistance or susceptibility pattern of the pathogen isolated from a patient at tertiary institutions with enhanced capabilities. In the absence of an antibiotic sensitivity test, health professionals in remote areas who do not have access to AMR testing have difficulties deciding which antimicrobial to use. Consequently, doctors are increasingly prescribing broad-spectrum antibiotics to treat infections caused by several bacteria species or illnesses for which determining the aetiology is difficult or time-consuming. This technique leads to the development of resistance since the treatment exerts selective pressure not only on the disease’s etiological agent but also on a significant portion of the patient’s microbiota [34,35].

Compliance, as previously indicated, is a crucial factor in the spread of AMR. Surviving microorganisms are exposed to sub-therapeutic quantities of the medicine due to these actions, which raise the likelihood of resistance [35]. The ‘misuse’ of antibiotics for self-limiting diseases such as coughs, colds, and viral upper-respiratory tract infections is also a significant reason for AMR [36]. Antimicrobial prescribing and dispensing practices in Low-

Middle-Income Countries (LMICs) have been blamed on a lack of awareness of antimicrobial resistance (AMR) and a lack of information about the best use of antimicrobials such as antimalarials and antibiotics [37,38]. In LMICs countries, data on resistance, incidence, and antimicrobial use is lacking. Therefore, there is a need for efficient antimicrobial resistance surveillance to develop disease mitigation strategies and promote rational prescribing by health professionals by providing relevant data [39].

Development of multidrug resistance and resistance to last-resort antibiotics

The multidrug resistance for *Mycobacterium tuberculosis*, *Salmonella*, and *Shigella* microbes are more prevalent in some tropical countries. The resistance to penicillin is mainly seen in *Streptococcus pneumonia* and *Neisseria gonorrhoea* [40]. From 2002 to 2004, surveillance research in seven Asian nations (Korea, Taiwan, Vietnam, Philippines, Singapore, Hong Kong, and Sri Lanka) found high rates of resistance to ampicillin (44%), chloramphenicol (46%), TMP-SMZ (43%), and tetracycline (43%). MDR strains accounted for 41% of the total. None of the bacteria was resistant to ciprofloxacin and ceftriaxone. MDR strains were 30% more common in Vietnam than in the other six nations [40].

The last resort treatment (carbapenem antibiotics), such as imipenem, meropenem, ertapenem, etc., is ineffective in more than half of the patients treated for *K. pneumonia* infections in several countries to the development of resistance. *E. coli* resistance to fluoroquinolone antibiotics, which are used to treat urinary tract infections, is widespread. In many regions of the globe, this therapy is no longer effective in more than half of the patients. Colistin is the sole last-resort therapy for infections caused by carbapenem-resistant Enterobacteriaceae that are life-threatening (i.e. *E. coli*, *K. pneumonia*). Bacteria resistant to colistin have been found in several nations and areas, producing illnesses for which no treatment is available [41].

Impact of AMR on community and hospital sites

In the 21st century, the discovery of newer antimicrobial drugs slowed down. As a result, there is a sharp rise in infection rate caused by resistant organisms such as *Enterobacter* species, *K. pneumonia*, *S. aureus*, *Acinetobacter baumannii*, *Enterococcus faecium*, led to soaring up of cases of inpatient rates in hospitals. It accounted for increased hospital stay and healthcare expenses, resulting in a higher death rate [42–47]. When a patient infected by a drug-resistant strain gets admitted to the hospital, it is primarily a cause for introducing drug-resistant organisms into a healthcare setting; these resistant organisms can transmit from one individual to the other [48]. Another critical component in the spread of such organisms is the unhygienic practices by healthcare personnel, infected surgical or medical devices, or contaminated objects in the hospital area. This form of dissemination and spread of drug-resistant microbe where a single microbe strain is transferred is the clonal transmission. Vancomycin-resistant enterococci, *Clostridium difficile*, Methicillin-resistant *S. aureus* (MRSA), and the gram-negative bacteria leading to multidrug-resistant outbreaks are linked to clonal transmission [49–51]. MRSA is among the most often diagnosed antimicrobial bacteria among hospital patients, despite significant variance in rates in different countries and among various hospitals [52].

Various species of Enterococcus bacteria can produce severe, deadly infections but are less pathogenic than *S. aureus*. Enterococci become resistant to vancomycin by producing specific precursors from the cell wall, which inhibit the binding to glycopeptides [53]. Penicillins (along with those paired

with β -lactamase inhibitor), cephalosporins, fluoroquinolones, trimethoprim-sulfamethoxazole, and aminoglycosides are often resistant against multidrug-resistant gram-negative bacteria. Colistin remains the sole treatment option for certain diseases when infecting bacteria resistant to carbapenems [54].

Community-acquired infection

AMR surveillance is required to curate empiric treatment regimens for infectious diseases [55]. Unfortunately, there is an immense shortage of study data in this region related to population-based epidemiological studies which emphasize the causes of community-acquired infection.

A study conducted among children less than five years of age revealed bacterial resistant strains of *S. pneumonia* and *Haemophilus influenzae* responsible for more than 65% of total deaths in South Asia and South-East Asia [56]. Another retrospective study conducted in Pakistan held irrational use of antibiotics responsible for the development of AMR [57]. In LMICs, antibiotic overuse and consequent AMR have higher development rates than in developed countries due to a variety of reasons, including inadequate cleanliness and overcrowding [58]. In low- and middle-income countries (LMICs), limited research is conducted on the mortality caused by multidrug-resistant (MDR) bacterial infection. The 30-day mortality result was obtained in a retrospective study from microbiology laboratory and hospital databases of nine public hospitals in northeast Thailand from 2004 to 2010 and connected to the national death registry. The 30-day death rate was 35% (549/1555) [59]. Viral infections had caused nearly 9% of total mortality in these regions, and influenza and the respiratory syncytial virus remained the prime cause of viral disease among children aged less than five years [60].

Hospital-acquired infections

Resistance rates for organisms isolated from bloodstream infections were greater in hospital-acquired/health-care-associated infections than in community-acquired infections [61]. The leading cause for hospital-acquired infection (HAI) is surgical site infection (SSIs) and those associated with devices. In a study conducted on HAIs, it was observed that there was a higher rate of HAIs and SSIs in developing countries than in developed nations [62]. The data suggested that, on average, the rate of HAIs in developing countries was 15.5% compared with developed countries like the USA, where the rate was 4.5%. In a retrospective study on 3424 patients in Thailand, the most widely causing hospital-acquired bacteremia was *Acinetobacter* sp. It caused infections in the blood, urinary tract, and lungs and accounted for 16.2% of total infections; the next causative bacterial organism was *K. pneumoniae* accounting for 13.9%. The other infections causing microbes were *E. coli*, *S. aureus* and *Pseudomonas* species [63]. There is considerable AMR in LMICs, according to data from the early setup of the global AMR surveillance system (GLASS) from 2017 to 2018; in Malawi, ceftriaxone resistance was more than 75% of 401 *K. pneumoniae* isolates and 964 *E. coli* isolates from blood cultures. Almost 75% of *K. pneumoniae* isolates in India were cefepime resistant, with approximately 50% resistant to carbapenems. According to estimates, more than 40% of *Acinetobacter baumannii* isolates were carbapenem-resistant in most South (India and adjacent countries) and Southeast Asian nations. In South Asia, rates of Carbapenem-Resistant Enterobacteriaceae exceeded 10%, whereas rates in Southeast Asia were lower, but growth rates were found [64]. US Centers for Disease Control and Prevention (US CDC) National Healthcare Safety Network (NHSN) reported device-associated infections to be significantly higher in India than that in the USA [65].

In a study conducted in India, evaluation of the infrastructure, staff, and other factors at 51 hospitals concerning the

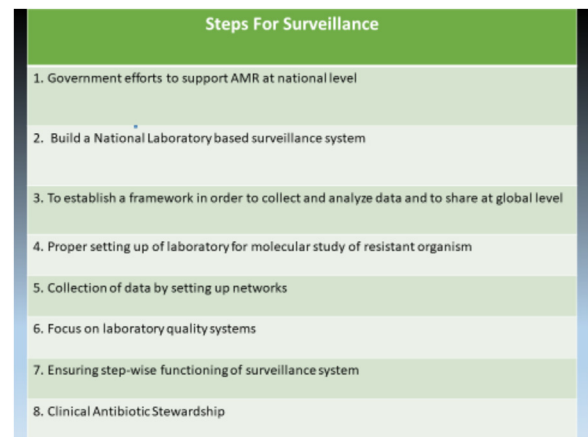


Fig. 2. Surveillance steps in infection prevention and control.

Antimicrobial-stewardship program (ASP), education, and training was conducted [66]. As per the report, 69% of respondents got some antimicrobial prescription instruction and training during pre- or post-graduation training. However, no formalized teaching program covers all aspects of ASP. Implementing IPC and ASPs can improve AMR surveillance by increasing diagnostic laboratory services and diagnostic stewardship [67,68].

Inadequate surveillance of AMR in LMICs

There is a high level of antimicrobial resistance (AMR) in many LMICs, and the primary reason behind it is the inadequate and reliable data on surveillance systems in these countries. Many health professionals tend to prescribe broad-spectrum antibiotics that lead to more severe resistance problems causing the pathogen to destroy the patient's microbiome [69,70]. Surveillance is an integral part of any AMR containment plan because it provides the data needed to discover an AMR problem. The hurdles to creating surveillance systems are massive, especially for developing countries, including the need for substantial initial investment. Community participation is essential to building effective monitoring systems. Global collaboration is required to ensure the rational use of antibiotics [71]. Collignon et al. studied in 63 countries the antibiotic use practices and how socio-economic factors affected the spread of AMR in these countries. The findings exhibited that providing better sanitation, promoting efficient governance, enhancing access to safe drinking water, improving public health-care by boosting expenditure and effective management of the private health sector was crucial for lowering AMR. Surveillance methods included in the government's infection prevention and control strategy in LMICs at the national level may be a more effective tool for the fight against AMR (Fig. 2). To reduce the burden of AMR worldwide, in 2015, a Global AMR Surveillance System was launched by WHO in which 40 countries participated; it aims to collect and analyse AMR. The systems like GLASS could create meaningful data, enhance analysis and impact the policies of nations using immunological, clinical and demographic-based data from these nations [72].

Fig. 2 illustrates the surveillance stages involved in the government's infection prevention and control procedure. After that, provide a system for collecting, analyzing, and sharing data on a worldwide scale. It is necessary to build up a competent laboratory with data collecting to comprehend resistant species' molecular research. To concentrate on laboratory quality systems, the step-by-step operation of monitoring systems, and establishing clinical antibiotic stewardship programs (ASPs).

Current surveillance practices in LMICs

As per the WHO Global Action Plan on AMR, the progress on AMR National Action Plans has shown that Thailand and Pakistan have approved and executed AMR action plans. Nepal, Laos, and Cambodia have yet to do so, while India, Bangladesh, and Vietnam are still implementing them. The data highlights a significant variation in capacity for surveillance in these countries [63].

Bangladesh began working on developing a national AMR monitoring program in 2016. Ten hospitals will carry out the monitoring activities throughout the country's eight divisions, where data collection is ongoing. India is aiming to develop a human AMR monitoring network, and it has recently made significant progress. In 2018, the AMR monitoring network gained ten other regional tertiary care institutions, increasing the total number of hospitals in the network to twenty. Thailand is one of the few Southeast Asian nations having a functioning AMR surveillance system, and it is continuing to extend its network. Since 2005, the National AMR Surveillance Center has been a WHO Collaborating Centre for AMR Surveillance for Southeast Asia [63].

Lack of capacity in the rural setting is another major hurdle in the surveillance of AMR. The data gathered from community-based settings can help treat patients without specific antimicrobial-susceptibility testing. However, surveillance is necessary as the resistance may vary with different geographical regions [73].

Antimicrobial control strategies

It is reported from various studies that irrational medication use leads to severe financial and social implications for patients and the general population. Therefore, WHO has conferred irrational prescribing as a chronic illness of the healthcare sector where treatment of such chronic illness is challenging to achieve, but prevention is attainable [74,75]. In recent years, several pharmaceutical companies have shifted their research focus to treating chronic diseases, owing to the potential for increased sales and profitability. However, on the other side, we have seen the development of new antimicrobials for Hepatitis C and new vaccines developed for COVID-19 based on incentives. In addition, the WHO and other agencies have advised decoupling research and development expenditures from manufacturing costs to encourage the development of new antibiotics. We saw the success of this model with the development of the Oxford/Astra Zeneca COVID-19 vaccine funded by the UK government and Astra Zeneca becoming the manufacturer.

Inadequate sanitization and overcrowding are among the major contributing factors to the spread of microorganisms resistant to antimicrobials. Resistant microbes can be transmitted from human-to-human contact by touching surfaces or objects through contaminated food, water, or various carriers [76]. Therefore, the WHO's World Health Assembly approved a Global Action Plan on Antimicrobial Resistance (GAP on AMR) in May 2015. In water, wastewater, and faeces, AMR elements such as resistant bacteria, antibiotic resistance, and antibiotic residues are ubiquitous. As a result, GAP concentrates on recognizing and addressing the role of water, sanitation and hygiene (WaSH) in combating AMR, particularly antibiotic resistance [77].

As per the recent report on "Situational analysis of antimicrobial resistance in the South-East Asia Region", 2018, Bangladesh showed improved results. The modern pharmacy regulation system prohibits the sale of antimicrobials without a prescription and regulates a complete list of medicines for OTC sale in the country. North Korea has developed successful access to well-regulated water supply and nationwide coverage of sanitation and hygiene with WASH practices. These measures have helped the government to

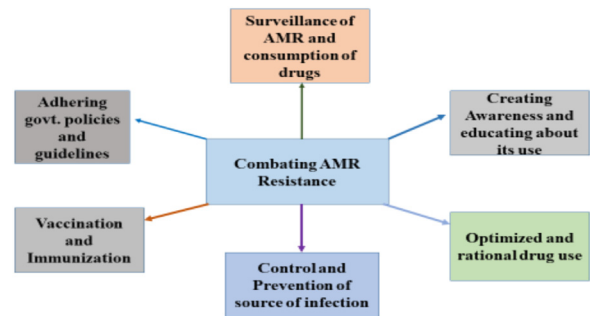


Fig. 3. Strategies to curb AMR menace.

achieve significant progress in adherence to safety measures. These accomplishments highlight the importance of these steps in counteracting AMR conditions that are constantly evolving. In India, the launch of the Swachh Bharat Abhiyan, Kayakalp (rejuvenation) and Swachh Swasth Sarvatra (war against impurity) programs have been cited as effective examples of how to raise awareness and information about AMR. These efforts promote behavioural changes in a variety of people and active participation from all segments of society in the effective promotion of hygiene and Infection Prevention and Control (IPC) programs [78]. In addition, we have seen a growth in country National Action Plans to help address concerns with AMR. These action plans include increasing awareness by establishing and aiding with the implementation of local AMR training and educational programmes, beginning conversations about the rational use of antimicrobials, improving equitable access to antimicrobials and lowering prescription prices.

Adequate legislative, institutional, and regulatory frameworks and networks must be developed [79]. The challenges include inaccessibility to effective antimicrobial therapy, a lack of regulation encircling antimicrobial use in humans and animals, a lack of monitoring of antimicrobial use and resistance levels, a shortage of updated antimicrobial treatment protocols, and a scarcity of upgraded antimicrobial treatment guidelines [78].

The primary mode of prevention of infectious disease is through vaccines. After getting vaccinated, a person develops protection against pathogens, and the intensity of illness also reduces [80–82]. Unfortunately, vaccines have a long history of being underappreciated as strategies for lowering AMR, even though their effectiveness in lowering AMR is widely documented. For example—*Haemophilus influenzae* type B (Hib) and *Streptococcus pneumoniae* (pneumococcal) conjugate vaccines have a long record of avoiding life-threatening illnesses caused by these bacteria and lowering antibiotic usage and AMR. Hence, vaccines over antibiotic might be considered an alternative as vaccines may target more than one organism, and they are less likely to produce resistance [83]. But the availability and use of vaccines for the commonly found pathogens in the community and hospitals are still limited. Currently, prophylactic antibiotics are still crucial for preventing surgical-site infections. Moreover, reducing AMR rates requires multiple coordinated activities across all sectors driven by Governments and others (Fig. 3) [84]. It is essential as we have seen excessive antimicrobial use in patients with COVID-19 driving up AMR rates and accelerating the threat of antimicrobial resistance [85,86].

Fig. 3 depicts strategies to combat the AMR threat, including monitoring AMR and drug consumption, raising awareness and educating about its use, optimizing and rational drug use, controlling and preventing infection sources, vaccination and immunization, and adhering to government policies and guidelines.

The use of bacteriophages is a modern tool for the treatment of bacterial infections. Bacteriophages are a group of bacterial virus that enters the bacteria and cause lysis of the bacteria. There is a vast scope in the phage treatment with the growing resistance and fewer newer antibiotics in the market [87]. Faecal transplant therapy or the use of probiotics has been done for a long time in the past [88–90]. In this therapy, the faecal matter of the healthy person, free from pathogens, is grown to multiply for the recipient's microbiota. Probiotics act by destroying pathogenic microbes by producing bacteriocins and organic acids, which help to improve digestion and absorption by stimulating the intestinal immune responses. Some examples of probiotics are *Pseudomonas*, *Lactobacillus*, *Streptococcus*, *Aspergillus*, etc.

There is a vital requirement for advanced training and educational strengthening in prescribing antimicrobials for health professionals. It is required that prescribing be done on scientific grounds, and at the academic level, professionals' curriculum should be developed to provide real-life prescribing skills. Several studies stress the requirement for the need to take steps to tackle the menace of irrational prescribing. Training professionals are essential in improving the irrational prescribing and combating AMR by prescribing safer and effective medicines to the public [91–94].

Role of Stakeholders and govt. regulatory agencies

The current global threat of antimicrobial resistance and the demanding need to control it and find new antibacterial products has prompted various stakeholders to work together to integrate research and public health and maintain and promote the national and international antimicrobial resistance research community [90]. The World Bank (2017) estimates that even in a low-AMR scenario, the loss on global output due to AMR could exceed US\$1 trillion annually after 2030, and potentially up to US\$3.4 trillion annually if not addressed, equivalent to 3.8% of annual Gross Domestic Product (GDP), with the costs of AMR significantly exceeding those of antibiotics prescribed [84]. Many low- and middle-income nations already have high levels of resistance, which are expected to rise excessively in the future. For example, resistant microbes cause 40–60% of morbidity and mortality in Brazil, Indonesia, and Russia. Resistance is expected to grow 4–7 times faster in these nations than in other European countries [95]. Stakeholders should form a coalition to address the need for novel antibiotics and their safe usage [96]. The adoption of specifically designed labels to designate all imported antimicrobials is one of the distinctive methods are done to raise awareness of the rational use of antimicrobials. Patients, prescribers and dispensers should be educated. Existing infection control programs should be better implemented; pharmaceutical company activities within hospitals should be monitored, and the use of antimicrobials for growth promotion in animals and plants should be phased out if they are also used in humans [97].

Irrational use of medicines shows significant pitfalls in the functioning of regulatory agencies. Since 2014, the United Nations (UN) and the World Health Organization (WHO) have issued actions against AMR, which have prompted the formulation of national strategies as well as the execution of particular initiatives ranging from heightened vigilance against AMR [98]. Another initiative is the breaking down of antibiotics into Access, Watch and Reserve (AWaRe), which is increasingly being used to assess and guide future prescribing [99].

Further studies are required to increase knowledge on the modifiable variables that drive disparities in antibiotic usage across nations; and changes in consumption over time, especially in developing countries [100,101]. Therefore, we expect to see activities

surrounding the AWaRe list grow to improve antibiotic use and reduce AMR.

Strategies built at Government Level

It is prudent to establish a national committee to track antibiotic resistance and offer inter-sectoral coordination. According to the WHO, such a council would develop AMR policies and recommend standards, legislation, training, and public awareness about antibiotic usage and AMR. Furthermore, WHO advises that all retailing outlets be registered, antimicrobials be provided exclusively on prescription, all manufacturers report antimicrobial distribution information, and incentives are provided for rational antimicrobial usage. Other critical national measures include adopting and implementing federal standard treatment guidelines, having an essential drug list (EDL), and increasing vaccination coverage.

For many years, the WHO has been striving to fight substandard and falsified medications. However, the progress has been seen with the launch of the recent WHO Lomé Initiative by the governments of African countries, which signed a political statement pledging to combat fake and substandard medicines together across the borders to maintain the integrity of the supply chain to counteract AMR [102].

A policy for the mitigation of AMR was created in 2011. The policy aims to comprehend AMR formation, dissemination, and causes impacting it and establish antimicrobial programs, rationalize antimicrobial usage, and support the development of newer, more effective antimicrobials. In addition, developing an AMR surveillance system, increasing infection prevention and control measures, educating, training and motivating all the stakeholders regarding the rational use of antimicrobials were some of the immediate action items listed in national policy. According to the WHO, only around half of all nations have basic procedures and controls, ensuring that medications are used correctly.

There have been multiple activities to improve antimicrobial use and stabilize limited use among countries such as Azerbaijan. After the price revisions, wholesalers and companies have to bear significant penalties if a pharmacy sells medicines to customers at rates that are not controlled. Consequently, overall antibiotic consumption in Azerbaijan has been steadily declining in recent years [103]. Over the last decade, the prescription limitations and audits were the most effective intervention in Slovenia, resulting in lower use of limited antibiotics than nonrestricted antibiotics [104]. In recent years, the Republic of Srpska had shown a lower consumption rate of antibiotics which could be to the Republic's healthcare and health-insurance laws ensuring all patients have access to good healthcare services, including medications and other forms of therapy [105]. It contrasts with Poland, where the authorities and other groups have only instigated limited activities, which has resulted in Poland having one of the highest rates of antimicrobial consumption in Europe between 2007–2018 [106].

Antimicrobial stewardship program

The concept of antimicrobial stewardship (AMS) is becoming more widely recognized component of practice for healthcare institutions to embrace and effectively implement. As far as morbidity, mortality, and healthcare expenditures, are concerned, antimicrobial resistance and abuse are rising. Thus AMS programs are becoming more common [107]. Antimicrobial stewardship has three objectives: the first objective is to work with healthcare professionals to ensure that each patient receives the most suitable antibiotic at the right dose and duration. The second objective is to prevent the overuse and misuse of antimicrobials. Antibiotics are not meant for prescribing in patients with viral infections and in processes that are not infectious—for example, febrile patients with

pancreatitis, bacterial infections that can be treated with incision or drainage. Antimicrobial overuse can be defined as the frequent use of one specific antibiotic preferentially over others by the prescriber due to relentless detailing by marketing representatives or, worse, due to financial interests. The third aim is to keep the development of antimicrobial resistance to a minimum. Antibiotic-exposed patients are more likely to get infected or colonized by resistant organisms [108]. The benefits of ASPs often result in downstream consequences that extend beyond antimicrobial use to better or maintained patient outcomes, lowering resource use and related costs [109]. These also include creating criteria for particular indications, tracking future use against these standards, and prompting clinicians to frequently evaluate antibiotic prescriptions [84].

Due to resource (financial and human) issues, we know that ASPs are more challenging in LMICs, due to resource (financial and human) issues. Still, we have seen this growing in Africa, where online free-of-charge training modules are progressively being produced [110]. In addition, the implementation of antimicrobial stewardship programmes in African countries has seen better results in Kenya, South Africa, and Tanzania, among the seven nations having national action plans on AMR [111].

- a **In Hospitals**—Key areas in hospital to reduce antibiotic use/AMR and ensure frequent hand washing, improve empirical antibiotic usage via establishing treatment advice based on local antibiograms, and regularly monitoring the situation. Furthermore, decreasing the overuse of antibiotics to avoid surgical site infections, such as extended administration following surgery due to ward cleanliness concerns, etc. Antibiotics are often used in hospitals to prevent SSIs. Many LMICs have implemented a variety of interventions to enhance surgical antibiotic prophylaxis (SAP), which has been split down into education, engineering, economics, and enforcement when applicable, as well as by year to give direction [112].
- b **In Ambulatory Care**—It is a crucial area since most antibiotics are prescribed here. The most inappropriate use (prescribing and dispensing without a prescription) is essential for viral infections like URTIs. Furthermore, there are a variety of measures that may be used to boost vaccination rates, even during pandemics [84]. These include, when appropriate, further education and training for doctors, including improved communication skills with patients, greater monitoring of antibiotic prescription for URTIs, and the use of quality indicators. There is also a need for educational campaigns for community pharmacists and the implementation of recommendations for patients with URTIs, and better antibiotic monitoring throughout the supply chain [113].

The situation among community pharmacists is trickier, and the situation may become problematic in rural areas of LMICs where the community pharmacists may be the only healthcare professional available. In addition, in countries with hefty co-payments and limited incomes, community pharmacists are more accessible and only paying for medicines. In this situation, banning self-purchasing without a prescription could be counterproductive. Monitoring pharmacy dispensing operations using mobile technologies and putting in place information technology (IT) surveillance systems to follow antibiotics along the supply chain are all possible techniques to prevent improper distribution [84]. Education on ASPs is also crucial, as it builds on pharmacists' potential role in leading ASPs in the community in the future after existing hurdles and limits are eliminated [113]. Multiple activities appear to be the primary way forward in developing and implementing national guidelines towards reducing AMR. Even though community health campaigns in LMICs are more complex, pharmacists should take the lead in enhancing antibiotic usage in the

community and reducing antimicrobial resistance by advocating pharmacists as antibiotic guardians [114].

Discussion

Antibiotics are one of the most powerful weapons to combat infections. The problem is that our battle with microbes will not end just by discovering novel antibiotics, and the fact is that this battle indeed will never end. However, it is our responsibility to use this weapon judiciously to pass it on to our future generations. It is said that “to prescribe a powerful new antibiotic is very easy but to protect it is very hard”. To control AMR, we as humans must not repeat the mistake of unrestrained antibiotic use in future.

The irrational prescribing by health professionals and the misuse by the patients is leading to fast-paced antimicrobial resistance. The spectrum of options to treat infectious diseases is decreasing rapidly and, if left unattended, may lead to health care crises in future. The majority of effort worldwide is directed towards healthcare professionals' training, so the rational prescribing of antibiotics is promoted. However, the public is also a massive contributor to the rising rate of antimicrobial resistance as they are not aware of the phenomenon of antibiotic resistance and thus rampant misuse due to easy availability without prescription and physician's consultation leads to abuse. This misuse results from acquiring antibiotics without consultation and proper diagnosis, stopping antibiotic course midway on relief of symptoms, using leftover medications from the previous prescriptions and sharing antibiotics with family and friends for similar symptoms. Thus the guidelines and policies need to be made at the national level to educate the general public through awareness programs about the rational use of antibiotics and the implications of antibiotic resistance. Healthcare professionals and pharmacies should be held accountable for the unreasonable prescribing and dispensing of antibiotics. In some of the LMIC, the guidelines and policies are in place to counteract AMC, but they are not followed. Authorities must ensure that the stakeholders abide by the regulations.

Besides this, there is market failure in discovering newer antibiotics on the pharmaceutical front. The sharp decline in investments in antibiotic research by pharmaceuticals is due to poor returns in investments. Some regulations and incentives must be in place to encourage the pharmaceutical companies to reengage in discovering novel antibiotics. There is also an urgent need to rekindle the research and development by finding new screening methodologies to find new antibiotics.

The quantum of antibiotic resistance development is understated in most LMIC. More studies need to be undertaken to know the real stature of AMR resistance and its impact on human health. Research should also focus on studying the loopholes in the government system or policies responsible for the failure of AMR resistance control programs. Finally, it is crucial to have awareness and stringent vigilance at community, hospital, and pharmacy levels to battle the AMR.

Global strategies need to be instituted to have uniform policies for controlling AMR, which not only be limited to the rational use of antibiotics or the development of new ones but should also be directed at ensuring a hygienic environment to slow the rate of acquiring infectious disease but also its spread.

Conclusion

Antimicrobial resistance is a global concern to human health. Antibiotic misuse and overuse lead to the development of antimicrobial resistance. Infectious diseases are common in underdeveloped nations, exacerbated by malnutrition and a lack of sanitation. One of the most significant contributors is self-

medication. There has also been a tendency of AMR spreading in hospitals. The actions that can prevent the emergence and spread of antibiotic resistance at the global level are rational antibiotic usage in all contexts, application of infection control methods in healthcare settings, creation of techniques to minimize the hazards of environmental exposure, development of quick diagnostic tests, and antibiotics research promotion. Vaccination can help prevent AMR, although it is not 100% effective. All parties (policymakers, public health authorities, regulatory agencies, pharmaceutical firms, and the scientific community) need to work together to implement these measures.

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