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REVIEW

Antimicrobial Stewardship: Fighting Antimicrobial Resistance and Protecting Global Public Health

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Abstract: Antimicrobial resistance (AMR) is a serious threat to global public health. It increases morbidity and mortality, and is associated with high economic costs due to its health care burden. Infections with multidrug-resistant (MDR) bacteria also have substantial implications on clinical and economic outcomes. Moreover, increased indiscriminate use of antibiotics during the COVID-19 pandemic will heighten bacterial resistance and ultimately lead to more deaths. This review highlights AMR's scale and consequences, the importance, and implications of an antimicrobial stewardship program (ASP) to fight resistance and protect global health. Antimicrobial stewardship (AMS), an organizational or system-wide health-care strategy, is designed to promote, improve, monitor, and evaluate the rational use of antimicrobials to preserve their future effectiveness, along with the promotion and protection of public health. ASP has been very successful in promoting antimicrobials' appropriate use by implementing evidence-based interventions. The "One Health" approach, a holistic and multisectoral approach, is also needed to address AMR's rising threat. AMS practices, principles, and interventions are critical steps towards containing and mitigating AMR. Evidence-based policies must guide the "One Health" approach, vaccination protocols, health professionals' education, and the public's awareness about AMR.

Keywords: antibiotics, antimicrobial resistance, multidrug-resistant, antimicrobial stewardship program, One Health, global health

Introduction

"As we gather more evidence, we see more clearly and more worryingly how fast we are losing critically important antimicrobial medicines all over the world." Dr. Tedros Adhanom Ghebreyesus, Director-General of the World Health Organization.[1]

Antimicrobial Resistance (AMR)

Antimicrobial resistance (AMR) is one of the biggest global public health challenges that currently affects humans, animals, and environmental health.[2,3] Although it is a natural evolutionary phenomenon, AMR's emergence and spread continue to pose serious threats by the overuse and misuse of antibiotics in humans and animals.[4] AMR impacts financial sustainability, global health, food sustainability and security, environmental wellbeing, and socio-economic development.[5,6] AMR has led to adverse consequences, including severe illnesses, more prolonged hospital admissions, increased healthcare costs, an overburdened public health system, higher costs in second-line-drugs, treatment failures, and even increased mortality rates.[5–7] In recent decades, the development of new antibiotics has

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declined sharply.[8,9] Moreover, existing antibiotics lose effectiveness due to AMR.[1,4–7,10] World Health Organization's (WHO) recent report (Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report: Early implementation 2020) published some alarming AMR rates from 78 countries (Box 1).[11]

AMR: Clinical and Financial Burden

AMR is responsible for the substantial clinical and financial burdens on the health care system, patients, and their families.[12–15] Every year at least 700,000 people succumb to AMR. If this uncontrolled pattern continues, a cumulative cost of US $100 trillion will develop by 2050, undermining the economy which will be comparable with the 2008 financial crisis.[14] AMR also threatens many sustainable development goals (SDGs).[14,15] Annually 33,000 people will die in the European Union and European Economic Area (EU/EEA) due to an infection with a resistant bacterial strain by 2050.[16] The hospital stays for patients with AMR averages around 13 days, causing an additional 8 million hospital days annually, costing up to US $29,000 per patient.[17,18] Table 1 shows the effects of antimicrobial resistance in health care systems by highlighting the estimated cases in hospitalized patients, deaths, and attributable healthcare costs in the USA.[19]

Box 1 Glass Report – Highlights of Reported Resistance

1. High rates of AMR observed against common bacterial infections
2. Median frequency of resistance in pathogens isolated from patients with bloodstream infections
   i. Methicillin-resistant *S. aureus* (MRSA): 12.11% (IQR 6.4–26.4)
   ii. *E. coli* resistant to third-generation cephalosporins: 36.0% (IQR 15.2–63.0)
   iii. *K. pneumoniae* resistant to third-generation cephalosporins 57.6% (IQR 33.4–77.8), with 12 countries reporting 80–100% resistance
   iv. *Acinetobacter spp.*: aminoglycosides 41.2% (IQR 5.20–83.31); carbapenems 63.2% (IQR 19.78 −81.63)
3. Median resistance to ciprofloxacin in urinary tract infections
   i. 43.29% (IQR 23.8–46.4) for *E. coli* in 33 reporting countries, territories and areas
   ii. 38.1% (IQR 8.41–63.53) for *K. pneumoniae* in 34 reporting countries, territories and areas

Note: Data from World Health Organization.[11]

Multidrug Resistance (MDR)

The AMR situation became further aggravated by multidrug resistance (MDR), one of the most significant clinical practice challenges.[20,21] Globally about 500,000 new cases of multi-drug-resistant tuberculosis (MDR-TB) are diagnosed yearly.[22] In 2018, 87% of new TB cases occurred in 30 countries in Asia, Africa, and Latin America.[21] The highest rates of drug-resistant tuberculosis (TB) have been reported from the European region, with an estimate of 77,000 people ill with MDR-TB/year and 966 cases of extensively drug-resistant TB (XDR-TB), ie, 23% of the global MDR-TB burden.[23] Most of the ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter species*), the leading causes of life-threatening nosocomial infections amongst critically ill and immunocompromised

Table 1 Impact of Antimicrobial Resistance in Health Care Systems

Organisms	Threat Level	Estimated Cases in Hospitalized Patients (2017)	Estimated Deaths (2017)	Estimated Attributable Healthcare Costs (2017) US
Carbapenem-resistant *Acinetobacter*	Urgent	8,500	700	$281M
Clostridioides difficile	Urgent	223,900	12,800	$1B
Carbapenem-Resistant Enterobacteriaceae	Urgent	13,100	1,100	$130M
Drug-Resistant *Neisseria gonorrhoeae*	Urgent	550,000	1.14M	$133.4M
Vancomycin-Resistant Enterococci (VRE)	Serious	54,500	5,400	$539M
Multidrug-Resistant *Pseudomonas aeruginosa*	Serious	32,600	2,700	$767M
Methicillin-Resistant *Staphylococcus aureus*	Serious	323,700	10,600	$1.7B
Extended-Spectrum Beta-Lactamase (ESBL) Producing Enterobacteriaceae	Serious	197,400	9,100	$1.2B
Drug-Resistant Tuberculosis (Tb)	Serious	847	62	$164,000 Per MDR case $526,000 Per XDR case

Note: Data from Centers for Disease Control and Prevention.[19]

individuals are multidrug-resistant isolates and these pose most significant challenges in clinical practice.[20]

COVID-19: Extra Burden on AMR

The Coronavirus disease, COVID-19, is a new threat to global public health. Many COVID-19 patients with mild disease without pneumonia or moderate disease with pneumonia take antibiotics (eg, azithromycin), which are not recommended by health authorities.[24] WHO has already warned that "increased use of antibiotics to combat the COVID-19 pandemic will strengthen bacterial resistance and will lead to more deaths during the crisis and beyond".[25] The pandemic may threaten antimicrobial stewardship (AMS) activities and increase AMR.[25,26] While reviewing antimicrobial prescribing in COVID-19 patients, it was found that 72% of 2,010 COVID-19 patients received broad-spectrum antimicrobial therapy in the hospitals, although only 8% suffered bacterial and fungal co-infection.[27] This antimicrobial prescribing pattern could increase the long-term threat of AMR.[27,28] WHO has discouraged the "inappropriate use of antibiotics, particularly among patients with mild COVID-19 symptoms".[29] Furthermore, increased antimicrobial use may occur due to increased hospital admissions during the COVID-19 period, which in turn may pose the risk of health-care-associated and multidrug-resistant infections.[30]

The Paucity of New Antibiotics! A Need for Urgent Action

Experts have declared that we are close to the age of no effective antibiotics as the crest of the AMR challenge appears.[31,32] Since the late 1990s, the discovery and development of new antibiotics have slowed dramatically, where only three new antibiotics received FDA approval in the last 30 years.[8,9] Two recent WHO reports on clinical and preclinical drug development highlighted a weak pipeline for antibiotic agents, which may threaten global efforts to contain drug-resistant infections.[33,34] The majority of 50 antibiotics in clinical studies in the drug development pipeline have limited benefits, and 252 products in the preclinical phase of the drug development are in the very early stages of testing and might be available in about ten years.[33–35] Due to the drought of new antibiotics and the withdrawal of some major pharmaceutical companies from the field of antimicrobials, WHO recently issued a fresh warning regarding the global threat of AMR.[34] To exacerbate the AMR threat, major pharmaceutical companies involved in AMR research have left the market due to a "lack of incentives" and dwindling funding.[36] Two recent WHO reports confirmed that clinical and preclinical drug development is predominantly driven by the small- or medium-sized enterprises (SMEs), as large pharmaceutical companies continue to leave the business.[33,34] Furthermore, the level of research and development (R&D) investment in clinical development is insufficient to meet global health needs, in contrast to the more robust and vibrant preclinical biotechnology pipeline.[37] Hence, there is a paucity of new drugs in the research and development pipeline of the pharmaceutical industry.

Aim of the Review

Against this background, it is important that appropriate antimicrobial prescribing and stewardship strategies evolve to support rational treatment and prevent AMR's unintended consequences. This review highlights AMR's scale and consequences, the importance and implications of the ASP, to fight resistance and protect global health.

Literature Search

Relevant literature was searched using PubMed, Scopus, and Google Scholar using specific keywords, eg "Antimicrobial resistance," "Multidrug-resistant," "Antimicrobial Stewardship Program," "Monitoring and evaluation," "One Health," and "Global Health." Original studies, reviews, editorials, commentaries, perspectives, short or unique communications, and policy papers on antibiotic resistance and antimicrobial stewardship were reviewed. Information from Websites of different professional associations and international or national organizations were searched to extract relevant information.

AMS – Definition

Antimicrobial stewardship (AMS) is defined as "an organizational or healthcare-system-wide approach for fostering and monitoring judicious use of antimicrobials to preserve their effectiveness".[38] The concept of AMS was promulgated by the Infectious Diseases Society of America (IDSA) in 2007. It was originally defined as organized interpositions with the premise of improving antimicrobial use when selecting the appropriate agents, the correct dose, route of administration, and the duration of therapy without prejudicing patient outcomes.[39,40] AMS refers to a set of coordinated strategies to (i) improve patient care, and outcomes by optimal therapy; (ii) reduce collateral damage by reducing antimicrobial use (less resistance), and (iii) reduce the cost for antibiotics.[41] These strategies can be used globally to help control AMR by increasing awareness of the public and educating healthcare professionals on the prudent use of antimicrobials as part of an ASP. Overall, AMR should be considered a global priority, and all countries and organizations should make coordinated efforts to implement new policies and research concerning ASP.

History of AMS

In the 1940s, Sir Alexander Fleming warned about antibiotic resistance, and his prediction became true within ten years due to the misuse of the drugs.[42] Since then, educational programs, quality management protocols, and clinical guidelines were developed by infectious-disease professional organizations to prevent and control the problem however, these were found mostly ineffective.[42] In a 1996 article, McGowan and Gerding pioneered the term "antimicrobial stewardship," emphasizing that the process should be considered an integral "part of every antimicrobial treatment decision".[43] They included the term "Antimicrobial Stewardship" in the antibiotic resistance prevention guidelines published in 1997 by the Society for Healthcare Epidemiology of America (SHEA) and IDSA.[44] In 2007, IDSA and SHEA formally adopted the term in a "programmatic activity".[45] Later, the term was assumed by the two European scientists in 1999, Ian Gould and Jos van der Meer, who helped to disseminate it through their organization called the European Society of Clinical Microbiology and Infectious Diseases Study Group for Antimicrobial Stewardship. This helped to popularize the term worldwide.[46]

In the USA, CDC launched the first educational program in 2009 to advocate the rational use of antibiotics in acute-care settings and adopted improved antibiotic use as a strategy in 2013 to tackle the problem.[47,48] Various accrediting agencies have highlighted the need for and importance of antibiotic stewardship programs (ASPs) in clinical practice settings.[49] A study conducted in 2014 showed that only 39% of clinical practices had used antimicrobial stewardship programs.[50] In 2017, the government urged that all hospitals must have stewardship programs in their organizational mandates.[51] In Europe, many countries implemented cost-effective antibiotic stewardship programs nationally or regionally to raise awareness about adequate antibiotic use, facilitate monitoring and surveillance, and provide feedback on prescribing behavior; and implement cost-effective approaches.[52] In 2017, the European Commission issued guidelines on the prudent use of antimicrobials in humans[53] and published a report highlighting the countries' progress in AMS.[54] WHO (Europe Region) has published a review of public awareness campaigns in relation to AMS.[55]

Though AMS programs have proven to improve antibiotic use in developed countries, AMS strategies to contain AMR are unsuccessfully executed in developing countries[56] which has led to an urgency to establish, implement and evaluate effective AMS programs[57–59] in these territories. To tackle this emergency, in 2016, the WHO and the United Nations General Assembly ratified the implementation of AMS programs globally and at the institutional-level.[60–62] Recently, WHO published an AMS toolkit for developing countries and highlighted the importance of local context in developing and implementing AMS programs.[63]

AMS – An Integral Component of Health Systems

AMS is a collaborative, multifaceted, and multidisciplinary approach that engages healthcare leaders, microbiologists, infectious disease specialists, physicians, nurses, farmers, veterinarians, IT experts, and clinical pharmacists to improve patient treatment outcomes and safety by reducing AMR development.[64,65] With the growing reciprocity between human and animal health, "veterinary antimicrobial stewardship" focuses on animal health (livestock and companion animals).[46] The "One Health" concept birthed through a multidimensional organizational approach resulting in the provision of policies, guidance documents, improved surveillance, prevalence and incidence reports, education, and audit of practice internal and external to the healthcare institution.[46,66,67]

One of the three tenets of an integrated approach to health systems strengthening is AMS. The other two are infection prevention and control (IPC) and medicine, followed by patient safety. ASP's success is Infection Control Programs' (IPC) inclusivity as the individual aspects of an IPC cannot be performed independently.[68,69] Infection preventionists and healthcare epidemiologists are critical in ASP's deployment and success.[70] The optimization of antimicrobial usage assists AMS to control AMR when associated with antimicrobial use, surveillance, and the WHO essential medicines list (EML) AWaRe16 classification (ACCESS, WATCH, RESERVE). In combination with AMR surveillance and the adequate supply of quality-assured medicines, these three pillars promote equitable and quality health care towards the goal of achieving universal health coverage.[63]

These areas are intrinsically linked to the issues associated with antimicrobial agents' use, the proliferation and spread of AMR, education, and require filiation and structure across the various coincident disciplines and clinical settings.[69] This multipronged approach means with no transmission of infection, the need for antimicrobial treatment is eliminated, therefore decreasing resistance development.[71] In 2019, the CDC developed seven (7) fundamentals for ASP implementation (Box 2).[71] Notably, leadership and accountability are the first two principles, responsible for the program's deliverables and outcomes, followed by education and local antibiogram implementation. The administrative component includes education and the institution of local antibiograms, which hinges upon the principle that the appropriate empiric therapy is administered for common infections.[71] Actionable items such as the preauthorization of prescriptions and resistance surveillance are performed by pharmacists and laboratorians, respectively, where the requisite interventions can occur as dictated by institutional guidelines and policies.[72]

AMS – Importance for Patient and Public Health

With AMR being a well-documented phenomenon that portends public health stability and national security, it has been recognized as a global threat by WHO.[73] Public health organizations' affiliation with healthcare providers (HCPs) is crucial. It facilitates the creation of prevention strategies, the promotion of education, and surveillance, all in an effort to limit the advancement of AMR.[74] Daily, physicians are confronted by patients who are unresponsive to currently available antimicrobials, forcing them to use reserved antibiotics such as carbapenems and polymyxins, which are expensive and may not be readily available in some countries and can have potentially unintended consequences (eg, colistin and acute kidney injury).[7,75,76] Clinicians are dealing with a global challenge of Multi-Drug Resistant Organisms (MDROs) in the ESKAPE pathogens, notoriously branded as "bugs without borders"[20,67,77,78] and are nosocomial pathogens capable of "escaping" the biocidal action of antimicrobial agents.[78,79] The urgency of addressing AMR is well recognized through the innocuous and operative healthcare delivery via ASP.[7,75] Since its inception, ASP has proven highly successful in improving antibiotic use. Notably, the 4 Ds of optimal antimicrobial therapy are; right Drug, right Dose, De-escalation to pathogen-directed therapy, and right Duration of therapy and infection control. These are the guiding principles of ASP.[79,80] These strategies are closely aligned to the public health objectives and are not limited to promoting AMS strategies, monitoring, transparency of data, infrastructure building, and increased knowledge and awareness at the patient and HCP levels (Box 3).[74,81,82]

Box 2 Core Elements of the Antibiotic Stewardship Program

- Leadership commitment towards necessary human, financial, and information technology resources.
- Accountability through a single physician/pharmacist leader for program management and outcomes.
- Drug expertise through an only pharmacy leader to help lead implementation efforts to improve antibiotic use.
- Action to implement interventions, such as prospective audit and feedback or preauthorization, to improve antibiotic use.
- Tracking prescription, the impact of interventions, resistance patterns, and other important outcomes.
- Reporting prescription and resistance information directly to prescribers, pharmacists, nurses, and hospital leadership.
- Education for health care professionals (prescribers, pharmacists, nurses) and patients about adverse reactions from antibiotics, antibiotic resistance, and optimal prescribing.

Note: Data from Centers for Disease Control and Prevention.[71]

The lack of antibiotic development requires the conservation of existing ones. IDSA and other organizations support the institution of capable ASP geared towards preserving the use of effective drugs through improved resistance and infection surveillance, data collection, infection prevention, and other control measures to ensure the judicious use of new antibiotics.[83] Furthermore, to reduce selective pressures that favor highly resistant pathogens, a set of structured antimicrobial steward programs have been globally implemented in medical settings.[84]

Successful implementation has seen annual cost savings of stewardship programs at US $200 000–$900 000.[85–87] One glaring example is from the University of Maryland, the USA, where over 3-years, a stewardship program reduced approximately US $3 million in antibiotic expenditures. When the program was discontinued, an immediate increase in approximately US $2 million antibiotic expenditure was observed over the next two years.[85] In Barbados, the antimicrobials used to treat patients during a Klebsiella pneumoniae carbapenemase (KPC) outbreak in 2012 accounted for 64% of hospital costs

Box 3 Antimicrobial Stewardship Aligns with the 10 Essential Services of Public Health

- Antimicrobial susceptibility patterns and antimicrobial utilization trends monitor and detect at the national, state, regional, and community levels.
- Surveillance of antimicrobial susceptibility across nations, states, regions, and communities.
- The provision of information through education empowers patients, healthcare providers, and other agencies on appropriate antimicrobial use.
- Collaborate with the community's organization, such as non-governmental and governmental organizations geared towards patient safety regionally and nationally, hospitals, long-term care facilities, and healthcare systems in promoting antimicrobial stewardship strategies across regions, particularly with shared patient populations.
- Identify and share best practices and policies in AMS widely.
- Provide advocacy initiatives for promoting legislation to improve patient safety, reduce exposure, and develop resistant infections.
- Establish linkages amongst healthcare entities to enhance AMS across regions.
- Ensure effective ASP is established within healthcare facilities.
- Monitor and evaluate ASP towards improvement in healthcare facilities.
- The creation of innovative research solutions to obstacles in AMS implementation.

Note: Data from these studies.[74,81,82]

associated with those antibiotics.[88] There was a 60% decline in carbapenems and vancomycin.[63,88]

Notably, most studies on AMS focus on pharmacy costs for antibiotics. Other savings can be garnered with a reduction in lengths of stay and readmission rate, making it even more significant.[64] Importantly, disability-adjusted life years (DALYs) caused by five reported infections associated with antibiotic-resistant bacteria across various populations in Europe was substantial compared to other infectious diseases inclusive of all the associated factors.[89,90] Although these cost-benefits are actualized readily amongst infectious disease specialists, if the benefits are truly seen, they must be embraced by patient groups and non-infectious disease specialists as they fit within the context of improving patient safety and reducing health related costs associated with AMR.

Antibiotic resistance impacts the immune system's capacity to fight infectious diseases. It introduces complexity in managing patients undergoing chemotherapy, transplantation, and other care areas reliant on effective antimicrobial therapy since antibiotics cause dysbiosis or disruption in the commonly "diverse" intestinal flora or gut microbiome.[7,75,91,92] Similarly, the management of comorbid conditions like diabetes, asthma, and rheumatoid arthritis are significantly impaired by antibiotic resistance.[91]

To monitor, evaluate, and inform further action on AMR's dispersal, surveillance is essential at the local, national, and global levels and assesses the strategies employed.[93,94] The WHO launched GLASS in October 2015 to "strengthen knowledge through surveillance and research"[93] and provides a homogenous approach to AMR data collection, analysis, and dissemination by country, seeking to register the authenticity of existing or newly developed national AMR surveillance systems.[93,94] It promotes a system that includes epidemiological, clinical, and population-level data compared to reliance on laboratory data only.[93,94]

GLASS promotes integration with other surveillance programs in public health, the animal and environment sectors, facilitating the surveillance of resistance in eight priority bacterial human pathogens, some with links to the food chain, and monitors antimicrobial consumption by humans.[93,94] The Tripartite Collaboration with the UN Food and Agriculture Organization (FAO), the World Organization for Animal Health (OIE) and GLASS provides a comprehensive understanding of AMR across the multiple sectors to promote the One Health Approach AMR control.[93,94] A calculation of the extent of AMS integration within the whole health economy is critical in understanding how a "One Health" approach is incorporated in combatting AMR.[95] The concentration of AMS activity has been primarily hospital-based, which may be practical but artefactual. It fails to address the bidirectional flow between hospital and community care services as antimicrobial use in the community is associated with AMR development in and outside hospitals.[95,96]

The One Health perspective on integration involves multiple sectors communicating and working together to design and implement programs, policies, legislation, and research to achieve better public health outcomes. However, the approach must be influential and supervisory in nature for public engagement.[95,97] However, AMS's medical strategies cannot be adopted wholesale to veterinary medicine due to disparaging factors not limited to the lack of fund and expertise, topographical reach, political commitment, and nominal mechanization supporting the AMS veterinary sector.[98] With this in mind, strategies for AMS which are innovative and appropriate to the size, inclusive and resourceful will be required. Behavioral change is an important factor in the program's sustainability and has proven effective in improving antimicrobial prescribing.[98–100] To add further complexity, increases in local temperature have been implicated in higher antibiotic resistance levels in *Escherichia coli, Klebsiella pneumoniae*, and *Staphylococcus aureus*. Hence, climate change and population increases will contribute to AMR, giving credence to ASP's need.[101] Public health organizations are poised to promote AMS across all health care disciplines and institutions, ideally for the preservation of antimicrobials for future use, reduction in collateral damage, decreased morbidity and mortality, and a reduction in antibiotic selection pressures.[74]

Principles and Practice of AMS

The right antibiotic, for the right indication (right diagnosis), the right patient, at the right time, with the right dose, route and duration of therapy, causing the least harm to the patient and future patients. (www/cdc.gov/get smart/healthcare/inpatient-stewardship).[102] This definition outlines the fundamental principles of antibiotic prescribing. If implemented strictly, these principles ensure that healthcare professionals only prescribe antibiotics for non-self-limiting bacterial infections.[103] Formulary policies, such as monotherapy used instead of combination therapy, which covers the likeliest etiological agent or pathogenic organism relevant to the site of infection, should be employed whenever possible.[104] Combined therapeutic agents consisting of two or more drugs together from different classes lead to synergism, particularly against resistant Gram-negative bacteria. Narrow-spectrum antibiotics should be chosen with low resistance potential.[105,106] "Antibiotic adjuvants are non-antibiotic compounds that increase antibiotic activity either by blocking resistance or by boosting the host response to infection"[107] Antibiotic adjuvants are also known as antibiotic resistance breakers (ARBs).[108] Currently, multiple studies reported that novel antibiotic adjuvants strategy opens new window as a substitute, equilateral, and supportive path to combat AMR. Quite a few ARBs are now in clinical use. For example, compounds that hinder the β-lactamases that converse resistance to β-lactam antimicrobials. Furthermore, these new molecules improve efficacy (re-sensitizing resistant pathogens to antimicrobials)[108] of frequently used antimicrobials against MDR Gram-negative microbes by overcoming resistance and virulence of these pathogens.[107,109–112] Three different categories of antibiotic adjuvants currently available include: (a) β-lactamase inhibitors; (b) efflux pump inhibitors; and (c) outer membrane permeabilizer.[11,113]

Limiting the number of accessible antimicrobials through a selectively restricted formulary is the optimal way to regulate resistance. Restrictions are applied only to high resistance-potential antibiotics, for example, imipenem (not meropenem or ertapenem), ceftazidime (not other third or fourth generation cephalosporin), and gentamicin/tobramycin (not amikacin).[114] Antimicrobial cycling employs antimicrobial rotation to reduce the selection pressure on a particular drug with scheduled substitutions of a class (or a specific member of a class) and a different class (or a specific member of a class) that exhibits a comparable spectrum of activity (Box 4).

Front-end restriction requires preauthorizing certain antimicrobials by a member from the AMS team or based on a set of pre-authorized criteria determined by a pharmacist. Back-end restrictions refer to the review and intervention after the antimicrobial is prescribed by an AMS member who reviews current antimicrobial regimens. Prescribers are provided with the recommendation of continuation, adjustment, discontinuation, or modification of the therapy based on the clinical and microbiological features of the case.[72,115] Both methods require prospective auditing, intervention, and feedback.[72]

Minimizing collateral damage, eg, *C. difficile* diarrhea/colitis and preferentially select antibiotics with low resistance to *C. difficile*, MRSA, ESBL, Metallo β-lactamase (MBL) strains, VRE, and Carbapenem-Resistant Enterobacteriaceae (CRE).[116–118] Switch from IV-to-oral antibiotic therapy after clinical defervescence and using oral antibiotics initially, if tolerable to the patient.[119–122] Therapeutic substitutions in consideration with the facility's antibiogram are employed, and a single antimicrobial per class is maintained to reduce pharmacoeconomic cost and inventory.[123] Implications of cost to the institution regarding dosing frequency, *C. difficile* development,

Box 4 Types of Stewardship Interventions

- Education and guidelines
- Formulary restrictions
- Intravenous to oral conversion
- Intravenous batching
- Therapeutic substitutions
- Antibiotic timeout
- Antimicrobial cycling

resistance potential, the measure of activity against the likely agent, and the cost of potential therapeutic failure given increased length of stay and legal implications must be considered.[124,125] Intravenous batching is also a consideration where single-use vials can be batched using written protocols to reduce costs and waste.[72] This intervention is the "timeout" of antibiotics after 72 hours of initiation. An interruption during interdisciplinary rounds to assess the indicated antimicrobial appropriateness, verify current culture and sensitivity results, followed by therapy de-escalation if indicated, is performed.[71,126] This ensures proper use, dosing, and duration of each antimicrobial agent and allows scrutiny by the AMS team.[72]

De-escalation and streamlining refer to prescribing antimicrobials based on the laboratory findings of culture and sensitivity. Thereby substituting to more selective therapeutic options from broad-spectrum antimicrobials. Additionally, the administration route needs to be altered, such as the intravenous to the oral route, or suspending antimicrobials if the infection is adequately controlled or not detected with advanced laboratory technology.[39] Other strategies include promotion of timely and appropriate microbiology sampling,[127,128] prospective audit with intervention and feedback,[39,74,129] surgical antibiotic prophylaxis optimization,[130,131] and therapeutic drug monitoring with feedback.[132,133]

AMS – A Shared Responsibility

The multidisciplinary team comprising microbiologists, infectious disease physicians, clinical pharmacists, nurses, laboratorians, and the infection control specialists make antimicrobial stewardship attainable. They are the program's backbone and provide feedback on prescribing practices, antimicrobial usage, medication safety incidents, local AMR patterns, antimicrobial resistance-related or complicated infections, and changes in national policies and guidelines, new therapeutic options, and innovative diagnostic interventions.[134–137] With the "One Health" approach, an even more comprehensive set of stakeholders are involved, including agriculturalists, veterinarians, economists, farmers, etc.[67] Nurses have an important role in antibiotic preparation, administration, prescription, and therapeutic monitoring.[138,139] A single leader (usually an ID specialist) should be appointed for accountability, drug expertise and program oversight. The pharmacist leader should be responsible for optimizing antibiotic use. This leadership commits to supporting a dedicated team of persons and providing budgetary and information technology resources. Figure 1 shows the stewardship team's fundamental approaches which are needed to overcome the AMR.[69]

Through the advent of rapid diagnostics such a molecular diagnostics and mass spectrometry, the prolonged use of broad-spectrum antibiotics is reduced, allowing earlier de-escalation, changing from combination to monotherapy where necessary or stopping antibiotic therapy entirely,[79,140,141] and facilitates the earlier optimized treatment regimen.[142–144] With cascading microbiology susceptibility reporting, the microbiology laboratory reports broad-spectrum drugs only if the primary drugs are resistant and only the narrowest-spectrum drugs (primary agents) are reported while withholding the susceptibilities of more broad-spectrum agents, higher-cost agents, high-toxicity agents, or those with the potential for over-prescription (secondary agents). The rationale behind cascade reporting is that they will be less likely to be prescribed.[145] The reduction of broad-spectrum antibiotics and a concerted effort to promote narrow-spectrum therapies will provide heterogeneity in prescribing instead of homogeneity, which increases resistance to heightened selective pressures.[114] In the form of empiric antibiotic recommendations for common infections, dosing guidelines, and other helpful information, treatment algorithms are devised, prompting the prescriber to make evidence-based decisions founded on antibiograms and national surveillance data.[146,147]

Dose optimization using pharmacokinetic/pharmacodynamic properties to improve drug efficacy based on the organism, infection site, and patient characteristics has also demonstrated clinical effectiveness.[148,149] Formulary restrictions, automatic substitution/therapeutic interchange policies, and preauthorization have been applied to control the misuse of antimicrobials by establishing order forms, consultation with infectious disease experts, and clinical pharmacists on the use of the high-cost broad-spectrum drugs.[39,150,151] These methods facilitate appropriate and timely antimicrobial administration in severe sepsis/septic shock, where urgent intervention is critical for patient survival.[152,153] The World Organization for Animal Health has listed and categorized antimicrobials not to be used in animals, plants, or aquaculture, particularly carbapenems, glycopeptides, oxazolidinones, and any new classes of antimicrobials developed for humans.[67,154] Clinical education regarding antimicrobial stewardship at all medical and health professional schools has prompted

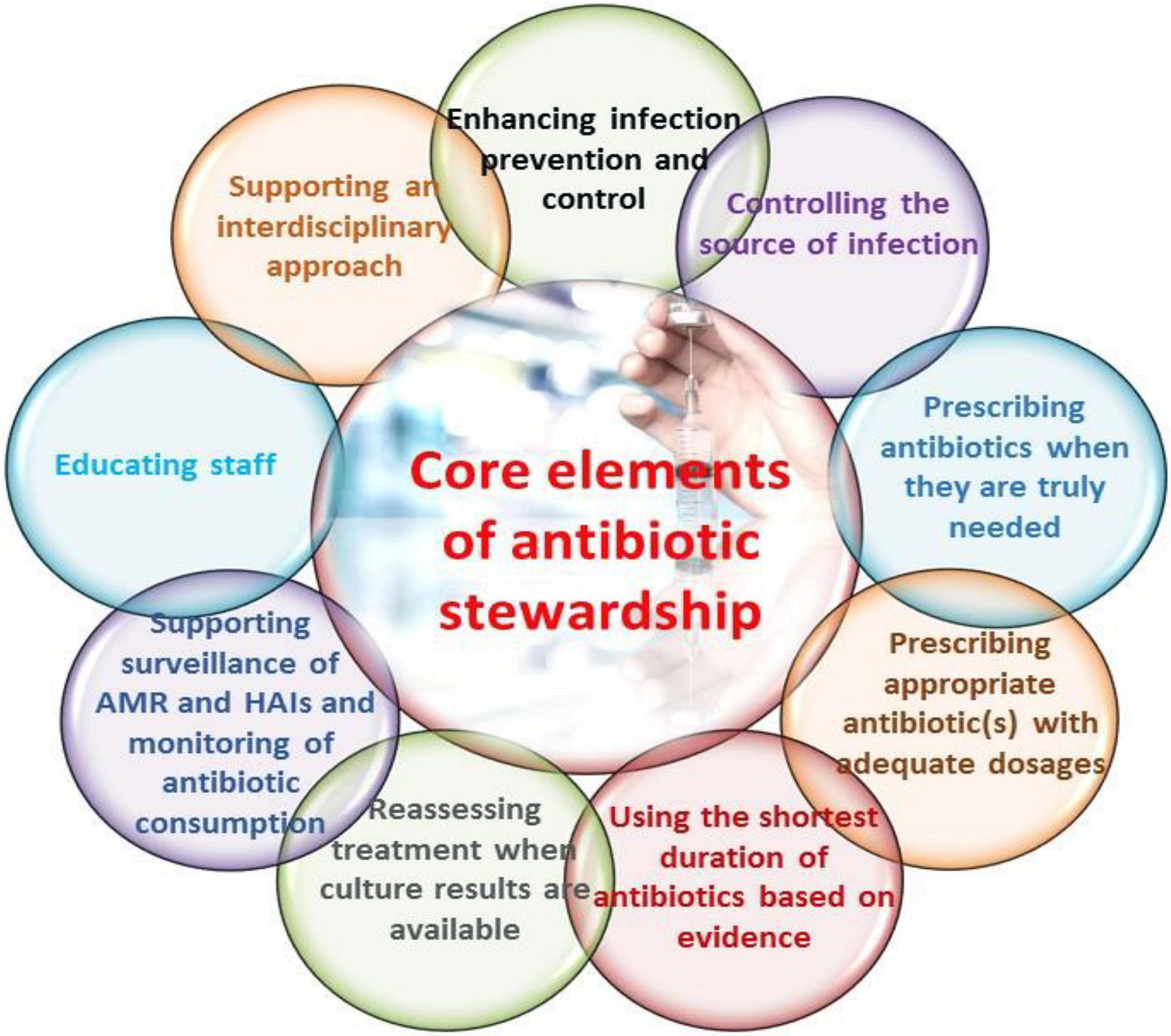

Figure 1 Core elements of ASP to optimize the treatment of infections and reduce adverse events associated with antibiotic use.
Notes: Copyright © 2020. Global Alliance for Infections in Surgery. Reproduced from Global Alliance for Infections in Surgery. Core elements of antibiotic stewardship. Available from: https://infectionsinsurgery.org/core-elements-of-antibiotic-stewardship/.[69]

the development of prescribing policies and competencies, antibiograms, infection control, and hand hygiene practices.[19,125] The continuity of care is maintained through multidisciplinary meetings engaging the various departments to discuss prescribing patterns, local antibiograms, and to address their concerns regarding de-escalation and appropriate antimicrobials utilization. Public education and awareness campaigns about mitigating AMR have been established.[135]

The CDC's seven core elements to establish a successful ASP at the institutional level (Box 2) exemplifies the integrative approach towards AMS.[71] AMS is a shared responsibility among primary prescribers, pharmacists, ID physicians, nurses, veterinarians, farmers, and microbiologists to provide appropriate antimicrobials to those who need them, essentially decreasing the acquisition of nosocomial infections and MDROs. Knowledge and awareness are critical components of successful implementation and sustainability to combat AMR.[139]

ASP – Monitoring and Evaluation

ASPs should be monitored and evaluated using appropriate and relevant outcome indicators. Empirical studies report that AMS programs positively affected the outcome indicators, eg, antibiotic consumption, the intensity of consumption, antibiotic prophylaxis, resistance rates, healthcare costs, and morbidity and mortality rates.[155,156] A number of recent meta-analysis and systematic reviews on ASPs demonstrate the potential to reduce similar outcomes in various healthcare settings.[157–161] Table 2 highlights the impact of ASPs in some recent studies in developed and developing countries.

AMS – Role of Education and Training

Education and training on appropriate antimicrobial prescribing and use, AMR, and AMS principles can provide the foundation of knowledge for effective AMS programs.[39,170] AMS principles should be taught at the undergraduate level and continue throughout professional careers.[71,103] AMS has been more successful if education began early in the undergraduate curriculum.[170] Studies showed that many undergraduate health professional students do not receive adequate education in relation to AMR, optimal antimicrobial use, and AMS.[171–174] Health professionals should receive education and training during the infancy of their career, where it helps shape their attitudes and behaviors and better equips them with AMS principles and strategies.[175,176]

AMS education should be available for health professionals as a continuing medical education (CME) program to receive current evidence-based information regarding rational and appropriate prescribing.[170] Some practical examples of continuing education include lectures, tutorials, in-service and grand rounds sessions, department or practice meetings, morbidity and mortality meetings, academic detailing, one-on-one patient-directed education, e-learning, and education combined with other AMS activities.[176,177] The training programs require continuous monitoring and evaluation to examine the impact of education on students' and professionals' knowledge and behavior.

A recent editorial published in the Bulletin of the World Health Organization emphasized integrating AMS activities into the COVID-19 pandemic response program of the health care system.[26] The first and important strategy was to increase the health personnel's clinical competence through targeted training.[26] The key competencies need to implement effective AMS programs are to (i) diagnose signs and symptoms of severe COVID-19 with superimposed bacterial or fungal diseases, (ii) avoid inappropriate antibiotic use including daily de-escalation, (iii) identify the use of medical devices and others that decrease the chances of hospital-associated infections and antibiotic use, and (iv) adopt strict infection prevention and control measures.

The Way Forward: Protecting Global Health

Global and National Strategies Against AMR

A comprehensive response against AMR must be embraced in a holistic manner to contain and mitigate health and the economic consequences associated with AMR. The WHO established The Global Action Plan on AMR after the plan's endorsement at the sixty-eighth World Health Assembly in May 2015.[62] Subsequently, global leadership has consistently highlighted AMR as a health priority, as illustrated by G7 and G20 countries in summit declarations since 2015.[178] At the core of the WHO's plan, there are five objectives which include i) improving awareness and understanding of AMR, ii) strengthening knowledge through surveillance and research, ii) reducing the incidence of infection, iv) optimizing the use of antimicrobial agents, and v) developing the economic case for sustainable approaches towards developing new medicines, diagnostic tools, vaccines and other interventions.[62]

While emphasizing the importance of the WHO's Global Action Plan and its endorsement by world leaders; pre-existing national and international strategies against AMR must continue in complete alignment with the global action plan.[179–181] In 2018 a WHO update stated that 105 countries had surveillance systems in place for reporting drug-resistant infections in human health, 68 countries had systems for monitoring the consumption of antimicrobials, and 123 countries had policies to regulate the sale of antimicrobials, including the requirement of a prescription for human use.[182]

National strategies against AMR must address country-specific priorities based on social demographic factors. The strategy should also focus on i) strengthening human and animal health surveillance for resistant microorganisms, ii) establishing human and veterinary AMS and infection-control programs, iii) conducting research on innovative diagnostic and therapeutic approaches, and iv) implementing educational programs that target professional groups and the public.[183] Both global and national

Table 2 Impact of ASPs on Antibiotic Usage, Microbiological, Clinical, and Financial Outcomes

Study Reference No.	Countries	Settings, Design, Time, and Health Personnel Involved	Interventions	Outcome Measured	Impact
Wang et al (2019)[156]	China	Tertiary hospital. A retrospective observational study. 2011 to 2016 Pharmacists	Multi-aspect interventions: activity program, performance management, and training.	Antibiotic prescriptions, the intensity of consumption, antibiotic prophylaxis, and resistance rates	↓Prescriptions: outpatients - 19.38% to 13.21%, inpatients −64.34% to 34.65%. ↓Intensity: 102.46 to 37.38 DDD[a]/100 PD[b] ↓Prophylaxis: 98.94% to 18.93%. ↓Resistance rates[c] ↓MRSA[d] incidence: 68.0% to 37.5% ↑Resistance rates[e]
Xiao et al (2020)[161]	China	Secondary and tertiary hospitals A retrospective observational study. 2010 to 2016	AMS campaign	Antibiotic prescriptions, intensity of consumption, antibiotic expense, and resistance rates	↓Prescription: outpatients - 19.5% to 8.5%; surgical patients - 97.9% to 38.3%. ↓Intensity: 85.3% to 48.5% DDD/100 bed-days. ↓Antibiotic procurement costs:22.3% to12.1%. ↓Resistance rates[f]: 30.8% to 22.3% ↓MRSA incidence: 54.4% to 34.4%
Mardani et al (2020)[162]	Iran	Tertiary teaching hospitals. An interventional quasi-experimental study. Before (2017 to 2018) and after (2018 to 2019) ASP implementation. Nurses and physicians.	AMS educational programs	Antibiotic prescriptions, the occurrence of CDI, and positive MDR cases	↓Prescription[g]: 22,464 to 17,262 g. ↓CDI[h] incidence: 11.2% to 2.7% cases per 10,000 patient days ↓MDR[i] cases: 145 t0 75
Onorato et al (2020)[163]	Italy	Intensive care units (ICUs) of a teaching hospital. Prospective, interventional, Interrupted time-series study. Time: 2017–2018.		Antibiotic prescriptions, incidence of BSI, hospital mortality rate, mean LOS, and antibiotic expense.	↓Prescription: 324.8 DDD/100 PD ↓Incidence of BSI[j]: 5.8 events/100 PD Hospital mortality rate: No difference Mean LOS[k]: No difference

(*Continued*)

Table 2 (Continued).

Study Reference No.	Countries	Settings, Design, Time, and Health Personnel Involved	Interventions	Outcome Measured	Impact
Savoldi et al (2020)[164]	Germany	Prospective quasi-experimental, Interrupted time-series study. Tertiary care teaching hospital. 2014 and 2017.	Non-restrictive ASP, 3 phases: 1-year pre-intervention, 2-year multifaceted intervention, and one year of post-intervention.	Antibiotic prescriptions, antibiotic expense, mean LOS, CDI incidence rate, and mortality in the patients' group were admitted from ED to medical wards.	↓Prescription: 31.1% to 7.2% DDD/100 PD. ↓Incidence of CDI ↓Mean LOS Mortality rate: No difference ↓Antibiotic expense: 691.5 to 263.3 EUROs/100 PDs
Singh et al (2018)[165]	India	Tertiary teaching hospital. Quasi-experimental study. 2015 to 2017. Infection control team	Post-prescriptive audit and establishment of institutional guidelines	Antibiotic prescriptions, antibiotic expense, compliance with ASP Recommendations	↓Prescription (DDD/100 PD). ↓Mean monthly cost for restricted drugs by 14.4% ↑Compliance: 54%
Wee et al (2020)[166]	Singapore	Tertiary teaching hospital. A retrospective cohort studies. 2016 to 2018.	Prospective audit and feedback strategy	Adherence to ASP recommendations	↑Adherence: 81.9% (5758/7028)
Abubakar et al (2019)[167]	Nigeria	Tertiary hospitals. Prospective pre- and post-intervention study. May and December 2016. Pharmacists.	Development of a protocol, educational meeting and audit and feedback	Antibiotic prescriptions, the intensity of consumption, antibiotic expense, and resistance rates	↓Prescription: 19.1% ↓Prescription: third generation cephalosporin (−8.6%), ↓Intensity: (3.8 DDD/procedure) ↓Cost: $4.2/procedure ↑Compliance: Timing (14.2% to 43.3%) and duration (0% to 21.8%)
Brink et al (2017)[168]	South Africa	Private hospitals. Prospective pre- and post-intervention study. Pharmacist. 2013–2015.	Prospective audit and feedback for perioperative antibiotic prophylaxis	SSI and compliance.	↑Compliance: 66.8% to 83.3% (95% CI 80.8–85.8). ↓SSI[l] rate 19.7%

Horikoshi et al (2017)[155]	Japan	Tokyo Metropolitan Children's Medical Center. Prospective pre- and post-intervention study. Quasi-experimental study. 2010–2017.	Computerized preauthorization and a prospective audit, an electronic chart-based drug ordering system	DOT in the post-intervention period, the resistance rate, and the correlation between DOT and resistance rates, average days of hospitalization, all-cause mortality, and infection-related mortality in the pre- and post-intervention periods.	↓DOT[m] in the post-intervention period: 59.3% ↓The resistance rate: 72.2% ↑positive correlation ↓Average hospitalization (days) ↓All-cause mortality rate (per 1000 patient-days) ↓Infection-related mortality rate (per 1000 patient-days)
D'Agata et al (2018)[169]	USA	Outpatient dialysis facilities. Quasi-experimental study. 2015–2016	ASP	Rates of antimicrobial use per 100 patient months, rates of use for specific antimicrobials or antimicrobial groups.	↓Antimicrobial doses per 100 patient months: 6%

Notes: [c]*E. coli* and *P. aeruginosa* to fluoroquinolones. [e]*E. coli* and *K. pneumoniae* to carbapenems. [f]Carbapenem-resistant *Pseudomonas aeruginosa* isolates. [g]Meropenem prescriptions. [h]*Clostridium difficile* infections. ↑: Increase. ↓: Decrease.
Abbreviations: [a]PD, patient-days; [b]DDD, defined daily doses; [d]MRSA, methicillin-resistant *Staphylococcus aureus*; [i]MDR, multidrug resistance; [j]BSI, bloodstream infections caused by multidrug-resistant (MDR) organisms; [k]LoS, length of stay; [l]SSI, surgical site infections; [m]DOT, day of therapy.

strategies must consider that the occurrence of AMR involves multiple links and domains from production to the use of antimicrobial agents. More so, holistic AMR control requires multiple sectors' joint actions.[183,184] The WHO "One Health" approach addresses a holistic, multi-sectoral approach, involving many different sectors (human medicine, veterinary medicine, research, animal husbandry, education, and communication) to increase the AMR action plan.[97]

Action Plans on AMR and ASP

Embedded in the global and national action plans' objectives should be key aspects of the more clinically guided ASP. The stewardship program contributes significantly to the health care system-wide or organizational approach to promoting and monitoring antimicrobial agents' use to preserve their future use in human and veterinary health.[103] The following illustrates key initiatives that could be led or influenced strongly by ASP for human and veterinary health. These initiatives require a multipronged but team approach with health care professionals, clinical and educational interventions, surveillance and monitoring procedures, and policy development.

Minimizing Antibiotic Pressure

The development of AMR is a natural phenomenon that occurs with or without exposure to antimicrobials. It is antibiotic pressure or antibiotic-induced natural selection that promotes and spreads resistant mutants. In contrast to common belief, AMR reversibility is a complex process affected by multiple factors. Although decreasing antibiotic pressure can reduce resistance levels, several studies have failed to demonstrate an impact on the individual or population level.[185] However, it is understood that control of multidrug resistance (MDR) should involve limiting the use of homogeneous antimicrobials classes by maintaining prescribing diversity.[186] Limitations on cost and drug availability can impact prescribing diversity. Therefore, there must be a multi-pronged emphasis in any strategy to curb AMR.

Rational Prescribing and Use of Antimicrobial Agents

The use of broad-spectrum antimicrobials by physicians and veterinarians is primarily attributed to the functional limitations in the rapid and reliable diagnosis of infectious disease, its causative organisms and the pathogens' susceptibility profile. Inadequate treatment for infections is related to poor outcomes, including higher morbidity and mortality and more extended stays in the health care facilities.[104] Narrowing the spectrum of antibiotics and combining chemotherapeutic principles can improve efficacy, reduce toxicity and the overall cost of care, and prevent AMR in the population.[186] Newer antibiotic drugs such as bedaquiline and modern fluoroquinolones have been reserved for MDR tuberculosis and need to be conserved to preserve their efficacy. The repurposing of withdrawn and underused antimicrobial drugs can provide an alternative or complementary approach to de-novo drug discovery and minimize cost and the impact of latency with new drug discovery and clinical trials. This is evident with the return of colistin and fosfomycin use for multidrug-resistant Gram-negative infections.[186] The environment's antimicrobial contamination must be monitored at the policy level, and adequate safeguards must be put in place.[185] The availability of antimicrobials in over-the-counter (OTC) preparations needs to be regulated, especially in low to middle-income countries. Irrational prescribing of antimicrobials may be a significant contributor to AMR due to self-diagnosis and access to OTC preparations, short duration of treatment and inappropriate choice of therapeutic class and dosage, lack of rapid microbiological diagnostic tools, physicians pressured by patients to prescribe antibiotics, and pharmaceutical pressure on physicians.[187]

Genomic Engineering

To monitor and treat widespread recalcitrant bacterial infections, the emergence of new bacterial genome engineering techniques offers promising diagnostic and treatment plans. Significant developments in genetic engineering techniques can effectively help target and alter pathogenic bacterial genomes to recognize and mitigate drug resistance mechanisms.[188,189] The clustered regularly interspaced short palindromic repeats – CRISPR-associated (CRISPR-Cas) system, a bacterial adaptive immune system, is a newly recognized approach for controlling antibiotic-resistant strains, utilizing genomic engineering tools geared for gene knock-out and knock-in of sequence-specific DNA antibiotic targets.[189–191] The system is aimed to neutralize "the invasion by foreign genetic material" such as, bacteriophages, plasmids and transposons where the CRISPR-Cas9 acts as a "RNA-guided-DNA cutter". Once foreign genetic material is encountered inside the bacteria, the Cas machinery barcodes small phage genome sequences into the genome of bacteria to assail it using the nuclease activity of CRISPR-Cas9 to cleave it.[192,193] It can be programmed to specifically detect any DNA target provided in the CRISPR array such as specific virulence genes and antibiotic resistance coding genes in bacterial populations.[194–197] This sequence-specific targeting ability allows it to discern between commensal and non-commensal bacterial species as it can be reused against the bacteria rather than defending against invaders as guide CRISPR-RNA can be constructed to target only chromosomal and virulence genes that are highly specific to pathogens.[192,198] The elimination of bacterial virulence factors carried on virulence plasmids and resistance determinants in commensal bacteria has been carried out by the CRISPR/Cas9 "pro-active" genetic system (Pro-AG), a recently developed system.[192,199] The enhanced cytotoxic potential is associated with the intentional or accidental targeting of the sequence of bacterial genome by Cas9 nuclease,[200] leading to apoptosis because of the introduction of irreversible chromosomal lesions.[201,202] Therefore, a CRISPR-guided RNA can be fabricated to exclusively target resistance or virulence genes, reverting to antibiotic susceptible ones by inducing a break inside the dsDNA of resistant bacteria.[198]

Effective Vaccination Policies for the Greater Good

Vaccines work by enabling the immune system to rapidly and efficiently identify and respond to a pathogen while mounting an immune response. While it is unlikely that vaccinations will protect against all the microbes contributing to the AMR, research and development prospects for vaccinations promise to mitigate AMR once proven efficacious, safe, and adequately implemented. There has been a decrease in the number of people and their children being vaccinated for different reasons, sometimes compromising an adequately implemented vaccination policy.[203] Improper implementation of vaccination can create pathogen reservoirs within the population, which may become resistant to antimicrobials. Given the importance of vaccination for global health and AMR, it may become a matter of global interest to implement vaccination policies that cater to the population's greater good but limit the risk associated with declination of vaccines.[204]

Clinical Treatment Strategies for Human and Animal Health

The transfer of resistant microbes from animals to humans is well established, but antibiotics in animal husbandry as growth promoters continue to be unregulated.

Plasmid-mediated colistin resistance was reported in China in 2015 and has been disseminated worldwide. Although colistin resistance was previously documented, there are significant epidemiological implications due to the plasmid-mediated nature of *mcr-1* (colistin resistance mechanism) gene resistance.[205] Though compliance is not mandatory, the WHO has established a list of essential antimicrobials for human use, which is to be avoided in non-human interventions.[206] It is likely that the list of essential antimicrobials for human use may become enforced to reduce AMR transfer from animals to humans or vice versa.

Conclusion and Recommendations

AMS' practices, principles, and interventions are critical steps towards containing and mitigating AMR. They are designed to promote, improve, monitor, and evaluate the rational use of antimicrobials to preserve their future effectiveness, along with the promotion and protection of public health. ASP has proven highly successful in promoting the rational use of antimicrobials through the implementation of evidence-based interventions. Its principles and core elements are embedded in the WHO Global Action Plan on AMR and should be factored in national strategies against AMR. The holistic and multisectoral "One Health" initiative is also needed to address AMR. The WHO recognized this global threat and strongly recommended implementing this approach at the national and global levels.

Moreover, at the healthcare system and organizational level, the implementation of an ASP is of utmost importance as it: i) transforms clinical and educational interventions, ii) facilitates the incorporation of new and more efficient diagnostic tools, iii) establishes AMR patterns through effective surveillance, and iv) reduces the cost of health-care expenditure by better outcomes in patients in clinical and veterinary settings.

Lastly, healthcare professionals must address the challenge of managing AMR's growing problem by leadership in human and veterinary medicine, pharmacy, and policy. The rational use of antimicrobials, "One Health" approach, vaccination protocols, healthcare workers' and patients' education, and the broader public awareness about AMR must be guided by strict evidence-based policy.

Professionals Annotation

AMR is one of the most persistent and tenacious public health perturbing issues.[32,207] Globally, every year over two million drug-resistant infectious disease cases and 23,000 deaths were reported.[7,31,208] Irrational, imprudent prescribing and utilization of antimicrobials are considered top reasons for AMR, often blamed, and evidenced as an irresponsible act by healthcare professionals.[32,209] AMR is increasingly accountable for difficulties and failures in managing infectious diseases.[210,211] Furthermore, AMR consumes a significant share of the public healthcare budget, increases out-of-pocket expenses for patients, and increases financial burden towards communities.[75,212,213] Lord J O'Neill and his group published a review appointed by the United Kingdom government titled, "Antimicrobial Resistance: Tackling a crisis for nations' health and wealth" in 2014.[214] They determined that AMR could result in 10 million dying per year with a cumulative cost of US $100 trillion by 2050.[214,215] The situation is further aggravated by MDRO being amongst the topmost three dangers to international public health.[216–219] Furthermore, the consumption of second-rate and counterfeit antimicrobials worldwide exacerbates the unnecessary, imprudent, irrational antimicrobials prescribing leading to MDR.[32,220–225] Thereby, MDR is currently one of the most significant clinical challenges and is a pandemic in its merit.[32,143,226–228] AMR is increasing; however, the new antimicrobial drug development process has slowed down.[229–231] Thereby, irrational, over, and redundant use of antimicrobials underwrites the advent of resistant microbes and the origins of patient impairment. Patients with AMR infections are more likely to experience treatment failure, repeated and persistent infection, prolonged hospitalization, postponed recovery, or succumbing to their infection.[232,233] Contemporary research regarding antimicrobials and AMR highlights the necessity of diminishing imprudent use of antimicrobials in all health care facilities.[18,32,234–237] According to the WHO:

AMR threatens the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses, and fungi.[238] The CDC reported that 30–50% of all antimicrobials prescribed in the US acute care hospitals are irrational, imprudent, and superfluous.[239]

Multiple research pieces reported that hospital-based ASPs improve antimicrobials prescribing patterns, infection control, and reduce adverse effects linked with antimicrobials consumption.[64,240–243] ASPs refer to a set of synchronized and timely strategic action plans to ensure the judicious practice of antimicrobial use, ensuring and maximizing the patients' benefits and averting death. It also diminishes AMR, decreases redundant healthcare costs, and reduces the possibility of the MDR gene distribution within the microbial community.[79,87,244–246] Moreover, ASPs supports physicians' progress in maximizing clinical benefits among their patients and minimizing adverse effects by improved correct prescribing, ie, appropriate antimicrobial selection, including adequate/balanced spectrum; administration at the right time, in the right dose, by the appropriate route, and at proper time intervals.[79,247]

CDC, in 2019, restructured the fundamental rules and regulations of US hospitals regarding ASPs, which comprised:[248] hospital leadership aptitude and obligation, answerability, pharmacy proficiency, actions promoting ideal antimicrobial use, surveillance of antimicrobial prescribing, consumption and AMR, and continued antimicrobial stewardship education.[240,248,249] The ASPs are widely recognized as competent planning and policy implementation mechanisms to battle AMR's mounting threat.[79,250,251] There is also the widespread belief that antimicrobial stewardship is a team's determination to comprise all healthcare workers in the continuum of care. ASPs may vary by healthcare institutions; therefore, flexible and tailored approaches to local needs are essential.[252,253]

Infection prevention and control, antimicrobial surveillance, and antimicrobial stewardship are believed to be the principal strategies for local, national, and international systems to prevent the development of AMR and reduce avoidable healthcare-associated infections (HCAIs).[79,243,254] Public health professionals advocate ways to reduce pointless prescriptions to evade the onslaught of AMR. This becomes evident when there are high levels of antimicrobial use among COVID-19 patients, highlighting the necessity to institute stewardship agendas.[26,28,102,255–257]

AMR is a cumulative risk to global health safety. This can be countered possibly by increasing public health awareness worldwide.[214] There is a need for a practical "One Health" approach to minimize imprudent or inappropriate use of antimicrobials, where local, national, and global action is required across human medicine, veterinary practice, and the agriculture sector.[258] The critical recommendations put forward by renowned international organizations include the following: (i) increased use of vaccinations to reduce the need for antimicrobial agents,[204,259] (ii) investment in the surveillance of AMR infections and sharing data to improve global responses,[260,261] (iii) investment in research and development directed toward the development of innovative antimicrobial agents, vaccines, diagnostics and other tools to avert AMR,[262] (iv) strengthen regulatory policies, agendas, and putting infection control and prevention methods in practice,[263] (v) educate and train healthcare professionals on antimicrobial stewardship,[177,264] (vi) facilitate the availability of antimicrobial agents only through a prescription provided by a certified health professional,[219,265,266] (vii) healthcare professionals should strictly follow clinical and treatment guidelines to manage patients,[267,268] (viii) increase awareness among the public regarding the harmful consequences of overuse and misuse of antimicrobial agents,[269,270] (ix) more emphasis of antimicrobial stewardship in health professional curricula,[271–273] (x) endorse and use hygienic practices and aseptic techniques at all stages of food handling and preparation whether from animal or plant sources[274–277] and (xi) promote and ensure adherence to hygiene measures and other infection prevention practices[278–283] eg washing hands, cooking food hygienically, evading close contact with infectious disease people, practicing safer sex, and keeping vaccinations up to date.

Article Highlights

- AMR is a significant urgent threat to global public health, responsible for increased morbidity and mortality and high economic burden.
- MDR bacteria and COVID-19 pandemic also have substantial implications on clinical and economic outcomes by increasing higher rate of AMR.
- AMS aims to optimize antimicrobial use, and AMS practices, principles, and interventions are critical steps towards containing and mitigating AMR.
- ASP has been widely employed and proven to improve the appropriate use of antimicrobials by implementing evidence-based interventions.
- "One Health" approach, a holistic and multisectoral approach, is also widely recommended to address the rising threat of AMR by implementing aligned AMS strategies at the individual, the national, and global levels, and across human health, animal health, and the environment.
- The rational use of antimicrobials, "One Health" approach, vaccination protocols, and education and training about AMR must be guided by evidence-based policies and guidelines prescribed by national and international organizations.

Consent for Publication

All authors reviewed and approved the final version and have agreed to be accountable for all aspects of the work, including any issues related to accuracy or integrity.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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