IFMSA Policy Document
Antimicrobial Resistance

Proposed by the IFMSA Team of Officials
Adopted at the 73rd IFMSA General Assembly March Meeting 2024

Policy Commission

- Salman Khan (Liaison Officer for Public Health Issues) - lph@ifmsa.org
- Anupreksha Jain (MSAI India)
- Alaa Elnahas (IFMSA-Egypt)

Policy Small Working Group

- Salman Khan (Liaison Officer for Public Health Issues) - lph@ifmsa.org - *SWG Co-coordinator*
- José Diogo Soares (SCOPH External Affairs Assistant, ANEM Portugal) - *SWG Co-coordinator*
- Christopher Haruna Dakat (NIMSA-Nigeria)
- Ana Teresa Martins Freire Leitão (ANEM-Portugal)
- Armand Koffi Sallah (AEM Burkina Faso)
- Arantza Jiménez Rodríguez (AMMEF Mexico)
- Cheung Wing Tung Rachel (AMSA HK Hong Kong)
- Charles Kevin Tiu (AMSA Singapore)
- Mennatullah Tarek Anwar Zayan (IFMSA Egypt)

Policy Statement

Introduction

The rising menace of Antimicrobial resistance (AMR) is an alarming global health crisis and a matter of utmost global security concern AMR, a natural evolutionary response to antimicrobial exposure, has been exacerbated by human activities, including the improper use and overuse of antimicrobials in human healthcare, agriculture, and animal health, as well as environmental contamination. These practices severely compromise our ability to effectively combat common infections and perform life-saving surgical procedures. Moreover, the rise of resistant pathogens increases the probability of future pandemics. The alarming global evidence underscores the urgent need to address AMR as a critical public health issue and engage various stakeholders, including medical students, policymakers, and society, in finding and implementing effective solutions against AMR.

IFMSA Position

The International Federation of Medical Students Associations (IFMSA) unequivocally acknowledges the critical and pressing nature of Antimicrobial resistance (AMR) as a formidable global health crisis, akin to a silent pandemic. The IFMSA firmly asserts the imperative for an interdisciplinary collaborative approach, engaging all key stakeholders, to effectively confront the complex challenge posed by AMR. This approach must specifically underscore the intricate interplay between antimicrobial resistance and both health and non-health sectors, with the ultimate aim of comprehensively addressing the underlying causes, intricate interrelationships, and far-reaching consequences of AMR through the prism of all policy-making endeavours.

Call to Action

Therefore, the IFMSA calls on:

Governments and national regulatory bodies to:

- Develop and enforce legal frameworks and regulations on antimicrobial usage in human health, agriculture and animal husbandry to curb misuse and overuse of antimicrobials, thereby limiting AMR spread.
- Implement monitoring programs on local, regional, and national levels to evaluate, monitor, and do surveillance of antimicrobial usage.
- Develop and fund national antimicrobial stewardship programs against AMR to encourage appropriate usage, to trigger stakeholders' compliance.
- Invest in research and development of new antibiotics, alternative antimicrobials, and other diagnostics methods for infectious diseases with the relevant sectors and stakeholders, like pharmaceutical, agriculture, and veterinary industries.
- Engage with all relevant stakeholders, including youth, in the planning, execution, monitoring, and assessment of initiatives focused on preventing antimicrobial resistance, as well as research and development efforts related to it.
- To develop policies and campaigns for the general public regarding the correct use of antimicrobials

WHO, UN, and other international organisations to:

- Develop policies and global guidelines regarding the use and tracking of antibiotics worldwide, and the education of healthcare professionals and healthcare students in different healthcare settings.
- Encourage and financially support collaborative endeavours with partner nations to create a comprehensive global evaluation of antimicrobial resistance.
- Promote and champion innovation and research initiatives in the realm of antimicrobial resistance, through the advancement of novel diagnostics, vaccines, and pharmaceutical drugs.

- Provide technical assistance and training to low-, middle-income and other countries in implementing AMR control strategies and developing their national AMR surveillance systems.
- Design and implement comprehensive awareness campaigns aimed at educating the public about antimicrobial resistance, its underlying causes, preventive measures, and the far-reaching consequences associated with it.

Pharmaceutical industry to:
- Promote research focused on novel antimicrobials, diagnostics, and vaccines, prioritising research targeting priority pathogens.
- Enforce ethical standards to prevent undue influence over prescribers and ensure responsible antimicrobial usage.
- Emphasise capacity-building initiatives to enhance antimicrobial stewardship knowledge among employees and healthcare professionals.

Agriculture and livestock sectors to:
- Provide education to livestock producers and farmers regarding the utilisation of antimicrobials for preventing and treating infections in animals.
- Establish data collection, monitoring, and surveillance systems to regulate the use of antimicrobials and curb resistance within the agriculture and livestock domains.

Healthcare facilities, institutions, and universities to:
- Develop comprehensive curricula that instruct future healthcare professionals on the proper utilisation and prescription of antibiotics, encompassing their efficacy, appropriate dosage, and duration of use.
- Enforce the establishment of antimicrobial stewardship programs between healthcare institutions;
- Engage students actively in research and development related to antimicrobials, vaccines, and diagnostics.

Health workforce and healthcare professionals to:
- Diagnose properly, treat efficiently according to global and national guidelines, and provide follow-up when dealing with patients infected by resistant microorganisms.
- Empower patients to be informed about antibiotic use and participate in shared decision-making with healthcare providers.
- Advocate for improved access to diagnostic tools and alternative treatment options for infections.
- Support research initiatives aimed at developing new diagnostic tools and alternative therapies for antibiotic-resistant infections.

IFMSA, NMOs and other healthcare student organisations to:
- Organise educational programs, training sessions, and workshops on AMR, antimicrobial stewardship, infection control, and rational antibiotic use for healthcare students.
- Organise advocacy campaigns to raise public awareness about AMR, responsible antibiotic use, and infection prevention measures, in collaboration with relevant stakeholders.
- Collaborate with healthcare professionals and policymakers to advocate for stronger AMR control policies, relevant research, and efficient surveillance initiatives.
- Advocate for the integration of AMR challenges and solutions into health school curricula.

Position Paper

Background information

Antimicrobials encompass a diverse range of therapeutic substances utilised to prevent or combat infections across various domains. This category includes antiseptics, antibiotics, antivirals, antifungals, and antiparasitics, each tailored to address specific types of microbial threats. The discovery and widespread use of these chemical agents in health represent a watershed moment in the history of medicine, revolutionising healthcare practices and drastically altering the trajectory of infectious disease management. (2) Nevertheless, the indiscriminate use of antimicrobials has led to the emergence of drug-resistant pathogens, leading to the phenomenon of Antimicrobial resistance (AMR). This presents a formidable challenge to the effectiveness of existing treatments and jeopardises our ability to treat common infections, leading to increased morbidity, mortality, and healthcare costs worldwide. (3)

According to the World Health Organization, antimicrobial resistance ranks among the top 10 global public health challenges, contributing to approximately 4.95 million deaths in 2019 alone. By 2050, if unchecked, AMR could result in a staggering economic toll of $100 trillion. The gradual escalation of AMR underscores the risk of diverting attention and resources away from addressing this pressing issue, especially amidst other emerging threats. However, existing policies, both at the national and international levels, are inadequately equipped to address the treatment of resistant infections and to effectively curb the development and dissemination of antimicrobial resistance. (3)

AMR presents a multifaceted challenge that demands coordinated action across various sectors including human health, food production, animal welfare, and the environment. The One Health approach advocates for an integrated strategy to address AMR by emphasising collaboration among stakeholders to develop and implement effective strategies for combating AMR. This approach seeks to enhance the design, implementation, and monitoring of programs, policies, legislation, and research aimed at mitigating AMR and achieving improved health and economic outcomes for all. (4) In addition, it is crucial to address AMR by investing in research funding, preventive strategies, enhanced diagnostics, public health surveillance, therapeutics, and innovative countermeasures that span across humans, animals, and our shared environment. (3)

Discussion

1. **Definition**

According to the World Health Organisation (WHO), the development of Antimicrobial Resistance (AMR) arises when bacteria, viruses, fungi and parasites evolve and become unresponsive to medications, making it more challenging to treat infections, heightening the likelihood of disease transmission, severe illness, and mortality.(5)

Due to the development of drug resistance, antibiotics, and other antimicrobial medications lose their effectiveness, making infections progressively more challenging or even impossible to treat. The emergence of untreatable diseases, the diminishing availability of reliable antibiotics, and the global spreading of drug-resistant strains significantly exacerbate this concern. Recognised as one of the top 10 global public health threats by the WHO, this issue engenders profound implications, such as prolonged hospitalisations, increased funding need for research, and increased expenses associated with the utilisations of expensive second and third-line medications, consequently affecting the global economy. (4)

2. Determinants of AMR

a. Biological causes

Antimicrobial resistance can be caused by biological factors such as selective pressure, genetic mutation and gene transfer. When using antimicrobials, microbes can be killed or those with resistance genes survive. Drug-resistant microbes replicate, making the resistant genes dominant in the microbial population. Most microbes also reproduce by division every few hours, allowing them to adapt to the environment. Mutations may arise from replication, where some mutations are beneficial to the survival of the microbe, making them drug-resistant. Microbes are also capable of gene transfer. Gene transfer can allow drug-resistant bacteria to transfer a copy of the drug-resistant DNA to non-resistant bacteria. The microbes with the new DNA can then survive under the presence of drugs, allowing the drug-resistant bacteria to multiply and survive. (6)

b. Human causes

Urbanisation and population density also contribute to antimicrobial resistance. According to estimations from the United Nations, approximately 55% of the population lives in urban areas and the global urban population is expected to increase to up to 6 billion people by 2045. (7) The large proportion of the population living in close proximity increases the risk of the rapid proliferation of infectious diseases due to the many opportunities for interpersonal contact, which facilitates the spread of resistant bacteria and genes. (8)

Furthermore, globalisation increases the spread of antimicrobial resistance due to the increase in trade and travel. On an individual level, individuals may carry resistant bacteria back to their home country after travelling, causing pathogens to be distributed globally. For instance, colistin, an antibiotic commonly used in livestock in China, has high rates of antibiotic resistance due to strong selection pressures. The resistant strains were also later found in the United States and Europe due to global trade. (9)

Overusing antimicrobials is a commonly cited reason behind increasing antimicrobial resistance. Epidemiological studies showed a direct relationship between antibiotic consumption and the emergence of resistant bacteria strains. (10) When introduced, antimicrobials were able to treat diseases rapidly without significant side effects, leading to widespread usage and a belief that antimicrobials were effective universally and should be the first line of treatment for all ailments. This caused an excessive use of antimicrobials and a strong selective pressure that fuelled the increasing rates of antimicrobial resistance. (11)

c. Clinical causes

Overuse of antimicrobials is partially due to the empirical use by clinicians. Between 2000 and 2015, the use of antibiotics increased by 65% globally, where there was a substantial increase across low and middle-income countries. (12) The inadequate diagnosis of disease and practical limitations in rapid and accurate diagnosis contribute to antimicrobial resistance. Administering different antimicrobials to control unidentified pathogens is particularly seen in extreme cases in hospital settings, where developing rapid and accurate diagnostic measures can be useful in reducing these practices. (11)

Other than the overuse of antimicrobials in acutely ill patients, the prescription of antimicrobials by general practitioners is also a common factor that increases resistance rates. General practitioners may prescribe antimicrobial therapy based on local epidemiology and experience instead of testing for pathogen and antimicrobial sensitivity to reduce the time from initial presentation to cure. In cases where the prescribed antimicrobial is inappropriate, this may prompt successive courses of different antimicrobials until an effective one is found. This causes a repeated selective pressure that facilitates the proliferation of drug-resistant microbes and can affect the patient's microbiota. (11)

The prescription of antibiotics is also impacted by patient demand. Patients may demand immediate resolution to illnesses and access to antibiotics, where practitioners may prescribe antibiotics to appease patients and garner business. Using appropriate diagnostic techniques to prescribe antimicrobials appropriately as well as decreasing the immediate prescription of antimicrobials to non-acute patients may alleviate the problem. (13)

Antimicrobial regimens may also influence antimicrobial resistance. Antimicrobials are often prescribed with a fixed regimen with a specified dose, rate, and period. Most regimes are regularly within a week, however, many are extended to two weeks or longer. The extended regimes are formulated on the basis that higher doses for a prolonged time increase the chances of eradicating infectious pathogens. However, limiting courses of treatment to minimum dose and period can reduce selective pressure on the microbes and limit the rate of resistance. (14)

d. Public perception and behaviour
The public perception of antibiotics is that it is a drug that is a quick and effective treatment for most illnesses. (11) For instance, patients may hoard antibiotics and not complete their prescribed treatment due to the fear of a future need.

Self-medication or unprescribed use of antimicrobials is listed as one of the most common causes of antimicrobial resistance. (15) This can be caused by individuals attempting to treat minor health issues on their own or being unable to afford the consultation fees of doctors. (15) Misuse of antibiotics is linked to increased risk of adverse drug reactions, increased severity of disease, and increase in drug-resistance microorganisms.(17)

Regulations and access to antimicrobials are also not standardised across the world. In many countries, selling and producing antimicrobials are largely unregulated, which leads to cheap access to large amounts of antimicrobials with variations in quality. Antimicrobials are also increasingly accessible to the public, where individuals can buy them without prescriptions. For instance, restricted antibiotics such as rifampicin and ciprofloxacin can be bought online. (18)

e. Agricultural applications
Antimicrobials are also used in stock and crops to increase agricultural yield. Justifications behind the use of antimicrobials in livestock and agriculture are food security and preventing famine. However, the selective pressure placed on the environment due to the widespread use of antimicrobials has increased the abundance and diversity of antimicrobial-resistant genes in urban and agricultural environments. (19)

3. Consequences of AMR, Health impacts, Social impacts, Economic impacts, Reemerging diseases, Infectious Diseases (including NTDs, HIV, etc)

The threat of antimicrobial resistance causing drug-resistant infections is now becoming visible at a global level. Antimicrobial resistance has resulted in different complex issues, variously impacting countries across the globe. Antimicrobial resistance significantly impacts re-emerging diseases, as it limits the effectiveness of treatment options and can lead to increased morbidity and mortality. (20) This is particularly concerning in the hospital environment, where resistant organisms can be transmitted, and in the case of nosocomial infections, where resistance is a common problem. (21) The development of highly resistant bacterial strains, dispersed globally due to travel, further complicates the issue. (22) The emergence of pathogens with various resistance mechanisms intensifies the challenges in infection control and treatment strategies. (23) Therefore, the prudent use of available antimicrobial agents and the implementation of measures to limit resistance spread are crucial.

Antimicrobial resistance (AMR) poses a significant threat to the treatment of infectious diseases, leading to inappropriate therapy, treatment failure, prolonged hospitalisation, increased costs, and mortality. (24) This is particularly concerning in developing countries, where the burden of infectious diseases is higher and access to newer antibiotics is limited. (25) The emergence of multidrug-resistant pathogens further exacerbates these challenges, resulting in worse clinical outcomes, longer hospital stays, and excess mortality. (26) The lack of a robust pipeline of new agents emphasises the importance of optimising current antimicrobials and promoting strict adherence to infection control practices. (27)

By 2050, AMR is estimated to cause around 10 million deaths worldwide if not addressed.(1) In the United States, 2 million people are impacted annually by AMR, with 23,000 deaths. (28) This number is similar to the European Union's annual mortality rate of 25,000. (29) Despite the difficulties of collecting specific death rates, official studies suggest that around 10 million people will die globally by 2050 if strong and successful anti-AMR action is not done. (30, 31) AMR also sabotages global fights against infectious diseases like tuberculosis, HIV, and malaria. (32) In Sub-Saharan Africa, 60% of HIV patients have developed resistance to HIV medicine, posing a threat to the global goal of ending AIDS by 2030. (33-35) Additionally, Plasmodium falciparum, the causative agent of malaria, has become resistant to antimalarial medicines, obstructing malaria control efforts to decrease the annual average of 445,000 deaths due to the disease.(36)

The U.S. CDC estimated that AMR could add $1,400 to hospital bills for treating bacterial infections in the US alone, potentially increasing to over $2 billion annually. (37-39) AMR is projected to cost from $300 billion to over $1 trillion annually by 2050 worldwide. (30, 40) Direct monetary effects include high costs associated with expensive treatments and resource utilisation. (30, 41) Patients with resistant infections may require longer hospital stays, more ICUs, and isolation beds. Additionally, nosocomial outbreaks with resistant pathogens may result in hospital closures and cancellations of elective surgeries. (42) AMR also generates secondary effects, such as difficulties in utilising antibiotics for procedures, challenges in organ transplants, and limitations in cancer treatments. (31, 41, 43-46)

The cost of AMR is estimated to be $55 billion annually in the United States, $20 billion for healthcare, and $35 billion for productivity loss. (39, 41, 47) Research by the World Bank indicates that AMR could increase poverty rates and impact low-income countries more than the rest of the world. (40) Annual global GDP could decrease by approximately 1%, with a 5-7% loss in developing countries by 2050, resulting in $100-210 trillion in (48) Multidrug-resistant TB alone could cost the world $16.7 trillion by 2050. (49) AMR also directly impacts labour through the loss of productivity caused by sickness and premature death. Deaths due to AMR decrease the workforce, negatively impacting population size and human capital quality. (43, 48) Taylor et al. created a theoretical model to estimate the economic impacts of AMR on the labour force. They found that if no change in the current pattern of AMR occurs, the world working-age population will decrease by two years, with Eurasia experiencing the most pronounced change. (50) Global trade will also be heavily affected by AMR, with the World Bank report showing that global exports might decrease significantly by 2050 due to its effects on labour-intensive sectors. (40, 51) AMR's long-term effects on the global economy are projected to be even more severe than the global financial recession (40) AMR will significantly impact livestock output, leading to mortality and morbidity, increased resistance to antimicrobials, and severe infections (40) This will decrease livestock production and trade, resulting in elevated protein prices. (40, 52-54) The World Bank predicts an 11% loss in livestock production by 2050, causing a decline in income generation and exacerbating the economic situation in low-middle-income countries. (40)

4. Consequences of AMR (Vaccination, WASH, Health Emergencies, UHC)

a. Vaccination

Vaccination plays a key role in reducing Antimicrobial Resistance. In a study published in the BMJ Global Health, over 500,000 lives can be saved annually through effectively using existing vaccinations and the development of new vaccines against priority pathogens. (55) Vaccines impact antimicrobial resistance by reducing the use of antimicrobials and preventing infections. Vaccines reduce the incidence of disease, morbidity, and mortality from resistant pathogens. By preventing people from transmitting infection, vaccines can also contribute to herd immunity, extending population protection. Vaccines also reduce antibiotic use. Antibiotics are often used as the empiric treatment for syndromic diseases. By reducing the incidence of syndromic diseases, antibiotic use can also be reduced. (56)

Resistant bacteria challenge vaccine development due to their genetic diversity, antigens and ability to cause infections of different outcomes. For instance, *K. pneumoniae* has increasing antimicrobial resistance. There are currently over 70 serotypes of *K. pneumoniae* globally, where adequate coverage of strains using a capsule-based vaccine may not be feasible. Furthermore, this highlights the importance of identifying the target population for vaccine development, strains with the highest burden and appropriate antigen selection methods for vaccination development with increasing antimicrobial resistance. (57)

b. WASH

Water, sanitation, and hygiene (WASH) and wastewater management are important in reducing the spread of antimicrobial resistance. Antimicrobial-resistant organisms can spread through contaminated wastewater, sludge, plant and animal production, and manufacturing of antimicrobials. (58)

Wastewater contains disease-causing pathogens, resistant microorganisms with low pathogenicity and active residues that contribute to antimicrobial resistance. Antimicrobials are required to treat diseases caused by pathogens in wastewater. With universal access to WASH, it can reduce the 60% of diarrhoea cases that are treated by antimicrobials. Wastewater also contains resistant microorganisms with low pathogenicity, where 14% of the global population has ESBL-producing *E. coli* in their faecal matter. This impacts antimicrobial resistance by infecting vulnerable populations or transferring genes to pathogens causing infections. Pharmaceutical waste contributes to the issue as up to 80% of antimicrobials are excreted as active residues, where onsite wastewater treatment is insufficient, not possible or unknown. (59)

c. Health Emergencies

Antimicrobial resistance has been declared one of the top 10 global health threats facing humanity by the World Health Organisation, where bacterial antimicrobial resistance contributed to 4.95 million deaths and are directly responsible for 1.27 million deaths across the world. (60)

Antimicrobial resistance can impact health emergencies by causing endemics and as a compounding factor in pandemics. The rising incidence of AMR in bacteria and hospital or community-acquired infections can be an endemic problem through the impact on a population level. This is caused by an increase in cases and patterns of antibiotic use in animals and humans over time. When considering AMR as a compounding factor in pandemics, it can contribute to death and disability on a large scale and short timeframe. (61) For instance, an increased prevalence of antimicrobial-resistant bacterial infection, ranging from 37.5% to 60.8%, has been seen among hospitalised patients with COVID-19. Such COVID-19 patients with secondary bacterial infections may not respond to commonly used antibiotics, leading to challenges in treatment and increased risk of complications and mortality. The study also found antimicrobial resistance to be more prevalent in patients from the Intensive Care Unit, where such patients may require more invasive interventions such as mechanical ventilation and intravascular access. This predisposes such patients to antibiotic treatment and nosocomial infection, increasing the risk of selecting more resistant strains. (62) Therefore, antimicrobial resistance can be considered a health emergency or a compounding factor leading to worse health outcomes in other global health emergencies.

d. Universal Health Coverage
Antimicrobial resistance poses a significant challenge to the financial sustainability of achieving universal health coverage. If no action was taken against antimicrobial resistance, between 1.1 to 3.8% of global GDP could be lost due to resistant infections prolonging hospital stays, increased infections and patients requiring more expensive treatments. Costs also arise from morbidity and mortality caused by antimicrobial-resistant bacterial infections. (62)

On an individual level, antimicrobial resistance also poses a significant financial impact, especially for financially vulnerable populations. By 2030, 24 million people could fall into extreme poverty due to antimicrobial resistance, according to estimations from the World Bank. Resistant infections come with higher costs of treatments, which are highly dependent on the individual's ability to afford healthcare and undermine efforts towards universal health coverage. Antimicrobial resistance disproportionally affects those living in poverty due to the inability to afford high costs of medicines to treat such infections, as well as the loss of income that is spent on intensive and prolonged treatment. The burden falls primarily on individuals from low to middle-income countries and can push populations into poverty and worsen health outcomes. (62)

5. Vulnerable Population to AMR

Children, due to their underdeveloped immune systems, are more vulnerable to resistant bacteria compared to adults. Their behaviours also expose them to a higher risk of germs and infections. This susceptibility is even greater among children living in poverty, as more than 300 million of them survive on less than $1.90 per day. Various factors contribute to their increased vulnerability. Lack of access to safe drinking water, sanitation, and hygiene (WASH) impacts these children, with over 785 million people globally still lacking clean water nearby. Additionally, poor housing conditions and inadequate nutrition contribute to their weakened state, leaving them more dependent on antibiotics for fighting infections. Moreover, these children often lack access to quality healthcare, with at least half of the global population lacking essential healthcare services. Even when available, the quality of healthcare can be dubious, as evidenced by data from a BMJ report revealing that one in four healthcare facilities lacks basic water services, one in five lack sanitation services, and two in five lack hand hygiene facilities at care points. Poverty and limited access to healthcare also contribute to the inappropriate use of antibiotics. In many low-income countries, antibiotics are often available over the counter without a prescription, leading to their misuse and overuse. This not only fuels the development of antimicrobial resistance but also puts individuals at risk of adverse effects from unnecessary medication. Moreover, poverty and AMR form a vicious cycle. The economic burden of treating drug-resistant infections is immense, and individuals and families living in poverty often struggle to afford the high costs of treatment. This can lead to delayed or inadequate treatment, further exacerbating the spread of resistant pathogens and the burden of AMR. Efforts to address AMR must go hand-in-hand with poverty alleviation and improving access to healthcare, clean water, and sanitation. This requires a comprehensive approach that involves strengthening healthcare systems, implementing effective infection prevention and control measures, promoting responsible use of antibiotics, and addressing social determinants of health. Additionally, addressing AMR must also consider the global dimension of poverty and inequity. Many low- and middle-income countries bear a disproportionate burden of AMR, while also facing challenges in terms of poverty, limited resources, and weak healthcare infrastructure. International cooperation and support are crucial in ensuring that all countries can address AMR effectively. (63, 64)

6. One Health and Interprofessional Approach to AMR

AMR is a complex issue with many stakeholders involved. By its very nature, AMR encompasses microbes that have an impact not only on human health but also on animal health. The same is true for the corollary – microbes found in and antimicrobials used in animals will also have an impact on human health. Often, the same or very similar pharmaceutical agents are used to treat animal infections as with human infections. (65) And these pharmaceutical products or their metabolites, and the pathogens resistant to them, will end up in the ecosystem or in the food chain – eventually having an impact on human health. (66) Thus, a holistic and interprofessional approach (e.g., concerning both animal and human healthcare providers) is imperative.

a. *One Health*

One Health is a concept used to describe the interrelatedness of human, animal, and ecosystem health. (67, 68) This unifying approach recognizes the links and the effects brought about by the health (or lack thereof) of humans to that of ecosystems or animals, and vice versa. This concept is frequently applied in AMR, as it is emerging to zoonotic infections, pollution, food safety, and vector-borne diseases. The principle emphasises that these three issues (three “healths”) should be addressed together through a close partnership of the three sectors.

The lack of appropriate and effective antimicrobials in animals will impact humans on two fronts: first, there may be issues in food security – as unhealthy (or dying) or infected livestock will not be fit for consumption. Second, the effect of antimicrobial resistance pathogens on health: e.g., human pathogens may (e.g., through horizontal gene transfer or related mechanisms) develop resistance against antimicrobials. (69) Furthermore, the unabsorbed and unmetabolized antimicrobials used in livestock can be excreted into the environment and affect the environmental microbial communities as well. (65)

In the realm of AMR, environmental health (or the lack thereof) also contributes to human health. Poor environmental health (for example, the case of untreated effluent waste) may lead to increases in incidences of faecal-oral transmittable diseases, which may include bacterial pathogens resistant to antibiotics. The use of antibiotics, coupled with the risk of resistance developing, may be reduced by improving environmental health. Access to water, sanitation, and hygiene (WASH), and improving food safety standards will help reduce the use of antimicrobials and, in turn, reduce the risk for AMR. (70, 71)

b. *The Quadripartite*

Acknowledging the need for a joint intersectoral response, four international bodies formed a group to address ARM: the Quadripartite. This group consists of the World Health Organization, the Food and Agriculture Organization, the World Organization for Animal Health, and the UN Environment Programme (the most recent addition, in 2022). It is working towards preserving the efficacy of antimicrobials and ensuring equitable access to the same. These international bodies recognize the importance of addressing AMR in varying fronts, and at the different phases of the antibiotic lifecycle, and the role of decreasing infection to decrease the incidences of AMR. (72)

7. Research and New Solutions against AMR

Work to study and address AMR is ongoing, and there is now a better understanding of the mechanistic processes of, and genes involved in AMR (in tuberculosis, for example). New classes of antibiotics have been developed (mainly in the 70s and 80s), and there is a better understanding of how the environment and animal health play a role in AMR in humans. Despite these advances, more must be done on the research front: developing novel therapeutics (73), and research on fungal AMR (74), to name two.

With the heyday of antimicrobial development behind us, the development of novel therapeutics is paramount, as there are not many novel antimicrobials in the development pipeline. From 2017 to 2021, only 12 novel antimicrobial agents were licensed, with 10 of them using mechanisms of action with known resistance pathways. (75) There are incentives for the development of antimicrobials, but there was determined to be a lack of a "pull factor" post-development. Thus, work needs to be done not only to increase innovation but also to ensure that there are sufficient financial incentives post-development to entice pharmaceutical companies to develop novel therapeutics. Research coordination on this front is also required; there is a need to avoid reduplication and to internationalise the antibiotic development pipelines. (76)

Of all the pathogen types that are affected by AMR, fungal AMR is most neglected. (74) There has been a rise in drug-resistant fungal infections around the world, driven by agricultural use of fungicides or by improper use of OTC antifungal creams. (77) While not as prominent as other AMRs, it is noted that fungal infections often cause complications and may become life-threatening. Coupled with their biology (in fungi being eukaryotic), and the lack of vaccines preventing fungal infections, fungal AMRs are an emerging threat that merits more research – in novel therapies, diagnostic strategies, and understanding mechanisms of resistance. (78)

a. *Monitoring mechanisms on AMR (through next-generation sequencing)*

The COVID-19 Pandemic saw an explosion of sequencing capabilities in many countries. Many public health authorities and research institutions adopted next-generation sequencing strategies to monitor the SARS-CoV-2 circulating strains to identify novel variants of concern.

Unlike typical molecular methods (e.g., PCR or quantitative PCR), next-generation sequencing (NGS) produces a large amount of sequence data, which allows researchers to study many aspects of AMR at the nucleotide and genome level. (79, 80) It is high throughput (one can test many samples at once), highly multiplexable, and allows for the researcher to study the whole genome of the pathogen.

With the progressive decrease in the cost of NGS and with the new data analysis pipelines available (81), NGS monitoring of AMR will only become more accessible and mainstream.

NGS has already been applied to AMR surveillance of wastewater. Samples taken at a water treatment facility can be performed to identify the presence of different types of AMR genes. One may be able to study the presence of different sets of AMR genes in different wastewater treatment settings, as in one study comparing a Namibian system with a German system. (82)

NGS can also be used to identify and study antibiotic resistance genes (83) and resistomes (79, 84). For example, NGS was used to study AMR genes in donors' faecal samples, where the researchers identified AMR genes in all samples. (85)

8. Global Efforts on AMR

There is significant variation among countries in their international efforts to control antimicrobial resistance. There is a need to enhance monitoring and evaluation efforts to continuously assess national and global progress. The international response to antimicrobial resistance may not adequately match the magnitude and seriousness of the problem. (86)

a. WHO Global Antimicrobial Resistance and Use Surveillance System "GLASS"

In 2015, the World Health Organization (WHO) Member States unanimously approved the Global Action Plan to tackle antimicrobial resistance (AMR), known as GAP-AMR. The goal of GAP-AMR is to ensure the continuity of successful treatment and prevention of infectious diseases with effective and safe medicines that are quality-assured, used responsibly, and accessible to all who need them. Surveillance is crucial in informing policies and infection prevention and control responses. It is essential for assessing the spread of AMR and monitoring the impact of local, national, and global strategies. In response to this need, the WHO launched the Global Antimicrobial Resistance and Use Surveillance System (GLASS) in 2015. GLASS is the first global collaborative effort to standardise AMR surveillance and is endorsed by the Sixty-eighth World Health Assembly. GLASS provides a standardised approach to collecting, analysing, interpreting, and sharing data from countries. It aims to support capacity building and monitor the status of existing and new national surveillance systems. GLASS promotes a shift from solely laboratory-based surveillance to a system that includes epidemiological, clinical, and population-level data. It also aims to incorporate data on AMR in humans, the food chain, and the environment. GLASS operates through various types of surveillance activities organised into technical modules. These modules include surveillance activities based on routinely available data, as well as targeted activities to generate information for specific purposes based on country and regional needs. GLASS also supports the design and implementation of surveys and studies to improve the quality and representativeness of data. Additionally, GLASS provides guidelines and technical documents to assist countries and regions in building capacity and taking appropriate actions. GLASS operates across all levels of WHO, supported by the WHO AMR Surveillance and Quality Assessment Collaborating Centres Network. It collaborates closely with regional AMR networks such as CAESAR, EARS-Net, ReLAVRA, and WPRACSS. By implementing GAP-AMR and utilising GLASS, countries can work together to combat antimicrobial resistance, ensure the responsible use of antimicrobials, and promote global health security. (87)

b. <u>CDC Investments and Actions</u>

The U.S. Centers for Disease Control and Prevention (CDC) is at the forefront of the country's efforts to combat antimicrobial resistance. Through the Antimicrobial Resistance (AR) Solutions Initiative, the CDC invests in establishing a nationwide infrastructure to identify, respond to, contain, and prevent infections resistant to antimicrobials. These efforts encompass various healthcare settings, communities, the food supply, and the environment like water and soil. The funding provided through the CDC's AR Solutions Initiative supports all 50 state health departments, numerous local health departments, and territories such as Puerto Rico, Guam, and the U.S. Virgin Islands. The CDC works in collaboration with other federal agencies, state and local health departments, patients, public health partners, and the private sector to collectively address this threat. (8) Since 2016, the CDC has invested in over 700 innovative antimicrobial resistance projects in more than 60 countries to mitigate the spread of resistance nationally and globally. These investments and partnerships have led to a transformative approach to combat antimicrobial resistance at all levels. The CDC's activities align with the objectives outlined in the U.S. National Action Plan for Combating Antibiotic-Resistant Bacteria, which was initially released in 2015 and updated in 2020. In fiscal year 2016, Congress allocated $160 million for the CDC to combat antimicrobial resistance. This allocation facilitated the implementation of the AR Solutions Initiative and the pursuit of national goals. The funding has increased to over $197 million as of fiscal year 2023. (88)

The CDC is taking several steps to address antimicrobial resistance globally. These include strengthening laboratory capacity, establishing national tracking systems, contributing to national action plans, implementing healthcare programs, providing technical assistance, establishing "learning laboratories," and improving international collaboration and capacities. (89)

c. <u>Regulatory efforts on AMR Antimicrobial stewardship Good practices - guidelines, toolkits, and Health sector role</u>

Access to quality medical products is crucial for universal health coverage, but substandard and falsified products enter the global supply chain, increasing disease prevalence, exacerbating antimicrobial resistance, and causing adverse health effects. These products also waste resources, lead to economic loss, and increase out-of-pocket spending on medical treatment. The WHO Member States confront a persistent public health challenge in preventing, detecting, and responding to these issues. Since its creation in 2012, the Member State Mechanism on Substandard and Falsified Medical Products has provided a collaborative, inclusive, and transparent means for countries to address this persistent problem. (90)

A range of regulatory efforts have been proposed to combat antimicrobial resistance worldwide. Uchil emphasises the need for a multidisciplinary, collaborative approach, including rational use of antimicrobials and improved infection prevention and control.(91) In the meantime, Diazgranados underscored the need for concerted efforts from multiple sectors, both domestically and internationally, and the strengthening of multinational/international partnerships and regulations. (92) Nwokike highlights the importance of product quality surveillance and other quality assurance measures, particularly in low- and middle-income countries. (93) Hayes calls for enhanced funding and regulations to support antimicrobial stewardship policy and program development, as well as educational interventions for trainees. (94)

Programs for antimicrobial stewardship, or ASPs, are essential and crucial in the battle against antimicrobial resistance. By cutting back on needless antibiotic use, rates of antibiotic resistance, healthcare-associated illnesses, and expenses, ASPs effectively deliver high-value treatment. (95, 96) Furthermore, ASPs are ideally suited to advance the vital domains of patient safety and quality, as well as promote higher healthcare value. (97) "To optimise clinical outcomes while minimising unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms, and the emergence of resistance" is the main objective of these programs, which strive to promote antimicrobial stewardship. (98) ASPs have been developed across all regions. (98-100) Some good practices of antimicrobial stewardship include: avoiding prescribing antibiotics for viral infections such as the common cold, flu, and most sore throats, prescribing antibiotics only when necessary, promoting immunisation, and practising good infection control. (100)

The CDC has specifically addressed antimicrobial stewardship by publishing guidelines known as the Core Elements of Hospital Antibiotic Stewardship Programs. (101) The main components are designed to help hospitals of all sizes and levels of complexity combat the danger of antibiotic resistance and advance patient safety through the use of effective ASPs. The guidelines acknowledge that antimicrobial stewardship is dynamic and that greater flexibility in project and program execution is necessary. Leadership dedication, accountability, pharmacy knowledge, action, monitoring, reporting, and education are among the essential components. (101) The guidance on antimicrobial stewardship (ASP) has led to federal policy mandates, including the U.S. Joint Commission's mandate for accreditation in 2017. (102)

Several organisations and initiatives, in addition to the U.S. CDC, have been involved in antimicrobial stewardship. Hospitalists have been identified as key players in this effort (103), and trainee-led structured antibiotic time-outs have been proposed as a method to improve antimicrobial use. (104) These efforts collectively underscore the need for a multi-faceted approach to antimicrobial stewardship.
Although ASPs are the most used strategy to combat AMR, it's still difficult to decide which interventions are best for each situation, though. The WHO Europe Practical Guide outlines ten stewardship strategies frequently employed to encourage the best possible use of antibiotics in healthcare settings. Administrators, leaders in the healthcare industry, and front-line physicians gain knowledge about the most popular interventions, the research supporting them, and crucial implementation factors, especially for environments with limited resources, which are described in this document. (105) ASPs should be reinforced by facility-specific treatment guidelines, prospective audit and feedback, microbiology, and epidemiological surveillance. Some expanded practices can also be used to make robust ASPs like diagnosis stewardship, discharge antimicrobial stewardship, pharmacy-driven protocols and collaborative practice agreements, and electronic clinical decision support systems in antimicrobial stewardship. (106)

In addition to antimicrobial stewardship programs, several other strategies can be employed to fight antimicrobial resistance. Infection prevention and control practices include measures such as hand hygiene, the use of personal protective equipment, and environmental cleaning to prevent the spread of infections. Improving antibiotic use involves ensuring that antibiotics are prescribed only when necessary, and that the right antibiotic is prescribed for the right duration. Developing new drugs, diagnostics, vaccines, and therapeutics is critical to ensure that we have effective treatments for resistant infections. (107) Strengthening regulatory capacity and quality assurance systems is important to ensure the quality, safety, and efficacy of medicines and other health products including antimicrobials. Building local, national, and regional advocacy and coalitions can help raise awareness about antimicrobial resistance and promote action to combat it. (108) It is indispensable to note that every country can take steps to slow antimicrobial resistance. A comprehensive plan with a One Health approach that involves multiple sectors such as healthcare, food, communities, and the environment can be created and implemented to achieve those goals. (109) Tracking progress and reporting results at the local and global levels is also crucial.

The health sector plays a crucial role in the fight against antimicrobial resistance. Pharmacists are integral to antimicrobial stewardship programs, helping to reduce inappropriate prescriptions and improve clinical outcomes. They can involve themselves in the patient evaluation, the choice of antimicrobial to prescribe, the prescription order, the dispensation of antimicrobials, and the patient monitoring. (109-111) Pharmacists are essential members of antimicrobial stewardship and play many roles in achieving the program's objectives. As antimicrobial stewardship spreads across the patient care continuum, pharmacists will play a critical role in protecting the antibiotic armamentarium and increasing patient care quality. (112) Physicians also have a significant role in preventing and controlling resistance, even though the fight against AMR requires the engagement of many sectors of society. (113) Family physicians play a crucial role in addressing antibiotic resistance by prescribing antibiotics with caution, educating patients, and finding and reporting unexpected treatment failures and suspected resistance (114) The public, including patients, also has a role to play in preventing the spread of resistance. The race against antimicrobial resistance should be a collective responsibility requiring coordinated action at local, national, regional, and international levels to ensure sustained utilisation of antimicrobials. (115) Overall, a coordinated effort involving all stakeholders is necessary to combat antimicrobial resistance.

9. Role of Youth and Medical Students in AMR

AMR poses a critical global health threat, demanding efforts from diverse sectors of society to mitigate its consequences. Thus, youth and medical students could play a pivotal role, by engaging in multifaceted approaches that encompass education, awareness, advocacy, and reshaping healthcare practices. However, within medical school curricula, AMR often receives insufficient attention, leaving graduating students ill-prepared to confront this critical issue.

Education and awareness stand as fundamental pillars in addressing this issue. Recent studies suggest that final-year medical students lack comprehensive knowledge regarding responsible antimicrobial prescribing. Consequently, there is a pressing need to educate students on AMR, not only to cultivate future prudent prescribers but also to ensure knowledge transfer to upcoming generations. (116)

While involvement in drug discovery may be suitable for research-oriented students, a more practical way lies in supporting antimicrobial stewardship, which encompasses evidence-based strategies to demonstrate efficacy in reducing infections caused by resistant organisms. Equipping young individuals and aspiring medical professionals with comprehensive knowledge about antibiotic misuse, the impact of AMR on public health, and the significance of prudent antibiotic stewardship is pivotal. Initiatives such as educational programs, workshops, and community-based campaigns facilitate broader understanding and behavioural change toward responsible antibiotic usage. (117)

To execute this advocacy effectively, it was proposed to the International Federation of Pharmaceutical Manufacturers and Associations the establishment of activist groups by medical students dedicated to addressing AMR. These groups could engage in multifaceted activities, encompassing educational outreach, lobbying for curriculum reforms, organising lecture series, and leveraging social media platforms to amplify their advocacy efforts. Therefore, collaborative ventures with peers from allied healthcare fields and diverse academic disciplines would be emphasised to comprehensively tackle AMR and mobilise a broader movement involving young individuals from various educational backgrounds. Medical students have a role in shaping the agenda against AMR, advocating for concerted action, interdisciplinary collaboration, and grassroots initiatives to combat this pressing healthcare challenge. (118)

Beyond academic settings, the role of youth and medical students extends to advocacy, research, and community engagement. Empowering them and providing platforms for their voices to be heard empowers them to drive substantial change in the fight against AMR, mitigating its impact and preserving antimicrobial efficacy for future generations. A notable example of this is the Quadripartite Working Group on Youth Engagement for Antimicrobial resistance, providing a platform for youth-led and youth-serving organisations across the globe to actively engage in addressing the growing threat and impact of AMR. The working group aims to build the capacity of youth organisations and reach out to the youth to address AMR and to increase the visibility of youth engagement in global AMR action. (119)

10. AMR in Post-Pandemic Recovery

The COVID-19 pandemic has had a significant impact on global health systems and exacerbated existing health challenges. A report by the Centers for Disease Control and Prevention (CDC) provides country-level estimates of the effect of COVID-19 on antimicrobial resistance in the USA. The report reveals a reversal of progress in controlling antimicrobial resistance, with an 18% decline in deaths from antimicrobial resistance from 2012 to 2017 being undone by a 15% increase in drug-resistant nosocomial infection rates in 2020. Pathogen-drug combinations classified as critical by WHO and urgent by the CDC showed alarming increases in infection rates. Strengthening responses to antimicrobial resistance after the pandemic requires recognizing that health security is transnational and that the causes and consequences of health threats transcend national boundaries. The USA, with support from the CDC, is well-positioned to lead efforts in rebuilding post-pandemic public health capacities and addressing antimicrobial resistance in multiple domains. These domains include infection prevention and control, diagnostics, therapeutics development, and surveillance, which present opportunities for shared benefits across health security. (120)

References

1. Environment UN. Antimicrobial resistance: a global threat [Internet]. UNEP - UN Environment Programme. 2020. Available from: https://www.unep.org/topics/chemicals-and-pollution-action/pollution-and-health/antimicrobial-resistance-global-threat
2. Di Martino P. Antimicrobial agents and microbial ecology. AIMS Microbiol. 2022;8(1):1-4.
3. American Society for Microbiology. Policy Pathways to Combat the Global Crisis of Antimicrobial Resistance. 2023.
4. World Health Organization. Antimicrobial resistance Geneva, Switzerland2023 [updated 21 Nov 2023. Available from: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance.

5. World Health Organization. Antimicrobial resistance 2024 [Available from: https://www.who.int/health-topics/antimicrobial-resistance.
6. National Institute of Allergy and Infectious Diseases. Causes of Antimicrobial (Drug) Resistance 2011 [updated 21 Dec 2011. Available from: https://www.niaid.nih.gov/research/antimicrobial-resistance-causes.
7. The World Bank. Urban Development 2024 [Available from: https://www.worldbank.org/en/topic/urbandevelopment/overview.
8. Bruinsma N, Hutchinson JM, van den Bogaard AE, Giamarellou H, Degener J, Stobberingh EE. Influence of population density on antibiotic resistance. Journal of Antimicrobial Chemotherapy. 2003;51(2):385-90.
9. World Health Organization, World Intellectual Property Organization, Organization WT. Antimicrobial resistance – a global epidemic. 2016. p. 1-4.
10. Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. P t. 2015;40(4):277-83.
11. Michael CA, Dominey-Howes D, Labbate M. The antimicrobial resistance crisis: causes, consequences, and management. Front Public Health. 2014;2:145.
12. Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc Natl Acad Sci U S A. 2018;115(15):E3463-e70.
13. McNulty CA, Boyle P, Nichols T, Clappison P, Davey P. The public's attitudes to and compliance with antibiotics. J Antimicrob Chemother. 2007;60 Suppl 1:i63-8.
14. Tellier G, Niederman MS, Nusrat R, Patel M, Lavin B. Clinical and bacteriological efficacy and safety of 5 and 7 day regimens of telithromycin once daily compared with a 10 day regimen of clarithromycin twice daily in patients with mild to moderate community-acquired pneumonia. J Antimicrob Chemother. 2004;54(2):515-23.
15. Nguyen CT, Nguyen HT, Boyer L, Auquier P, Fond G, Do KN, et al. Prevalence and impacts of self-medication in a disadvantaged setting: the importance of multi-dimensional health interventions. Frontiers in Public Health. 2023;11.
16. Rather IA, Kim BC, Bajpai VK, Park YH. Self-medication and antibiotic resistance: Crisis, current challenges, and prevention. Saudi J Biol Sci. 2017;24(4):808-12.
17. Sachdev C, Anjankar A, Agrawal J. Self-Medication With Antibiotics: An Element Increasing Resistance. Cureus. 2022;14(10):e30844.
18. Van Duong D, Binns CW, Van Le T. Availability of antibiotics as over-the-counter drugs in pharmacies: a threat to public health in Vietnam. Trop Med Int Health. 1997;2(12):1133-9.
19. Wright GD. Antibiotic resistance in the environment: a link to the clinic? Curr Opin Microbiol. 2010;13(5):589-94.
20. McCormick JB. Epidemiology of emerging/re-emerging antimicrobial-resistant bacterial pathogens. Current Opinion in Microbiology. 1998;1(1):125-9.
21. Jones RN. The current and future impact of antimicrobial resistance among nosocomial bacterial pathogens. Diagn Microbiol Infect Dis. 1992;15(2 Suppl):3s-10s.
22. Nolte O. Antimicrobial resistance in the 21st century: a multifaceted challenge. Protein Pept Lett. 2014;21(4):330-5.
23. Thabit AK, Crandon JL, Nicolau DP. Antimicrobial resistance: impact on clinical and economic outcomes and the need for new antimicrobials. Expert Opin Pharmacother. 2015;16(2):159-77.
24. French GL. Clinical impact and relevance of antibiotic resistance. Adv Drug Deliv Rev. 2005;57(10):1514-27.
25. Sosa AbdJ. Antimicrobial resistance in developing countries. New York: Springer; 2010. xxiii, 554 p. P.
26. Gajdács M, Urbán E, Stájer A, Baráth Z. Antimicrobial Resistance in the Context of the Sustainable Development Goals: A Brief Review. Eur J Investig Health Psychol Educ. 2021;11(1):71-82.
27. Rice LB. The clinical consequences of antimicrobial resistance. Curr Opin Microbiol. 2009;12(5):476-81.
28. Davis ME, Liu TL, Taylor YJ, Davidson L, Schmid M, Yates T, et al. Exploring Patient Awareness and Perceptions of the Appropriate Use of Antibiotics: A Mixed-Methods Study. Antibiotics (Basel). 2017;6(4).
29. World Health Organization. WHO report on surveillance of antibiotic consumption: 2016-2018 early implementation. WHO; 2018.
30. Chokshi A, Sifri Z, Cennimo D, Horng H. Global Contributors to Antibiotic Resistance. J Glob Infect Dis. 2019;11(1):36-42.
31. Laxminarayan R, Duse A, Wattal C, Zaidi AK, Wertheim HF, Sumpradit N, et al. Antibiotic resistance-the need for global solutions. Lancet Infect Dis. 2013;13(12):1057-98.
32. O'Neill J. Tackling drug-resistant infections globally: final report and recommendations. Government of the United Kingdom; 2016 19 May 2016.

IFMSA
International Federation of Medical Students' Associations

33. Jasovský D, Littmann J, Zorzet A, Cars O. Antimicrobial resistance-a threat to the world's sustainable development. Ups J Med Sci. 2016;121(3):159-64.
34. Llibre JM. Time to get serious with HIV-1 resistance in sub-Saharan Africa. Lancet Infect Dis. 2017;17(3):241-3.
35. Fiebig U, Altmann B, Hauser A, Koppe U, Hanke K, Gunsenheimer-Bartmeyer B, et al. Transmitted drug resistance and subtype patterns of viruses from reported new HIV diagnoses in Germany, 2017-2020. BMC Infect Dis. 2023;23(1):673.
36. Aung Pyae P, François N. The Artemisinin Resistance in Southeast Asia: An Imminent Global Threat to Malaria Elimination. In: Sylvie M, Vas D, editors. Towards Malaria Elimination. Rijeka: IntechOpen; 2018. p. Ch. 2.
37. Shrestha P, Cooper BS, Coast J, Oppong R, Do Thi Thuy N, Phodha T, et al. Enumerating the economic cost of antimicrobial resistance per antibiotic consumed to inform the evaluation of interventions affecting their use. Antimicrob Resist Infect Control. 2018;7:98.
38. Thorpe KE, Joski P, Johnston KJ. Antibiotic-Resistant Infection Treatment Costs Have Doubled Since 2002, Now Exceeding $2 Billion Annually. Health Aff (Millwood). 2018;37(4):662-9.
39. Antibiotic resistance threats in the United States, 2013. 2013.
40. Jonas OB, Irwin A, Berthe FCJ, Le Gall FG, Marquez PV. Drug-resistant infections : a threat to our economic future. The World Bank; 2017.
41. Prestinaci F, Pezzotti P, Pantosti A. Antimicrobial resistance: a global multifaceted phenomenon. Pathog Glob Health. 2015;109(7):309-18.
42. Friedman ND, Temkin E, Carmeli Y. The negative impact of antibiotic resistance. Clin Microbiol Infect. 2016;22(5):416-22.
43. Naylor NR, Atun R, Zhu N, Kulasabanathan K, Silva S, Chatterjee A, et al. Estimating the burden of antimicrobial resistance: a systematic literature review. Antimicrob Resist Infect Control. 2018;7:58.
44. Li B, Webster TJ. Bacteria antibiotic resistance: New challenges and opportunities for implant-associated orthopedic infections. J Orthop Res. 2018;36(1):22-32.
45. Santoro-Lopes G, de Gouvêa EF. Multidrug-resistant bacterial infections after liver transplantation: an ever-growing challenge. World J Gastroenterol. 2014;20(20):6201-10.
46. Anderson M, Clift C, Schulze K, Sagan A, Nahrgang S, Ait Ouakrim D, et al. European Observatory Policy Briefs. Averting the AMR crisis: What are the avenues for policy action for countries in Europe? Copenhagen (Denmark): European Observatory on Health Systems and Policies © World Health Organization 2019(acting as the host organization for, and secretariat of, the European Observatory on Health Systems and Policies). 2019.
47. Utt E, Wells C. The global response to the threat of antimicrobial resistance and the important role of vaccines. Pharmaceuticals Policy and Law. 2016;18:179-97.
48. O'Neill J. Antimicrobial resistance : tackling a crisis for the health and wealth of nations / the Review on Antimicrobial Resistance chaired by Jim O'Neill.; 2014 Dec 2014.
49. TB Alliance. TB is a Pandemic 2024 [Available from: https://www.tballiance.org/why-new-tb-drugs/global-pandemic.
50. Taylor J, Hafner M, Yerushalmi E, Smith R, Bellasio J, Vardavas R, et al. Estimating the economic costs of antimicrobial resistance: Model and Results. Santa Monica, CA: RAND Corporation; 2014.
51. Lekagul A, Tangcharoensathien V, Yeung S. Patterns of antibiotic use in global pig production: A systematic review. Vet Anim Sci. 2019;7:100058.
52. Food and Agriculture Organization of the United Nations. Animal production: FAO; 2024 [Available from: https://www.fao.org/antimicrobial-resistance/key-sectors/animal-production/en/.
53. Hao H, Cheng G, Iqbal Z, Ai X, Hussain HI, Huang L, et al. Benefits and risks of antimicrobial use in food-producing animals. Front Microbiol. 2014;5:288.
54. Van Boeckel TP, Brower C, Gilbert M, Grenfell BT, Levin SA, Robinson TP, et al. Global trends in antimicrobial use in food animals. Proc Natl Acad Sci U S A. 2015;112(18):5649-54.
55. Kim C, Holm M, Frost I, Hasso-Agopsowicz M, Abbas K. Global and regional burden of attributable and associated bacterial antimicrobial resistance avertable by vaccination: modelling study. BMJ Global Health. 2023;8(7):e011341.
56. World Health Organization. Leveraging Vaccines to Reduce Antibiotic Use and Prevent Antimicrobial Resistance: An Action Framework. WHO; 2020.
57. Micoli F, Bagnoli F, Rappuoli R, Serruto D. The role of vaccines in combatting antimicrobial resistance. Nature Reviews Microbiology. 2021;19(5):287-302.

58. World Health Organization. WASH and antimicrobial resistance 2024 [Available from: https://www.who.int/teams/environment-climate-change-and-health/water-sanitation-and-health/burden-of-disease/wash-and-antimicrobial-resistance.
59. Sutherland D. Effective WASH to prevent infections and reduce the emergence of AMR. Food and Agriculture Organization of the United Nations,; 2022.
60. World Health Organization. Antimicrobial Resistance Fact Sheet.
61. MacIntyre CR, Bui CM. Pandemics, public health emergencies and antimicrobial resistance - putting the threat in an epidemiologic and risk analysis context. Arch Public Health. 2017;75:54.
62. ReAct Group. Antimicrobial resistance and universal health coverage: What's the deal? ; 2019.
63. ReAct Group. Why are children more vulnerable to resistant infections? 2019 [updated 14 Nov 2019. Available from: https://www.reactgroup.org/news-and-views/news-and-opinions/year-2019/why-are-children-more-vulnerable-to-amr/.
64. Satyavrath A, Serrano S, Kalanxhi E. Poverty and Antimicrobial Resistance 2022 [updated 25 Nov 2022. Available from: https://onehealthtrust.org/news-media/blog/poverty-and-antimicrobial-resistance/.
65. Caneschi A, Bardhi A, Barbarossa A, Zaghini A. The Use of Antibiotics and Antimicrobial Resistance in Veterinary Medicine, a Complex Phenomenon: A Narrative Review. Antibiotics (Basel). 2023;12(3).
66. Yuan M, Huang Z, Malakar PK, Pan Y, Zhao Y, Zhang Z. Antimicrobial resistomes in food chain microbiomes. Critical Reviews in Food Science and Nutrition.1-22.
67. US Centers for Disease Control and Prevention. One Health Basics: US CDC; 2023 [updated 28 Sept 2023. Available from: https://www.cdc.gov/onehealth/basics/index.html.
68. Lerner H, Berg C. The concept of health in One Health and some practical implications for research and education: what is One Health? Infect Ecol Epidemiol. 2015;5:25300.
69. Alam M-U, Rahman M, Abdullah Al M, Islam MA, Asaduzzaman M, Sarker S, et al. Human exposure to antimicrobial resistance from poultry production: Assessing hygiene and waste-disposal practices in Bangladesh. International Journal of Hygiene and Environmental Health. 2019;222(8):1068-76.
70. Pinto Jimenez CE, Keestra S, Tandon P, Cumming O, Pickering AJ, Moodley A, et al. Biosecurity and water, sanitation, and hygiene (WASH) interventions in animal agricultural settings for reducing infection burden, antibiotic use, and antibiotic resistance: a One Health systematic review. The Lancet Planetary Health. 2023;7(5):e418-e34.
71. Musoke D, Namata C, Lubega GB, Niyongabo F, Gonza J, Chidziwisano K, et al. The role of Environmental Health in preventing antimicrobial resistance in low- and middle-income countries. Environ Health Prev Med. 2021;26(1):100.
72. Food and Agriculture Organization of the United Nations. Antimicrobial Resistance 2024 [Available from: https://www.fao.org/antimicrobial-resistance/quadripartite/who-we-are/en.
73. Lack of innovation set to undermine antibiotic performance and health gains [press release]. Geneva, Switzerland: WHO, 22 Jun 2022 2022.
74. Fisher MC, Alastruey-Izquierdo A, Berman J, Bicanic T, Bignell EM, Bowyer P, et al. Tackling the emerging threat of antifungal resistance to human health. Nature Reviews Microbiology. 2022;20(9):557-71.
75. World Health Organization. 2021 Antibacterial agents in clinical and preclinical development: an overview and analysis. WHO; 2022 27 May 2022.
76. Mattar C, Edwards S, Baraldi E, Hood J. An overview of the global antimicrobial resistance research and development hub and the current landscape. Current Opinion in Microbiology. 2020;57:56-61.
77. Lockhart SR, Chowdhary A, Gold JAW. The rapid emergence of antifungal-resistant human-pathogenic fungi. Nature Reviews Microbiology. 2023;21(12):818-32.
78. Gow NAR, Johnson C, Berman J, Coste AT, Cuomo CA, Perlin DS, et al. The importance of antimicrobial resistance in medical mycology. Nature Communications. 2022;13(1):5352.
79. Cason C, D'Accolti M, Soffritti I, Mazzacane S, Comar M, Caselli E. Next-generation sequencing and PCR technologies in monitoring the hospital microbiome and its drug resistance. Front Microbiol. 2022;13:969863.
80. Bengtsson-Palme J, Larsson DGJ, Kristiansson E. Using metagenomics to investigate human and environmental resistomes. Journal of Antimicrobial Chemotherapy. 2017;72(10):2690-703.
81. Sherry NL, Horan KA, Ballard SA, Gonçalves da Silva A, Gorrie CL, Schultz MB, et al. An ISO-certified genomics workflow for identification and surveillance of antimicrobial resistance. Nature Communications. 2023;14(1):60.

82. Agrawal S, Orschler L, Sinn J, Lackner S. High-throughput profiling of antibiotic resistance genes in wastewater: comparison between a pond system in Namibia and an activated sludge treatment in Germany. Journal of Water and Health. 2020;18(6):867-78.
83. Li B, Yan T. Metagenomic next generation sequencing for studying antibiotic resistance genes in the environment. Adv Appl Microbiol. 2023;123:41-89.
84. Afridi OK, Ali J, Chang JH. Next-Generation Sequencing Based Gut Resistome Profiling of Broiler Chickens Infected with Multidrug-Resistant Escherichia coli. Animals (Basel). 2020;10(12).
85. Guernier-Cambert V, Chamings A, Collier F, Alexandersen S. Diverse Bacterial Resistance Genes Detected in Fecal Samples From Clinically Healthy Women and Infants in Australia-A Descriptive Pilot Study. Front Microbiol. 2021;12:596984.
86. Patel J, Harant A, Fernandes G, Mwamelo AJ, Hein W, Dekker D, et al. Measuring the global response to antimicrobial resistance, 2020–21: a systematic governance analysis of 114 countries. The Lancet Infectious Diseases. 2023;23(6):706-18.
87. World Health Organization. Global Antimicrobial Resistance and Use Surveillance System (GLASS) 2024 [Available from: https://www.who.int/initiatives/glass.
88. US Centers for Disease Control and Prevention. National Center for Emerging and Zoonotic Infectious Diseases (NCEZID) Accomplishments 2022: US CDC; 2022 [Available from: https://www.cdc.gov/ncezid/what-we-do/2022-highlights/index.html.
89. US Centers for Disease Control and Prevention. Global Action to Fight Antimicrobial Resistance 2021 [Available from: https://www.cdc.gov/drugresistance/solutions-initiative/global.html.
90. World Health Organization. The WHO Member State Mechanism on Substandard and Falsified Medical Products. WHO; 2020.
91. Uchil RR, Kohli GS, Katekhaye VM, Swami OC. Strategies to combat antimicrobial resistance. J Clin Diagn Res. 2014;8(7):Me01-4.
92. Diazgranados CA, Cardo DM, McGowan JE, Jr. Antimicrobial resistance: international control strategies, with a focus on limited-resource settings. Int J Antimicrob Agents. 2008;32(1):1-9.
93. Nwokike J, Clark A, Nguyen PP. Medicines quality assurance to fight antimicrobial resistance. Bull World Health Organ. 2018;96(2):135-7.
94. Hayes JF. Fighting Back against Antimicrobial Resistance with Comprehensive Policy and Education: A Narrative Review. Antibiotics (Basel). 2022;11(5).
95. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. Executive Summary: Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. 2016;62(10):1197-202.
96. Dellit TH, Owens RC, McGowan JE, Jr., Gerding DN, Weinstein RA, Burke JP, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis. 2007;44(2):159-77.
97. Nagel JL, Stevenson JG, Eiland EH, 3rd, Kaye KS. Demonstrating the value of antimicrobial stewardship programs to hospital administrators. Clin Infect Dis. 2014;59 Suppl 3:S146-53.
98. Saleem Z, Godman B, Cook A, Khan MA, Campbell SM, Seaton RA, et al. Ongoing Efforts to Improve Antimicrobial Utilization in Hospitals among African Countries and Implications for the Future. Antibiotics (Basel). 2022;11(12).
99. Apisarnthanarak A, Kwa AL, Chiu CH, Kumar S, Thu LTA, Tan BH, et al. Antimicrobial stewardship for acute-care hospitals: An Asian perspective. Infect Control Hosp Epidemiol. 2018;39(10):1237-45.
100. Howard P, Pulcini C, Levy Hara G, West RM, Gould IM, Harbarth S, et al. An international cross-sectional survey of antimicrobial stewardship programmes in hospitals. J Antimicrob Chemother. 2015;70(4):1245-55. 100 HSE.ie. Antimicrobial Stewardship 2024 [https://www.hse.ie/eng/about/who/healthwellbeing/our-priority-programmes/hcai/antimicrobial-resistance/antimicrobial-stewardship/]. Available from: https://www.hse.ie/eng/about/who/healthwellbeing/our-priority-programmes/hcai/antimicrobial-resistance/antimicrobial-stewardship/.
101. US Centers for Disease Control and Prevention. Core Elements of Antibiotic Stewardship: US CDC; 2023 [Available from: https://www.cdc.gov/antibiotic-use/core-elements/index.html.
102. APPROVED: New Antimicrobial Stewardship Standard. Jt Comm Perspect. 2016;36(7):1, 3-4, 8.
103. Srinivasan A. Engaging hospitalists in antimicrobial stewardship: the CDC perspective. J Hosp Med. 2011;6 Suppl 1:S31-3.

IFMSA
International Federation of Medical Students' Associations

104. Lee TC, Frenette C, Jayaraman D, Green L, Pilote L. Antibiotic self-stewardship: trainee-led structured antibiotic time-outs to improve antimicrobial use. Ann Intern Med. 2014;161(10 Suppl):S53-8.
105. World Health Organization. Antimicrobial stewardship interventions: a practical guide. WHO; 2021.
106. Tinker NJ, Foster RA, Webb BJ, Haydoura S, Buckel WR, Stenehjem EA. Interventions to optimize antimicrobial stewardship. Antimicrob Steward Healthc Epidemiol. 2021;1(1):e46.
107. US Centers for Disease Control and Prevention. Global Strategies to Fight Antibiotic Resistance: US CDC; 2021 [Available from: https://www.cdc.gov/drugresistance/intl-activities/global-strategies.html.
108. Majumder MAA, Rahman S, Cohall D, Bharatha A, Singh K, Haque M, et al. Antimicrobial Stewardship: Fighting Antimicrobial Resistance and Protecting Global Public Health. Infect Drug Resist. 2020;13:4713-38.
109. Garau J, Bassetti M. Role of pharmacists in antimicrobial stewardship programmes. Int J Clin Pharm. 2018;40(5):948-52.
110. Apisarnthanarak A, Camins B, Jantarathaneewat K. The role of the clinical pharmacist in antimicrobial stewardship in Asia: A review. Antimicrobial Stewardship & Healthcare Epidemiology. 2022;2(1):e176.
111. Otieno PA, Campbell S, Maley S, Obinju Arunga T, Otieno Okumu M. A Systematic Review of Pharmacist-Led Antimicrobial Stewardship Programs in Sub-Saharan Africa. Int J Clin Pract. 2022;2022:3639943.
112. Parente DM, Morton J. Role of the Pharmacist in Antimicrobial Stewardship. Med Clin North Am. 2018;102(5):929-36.
113. Duncan S, Duncan CJ. The emerging threat of untreatable gonococcal infection. N Engl J Med. 2012;366(22):2136.
114. Solomon SL, Oliver KB. Antibiotic resistance threats in the United States: stepping back from the brink. Am Fam Physician. 2014;89(12):938-41.
115. Premanandh J, Samara BS, Mazen AN. Race Against Antimicrobial Resistance Requires Coordinated Action - An Overview. Front Microbiol. 2015;6:1536.
116. Launer D. Can medical students do anything useful to support the antimicrobial resistance agenda? JAC Antimicrob Resist. 2022;4(5):dlac110.
117. Reframing Resistance | Reports [Internet]. Wellcome. Available from: https://wellcome.org/reports/reframing-antimicrobial-resistance-antibiotic-resistance
118. Luka S, Khan MI. Youth perspective: The AMR burden and opportunities to overcome it: IPFMA; 2021 [Available from: https://www.ifpma.org/insights/youth-perspective-the-amr-burden-and-opportunities-to-overcome-it/.
119. Report of the inaugural meeting of the Quadripartite working group on youth engagement for AMR [Internet]. www.who.int. [cited 2024 Jan 29]. Available from: https://www.who.int/publications/m/item/report-of-the-inaugural-meeting-of-the-quadripartite-working-group-on-youth-engagement-for-amr
120. Patel J, Sridhar D. The pandemic legacy of antimicrobial resistance in the USA. The Lancet Microbe. 2022;3(10):e726-e7.