IFMSA Policy Document
Antimicrobial Resistance

Proposed by IFMSA Team of Officials
Adopted at the IFMSA Hybrid General Assembly August Meeting 2021.

Policy Commission

- **Salman Khan; MSAI India**
- **Anika Zainab; IFMSA Pakistan**
- **Liaison Officer to Student Organizations Olayinka Fakorede**

[skhan2929@gmail.com, zainabanika50@gmail.com, loso@ifmsa.org]

Policy Statement

Introduction

Antimicrobial resistance (AMR) is defined as the process by which bacteria, viruses, fungi and parasites change by time and are no longer responding to antimicrobials, making infections more difficult to treat and increasing the risk of disease spread, severe illness and death. AMR is considered one of the greatest challenges the world is facing and has been declared by the WHO as one of the top 10 global health threats facing humanity. This highlights the need for more focus on addressing AMR, tackling its causes and preventing its detrimental consequences.

IFMSA Position

The International Federation of Medical Students Associations (IFMSA) acknowledges the critical situation of Antimicrobial resistance as a global health issue and a silent pandemic. The IFMSA affirms the need for an intersectoral collaborative approach, between all key stakeholders, in addressing the AMR challenge, while focusing on the interlinkage between Antimicrobial resistance and health and non-health sectors, in order to ensure that its causes, existing relations and consequences can be tackled in all policies.

Call to Action

Governments

- Collaborate with all key stakeholders, including youth, in the formulation, implementation, monitoring and evaluation of Antimicrobial Resistance-related prevention, research, and development initiatives.
- Provide technical and financial assistance to strengthen and support interprofessional collaboration initiatives to raise awareness, advocate, and lead antimicrobial stewardship via One Health approach.
- Adopt, implement and monitor effective and sustainable National Action Plans to counter the antimicrobial resistance through promotion, surveillance, regulation, monitoring, vaccination, and evaluations.
- Create, adopt and monitor a regulatory framework to extinguish antimicrobial over-the-counter access in veterinary, environmental and human health.
- Support research and development of new diagnostic tools and methods for infectious diseases and new antimicrobial classes with the relevant manufacturers and pharmaceutical companies.
- Update antimicrobial drug registration requirements to facilitate their entry to the market without compromising their safety and effectiveness.

WHO, UN and International Agencies

- Encourage member states to work on research regarding antimicrobial resistance and the development of new antibiotics and vaccines.
- Create policy guidelines and provide support to the Member States in developing a regulatory framework to extinguish antimicrobial agents misuse in all sectors.
- Educate consumers and healthcare professionals on the correct use of antibiotics through the creation of campaigns and other suitable initiatives, with other key stakeholders, including youth
- Encouraging and advocating for AMR-related innovation and research, as well as the development of novel diagnostics, vaccines, and medicines.
- Develop campaigns and promote public awareness on AMR, including its causes, prevention measures and its consequences.

- Assist more countries in developing their national AMR surveillance system to meet GLASS requirements and encourage them to enroll in it.

International Organizations and NGOs

- Advocate for developing more patent-free antimicrobial drugs to reduce their costs for lower and middle-income countries (LMICs).
- Foster the international collaboration efforts towards researching and developing new antimicrobial drugs and vaccines.
- Assist governments in their assessment and planning of their financial needs to achieve their AMR national action plan.
- Promote preventive plans and screening to avoid unnecessary use of antimicrobials.

Healthcare facilities, institutions and universities

- Incorporate interprofessional-approach-based competency framework, antimicrobials rational prescription, infection control, and surveillance.
- Implement antimicrobial stewardship programs.
- Involve students in the antimicrobial, vaccine, and diagnostics research and development.
- Apply national and international guidelines regarding infectious disease diagnosis and management.

Health workforce and healthcare professionals

- Follow infectious diseases management guidelines by governments and healthcare facilities.
- Provide AMR-related information in a language, format, and technical level that is understandable to patients.
- Raise awareness on the importance of following antibiotics prescription by practitioners and the consequences of its unnecessary use.
- Educate patients on hygiene measures, prevention of infections, and vaccination.

Agriculture and livestock sectors

- Educate livestock producers and farmers on the evidence-based use of antimicrobials in the prevention and treatment of infections in farm animals and crops.
- Establish data collection, monitoring, and surveillance systems to control antimicrobial use and resistance in the agriculture and livestock sectors.

Pharmaceutical Companies

- Invest in research and development on new antimicrobials, diagnostics, and vaccines, with a special focus on priority pathogens.
- Employ ethical standards to regulate the exertion of undue influence over prescribers.
- Prioritize capacity building on Antimicrobial Stewardship (AMS) technical knowledge for employees and healthcare professionals.
- Implement internal manufacturing quality and surveillance policies to ensure minimum waste discharge.

IFMSA NMOs and other healthcare student organizations

- Advocate for implementation and incorporation of AMR and One Health in medical curricula
- Initiate active advocacy and promotions for accountable use of antimicrobial agents as well as prioritization of AMR in national action plans and policies.
- Initiate national youth health students' alliances to tackle AMR and promote the importance of One Health approach among youths.
- Promote interprofessional, governmental, and civil society collaborations in tackling AMR.
- Raise the awareness of medical students about the possible public pressure and demand to prescribe antibiotics and how to overcome it.

Position Paper

Background information:

Antimicrobials have long been recognised as one of the most important medical breakthroughs of the twentieth century. Millions of lives have been saved thanks to antibiotics, which have permitted crucial medical treatments such as surgeries and cancer treatments.[1] The World Health Organization (WHO) defines antimicrobial resistance (AMR) as the ability of microorganisms (including bacteria, fungi, viruses and parasites) to become resistant when they are exposed to antimicrobial drugs (such as antibiotics, antifungals, antivirals and antimalarials) used to treat the infections they cause. They are referred to as "superbugs".[2][3] Antimicrobial resistance (AMR) threatens the effective course of medicines available to treat large numbers of bacterial, viral, fungal and parasitic diseases. It occurs when the microbial agents change their characteristics over time leading to resistance against medicines rendering pre-existing drugs useless.[2]

The World Health Organization has proclaimed AMR to be one of the top ten global public health challenges confronting mankind, with irrational medication usage being the primary cause of drug-resistant diseases.[3] AMR is estimated to cause 700,000 deaths worldwide each year. Up to 9.5 million individuals might die each year if current resistance rates rise by 40%. Hospitals spend, on average, an additional USD 10 000 to 40 000 to treat a patient infected by resistant bacteria according to the "AMR Policy Insights 2016" by The Organisation for Economic Co-operation and Development countries (OECD). At current resistance rates, the total GDP effect in The Organisation for Economic Co-operation and Development countries, accounting for increased healthcare expenditure, would amount to 2.9 trillion USD by 2050.[4]

The World Health Organization (WHO) has long recognised the need for a more effective and well-coordinated global response to AMR. The Evolving Threat of Antimicrobial Resistance - Options for Action was issued by WHO in 2012, and it proposed a mixture of actions, including strengthening health systems and surveillance, encouraging the development of appropriate new vaccines and drugs, improving antimicrobial use in the community and hospitals, infection prevention and control, in addition to political commitment.[5] The formulation of this global action plan on antimicrobial resistance, which was adopted by the United Nations General Assembly in resolution WHA67.25 in May 2015, represents a global consensus that antimicrobial resistance is a serious threat to human health.[6]

Antimicrobial resistance: a global concern

AMR develops over time, most commonly as a result of genetic alterations. People, animals, food, plants, and the environment all have antimicrobial-resistant microbes (in water, soil and air). They can be transmitted from person to person or between humans and animals, as well as through animal-derived foods. The misuse and overuse of antimicrobials; lack of access to clean water, sanitation, and hygiene (WASH) for both humans and animals; poor infection and disease prevention and control in healthcare facilities and farms; and poor access to high-quality, affordable medicines, vaccines, and diagnostics; lack of awareness and expertise; and lack of legislative enforcement are all major drivers of antimicrobial resistance.[3]

The emergence and spread of drug-resistant organisms/superbugs pose a challenge to current therapies, even for common illnesses, due to the development of several acquired mechanisms. In addition, quality antimicrobials have been scarce. Antibiotic shortages are wreaking havoc on many countries' healthcare systems at different stages of development. The impact of AMR on different nations' economies and health systems is substantial since it impacts the quality of care provided to patients by lengthening hospital stays and making treatment more expensive and intense. This,

therefore, emphasizes the importance of AMR as a global health issue that needs much focus and attention. [3]

Discussion

Determinants of AMR

Alongside people's individual characteristics and behaviors that influence their health, there are socio-economic and environmental factors, the Determinants of Health. [7] The socio-economic environment - the conditions in which people are born, grow, live, and age driven by money, power, and resources distribution - can contribute to 45% to 0% of the variations in health status. [8]

AMR is a complex global health problem with complex causes and determinants. [3] To better understand these determinants we referenced two sources with two different approaches to identifying and categorizing them; The first grouped them into four categories: pathogen and microbial ecology, prescribing practices of physicians, population characteristics, and politics and healthcare policy [9]; while the other source grouped them into three categories: determinants of antibiotics used by the community, determinants of prescribing antibiotics, and determinants of antibiotics dispensing and sales. [10]

Determinants of prescribing antimicrobials

One of the main determinants of antimicrobial prescribing is diagnostic uncertainty. [9] It leads to increased antibiotic prescribing in some infections and antimicrobial resistance rates. [9][11] This uncertainty usually arises from limitations in resources and diagnostic capacities, especially in the primary health care setting; [11][12] among these is the lack of rapid and sufficient diagnostic tests. [13]

Molecular microbiological tests help differentiate between bacterial and viral infections, and provide information about the type of antimicrobial needed for treatment. However, conventional microbiological tests such as cultures and susceptibility tests take time. [14] Oftentimes, physicians initiate empirical antimicrobial therapy while waiting for the results of conventional tests in fear of complications of untreated infection. [9][13] As an example, microbiological diagnosis of community-acquired pneumonia (CAP) - the fourth cause of death in 2019 among other lower respiratory tract infections [15] - was successful in less than 50% of cases. To avoid complications and possible mortalities, physicians have to initiate empirical antimicrobial therapy. [14]

Developing faster and more reliable microbiological tests may contribute to better prescribing of antimicrobials. [14] In a study on molecular detection of microbes in different types of infections, nucleic acid amplification tests (NAAT) resulted in rapid pathogen identification and early initiation of specific antimicrobials. [16] However, it is crucial to couple rapid diagnostic tests with antimicrobials stewardship programs to improve antimicrobial drugs prescription. [17]

Other determinants of prescribing antimicrobial drugs are related to patients' behavior. In several studies, physicians reported patients' pressure and demand as an impeller to prescribe unnecessary antibiotics [18][19][20]. Doctors submitted to patients' pressure due to several factors: fear of repercussions of patient dissatisfaction, fear of medicolegal sanctions, fear of decreased income, and avoid wasting time to explain their decision. [20]

Determinants related to population characteristics

Several determinants are related to population characteristics: travel, health beliefs and education, self-medication, and financial considerations. [21][9]

Globalization paved the path for easier traveling and migration between countries. As people travel to other communities and populations they are likely to be exposed to resistant microbes or introduce such microbes to these populations; There are variations between countries when it comes to the prevalence of AMR. [22]

Health beliefs and illiteracy in some populations lead them to believe that antibiotics treat any type of infection. [10] Barker et al. conducted a study in a village in India that showed that almost half of the participants reported receiving health education in their community. Yet, none could correctly define antibiotics or their function. [21] Another large study in Japan reported that 80% of the participants did not know that antibiotics do not treat viral infections and are ineffective against common colds. The same study reported that 10% of the participants requested antibiotics from their doctors, and almost 23% adjusted their dosage without consulting their doctors. [23]

Inadequate access and expensive high-quality antimicrobial treatment are some of the main factors driven by poverty and increased AMR. [24] Some patients avoid doctor consultation and self-medicate instead to save on costs. Others buy a few tablets of antimicrobial drugs and stop medicating once the symptoms disappear. [21]

Consequences of AMR

One of the major consequences of drug resistance is decreasing the effectiveness of antibiotics leading to difficulty in treating infections which could increase morbidity and mortality. [3] According to a study, 700, 000 individuals lose their lives because of infections that cannot be treated due to drug resistance. [25] Globally, the rise of AMR on an individual level will mean that life-saving medical procedures such as debridement, disinfection, amputation, and isolation will take longer in treatment. It will also mean that these procedures will become more invasive, and less successful. [26]

As an effect of longer and less successful infection treatment from AMR, the economic burden will also become a significant issue because the productivity of the population will be affected through prolonged hospital stays and the need for more expensive and intensive care [3]. AMR is projected to cost from $300 billion to more than $1 trillion annually by 2050 worldwide. Organ transplantation will also become a challenge because of AMR due to risks of exposure to different infections. [25] In addition, there will be an increased load of burden that will be placed on the family and communities who will care for those suffering which will widen the gap of health equity. [26]

Overall, the consequences of AMR will become a barrier to achieve Universal Health Coverage (UHC), which is deemed as the single most powerful concept that public health has to offer. An essential component of UHC is medicines, including antibiotics and AMR can render existing antibiotics ineffective, in addition to the fact that the availability of new ones will take time and will most likely be unaffordable. [27] Reports estimated that if there will be no strong and effective action taken against AMR, there will be 10 million people that will die across the world by 2050. [25]

AMR and infectious diseases

AMR and Emerging and Reemerging Infections

The twenty-first century has seen the emergence of many new, high-profile diseases from severe acute respiratory syndrome (SARS) to avian influenza A (H7N9). Such diseases - called emerging infectious diseases - are of great public health concern. The World Health Organization defines an emerging infectious disease as one that has appeared in an affected population for the first time, or has existed previously but is rapidly increasing, either regarding its spread to other geographical areas or the number of new cases within a population. In addition, old diseases in a new clinical form that may be severe or fatal, these are known as re-emerging diseases. [28] Many emerging and re-emerging diseases are zoonotic in origin, and data show that of all known infectious diseases zoonoses constitute about 60%. While by classification, 40% of fungi, 50% of bacteria, 70% of protozoa, 80% of viruses, and 95% of helminths that infect the human population are zoonotic. [29] There are many factors that precipitate the emergence of new diseases, and this eventually allows infectious diseases to spread more easily among the new hosts. It also enables infectious agents to evolve into new ecological niches, to reach and adapt to new hosts. These factors include urbanization and destruction of natural habitats, resulting in humans and animals living in close proximity; global climate change and changing ecosystems; changes in populations of reservoir hosts or intermediate insect vectors; and microbial genetic mutation. [28]

In 2013, the Central Asian Journal of Global Health mentioned that there is a poor understanding of how zoonotic pathogens evolve from natural ecology and cause diseases. The dynamics of disease exposure to human beings may be altered by various circumstances, such as animal production, extraction of natural resources, and antimicrobial application. When factors that affect emerging and reemerging diseases are not addressed, there will be no borders between ecosystems, which will lead to AMR. [29] The most important risk factors for a patient to develop a resistant bacterial infection are poor infection prevention and overuse of antimicrobials, while many of the infections are treatable but due to AMR, there is shrinkage of the existing therapeutic arsenal of antimicrobial agents. [30]

There are also potential threats that could affect antimicrobial stewardship and drive antimicrobial resistance during the current COVID-19 pandemic. Many individuals who are presented with mild or without pneumonia or moderate disease pneumonia receive antibiotics. [31] Thus, there is a need to reduce the number of prescriptions for these types of infections to prevent AMR and empower the public to self-manage their symptoms without the use of antimicrobial agents. [30]

AMR and Vaccination

The correlation between AMR and vaccines is simple yet fundamental. In other words, getting a vaccine will ensure protection against the targeted microbial(s), and in case of disease contraction, chances of antibiotic need are lower. The reasons why vaccines help in preventing AMR are simple, but the work that needs to be done is a little bit more complicated. [32]

Although it might seem that vaccines, against bacteria, are the only way to prevent AMR, the role vaccines play, in this fight, is broader and often overlooked. Starting with viral vaccines, they can help prevent AMR, by reducing secondary bacterial infections thus decreasing the need for antibiotics to treat them. Studies conducted in Turkey and Canada showed a decrease in otitis media infections and fewer influenza-related antibiotic prescriptions after the introduction of the influenza vaccine. [33][34] Another way is reducing inappropriate writing of antibiotic prescriptions for viral infections. Vaccines

are also important where antibiotics are overused, like in veterinary and agriculture to limit prophylactic use of antibiotics in these sectors. [35]

With all the benefits that come from vaccines in preventing AMR, there are still some challenges. Even though promising results have been apparent as aforementioned, many more vaccines for antibiotic-resistant bacteria are still needed; hence the need for more funds and work allocated to research on vaccines and trials, while orienting the work towards target populations to achieve better results. [33]

With proper usage of tools, vaccines can help further in fighting AMR, but for that, an assessment and a plan are needed. In a WHO AMR initiative meeting, a report was shared on the potential of vaccines to prevent AMR. What is needed is not only research, but also to prioritize vaccines in the context of AMR, and to standardize the discussion on vaccines while evaluating the future and solutions of AMR. [32]

AMR and WASH

The discharge of excreta and the presence of antimicrobial agents and pollutants weaken or deplete most populations of target bacteria thus, allowing resistant strains to remain. When this continues, antimicrobial resistance can occur in microorganisms in an environmental setting. [36] As a result of decades of overuse, inappropriate use of antibiotics and other antimicrobial agents -- antimicrobial-resistant bacteria and AMR genes persist and become widespread contaminants in water and other environmental media, including wastewater and human excreta used for agricultural or aquaculture purposes or eventually discharged to the environment where they can flourish for long periods. Consequently, there is evidence on further emergence and selection of new AMR traits in bacteria, including pathogenic bacteria of human health concern. The (aquatic) environment plays a significant role in the emergence and spread of AMR, by acting as a collecting vessel of resistant bacteria from animals and humans treated with antibiotics; offering route of exposure in a direct and indirect way to humans and animals; facilitating the spread of resistant bacteria and resistant through surface water, groundwater, air, dust, and wildlife; acting as a reservoir for natural resistance markers; and enabling the exchange of resistance markers between bacterial species. [37]

Each year, hundreds of millions of cases of diarrhea are treated with antimicrobials caused by dispersal via water, sludge, and manure resulting in the transmission of disease-causing pathogens to humans, and animals thus increasing the need for treatment with antimicrobial agents. Total coliforms, fecal coliforms, Escherichia coli, and enterococci are commonly used microbial indicators of water quality. Data by the World Health Organization in 2020, shows that 14% of people globally carry E. coli in their feces that produce extended-spectrum beta-lactamase (ESBL) enzymes which causes resistance to penicillins, cephalosporins, cephamycins, and to some extent carbapenems. [38]

A study in Australia shows that susceptibility tests followed by PCR reveal 81.8% of E. faecalis SNP profiles and 70.21% of E. faecium SNP profiles were associated with antibiotic resistance. [38] If the contamination of the environment continues by releasing fecal and other pollutants, including antimicrobial compounds, creates conditions favorable to transfer or emergence of new resistance genes and AMR will inevitably occur. [39] 90% of all wastewater is discharged untreated, as reported in 2014 on AMR and Water, Sanitation, and Hygiene (WaSH) directly into rivers, lakes, or the oceans. Exposure to these bacteria via environmental media (water, wastewater, irrigated produce) and related pathways (e.g. faecally contaminated vectors such as flies, contact surfaces, and contaminated hands) will have a greater disease burden. Human health concerns will continue to emerge as new

strains or variants of highly resistant enteric bacteria are detected in the environment thus posing increased human health risks. [37]

There is no specific or general information on antibiotics and antimicrobial agents, their metabolites, antimicrobial-resistant bacteria, or their AMR genes in the current WHO guidelines for drinking water, recreational water, and use of wastewater in agriculture and aquaculture with includes the discharge of excreta. Furthermore, there is also no specific guidance on how to assess, manage, or minimize the potential human health risk associated with the presence of antimicrobial agents and antimicrobial-resistant bacteria in human exposure. [37] That is why there is a need to understand and address the role of water, sanitation, and hygiene (WaSH) in combating AMR to bridge the gap on AMR. [39]

AMR and Health Emergencies

Determining what constitutes a public health emergency is essential. In its 2015 International Health Regulations (IHR), The WHO defined Public Health Emergency of International Concern (PHEIC) as "an extraordinary event" that comprises a "public health risk to other states" and to "potentially require a coordinated international response". The IHR identifies an event as a Public health risk when it is likely to cause adverse effects to the health of human populations. [40]

Examples of emergencies with health consequences include infectious diseases outbreaks, zoonotic diseases, food and water contamination, natural disasters, antimicrobial resistance, chemical and radio-nuclear contamination. [41][42]

AMR is an endemic global health threat and not an epidemic yet. It can, however, have an impact on epidemics and pandemics.
This impact can be estimated by identifying the mortality impact of AMR, which depends on four factors:

- the availability of antimicrobial treatment to the infection;
- the degree of AMR - complete or partial;
- the total mortality that the infection cause;
- and the proportion of preventable deaths by that antimicrobial [43]

COVID-19 impact on AMR

COVID-19 has affected all the three factors that influence the spread of AMR in a population: emergence, transmission, and infection burden at the population level; through direct or indirect consequences of pandemic responses. Varied interventions set in place to combat COVID-19 have been put in place. The consequences of these changes have disrupted supply chains & healthcare and had economic impacts and rising inequalities. [44]

There has been increased use of antimicrobials in the prescription of medications while treating COVID-19 worldwide to prevent superinfections and limit the damage caused due to widespread infection of virus in the body. [45] For example, in a study that took place in January 2020 in an adult infectious disease unit in China, 71% of the patients hospitalized for COVID-19 were found to have received antibiotics despite a confirmed bacterial co-infection rate of only 1%. Another study in two hospitals in China mentioned that 95% of COVID-19 patients had received antibiotic regimens in spite of the fact that a secondary bacterial infection was only found in 15% of the patients.[46]
Antimicrobials have also been employed due to their supposed direct effect on SARS-CoV-2, despite the lack of scientific evidence that supports this matter. This possibly can lead to developing

resistance to co-infecting or co-colonising pathogens and this might enhance the likelihood of AMR due to an increase in incidence and further prevalence of AMR. [44][47]

In addition, in community settings, where vaccination has been delayed, rapid antigen tests may detect SARS-CoV-2 infections earlier and can provide some curb in the advancement of AMR by the reduction in prescription and consumption of antimicrobials. However, some current tests employed for testing are insensitive and provide "false negatives" increasing the spread of infection. [44]

One way to diminish the impact of COVID-19 on AMR is to prioritize public health issues in relation to key aspects such as the mortality burden. [45] COVID-19 pandemic has shown still how susceptible we are to infectious diseases. Healthcare systems that have been more prepared to combat infectious diseases due to the increased frequency of other communicable diseases previously have demonstrated stronger resilience in the spread of COVID-19 infection, hence reducing AMR. Thus, setting up response structures and mechanisms emphasizing possible future antimicrobial-resistant organisms(ARO) emergence needs to be done to ensure minimal AMR and prevent competition due to low resources. COVID-19 has not only disrupted public health services but has impacted the way our society functions. Thus, the notion of treating COVID-19 as a priority may not be changed, as it may cause millions of deaths. However, moving forward, it is important to create a balance between fighting COVID-19 and public health issues such as AMR. [44]

AMR and the SDGs

Antimicrobial resistance has an impact on social, environmental and economic levels, affecting the SDG framework. [48] In 2015, AMR was recognized as a threat to the UN's sustainable development goals (SDGs). Although not being in any specific SDG targets, AMR is referenced in the following paragraph "equally accelerate the pace of progress made in fighting malaria, HIV/AIDS, tuberculosis, hepatitis, Ebola and other communicable diseases and epidemics, including by addressing growing antimicrobial resistance and the problem of unattended diseases affecting developing countries" of the "Transforming our world: the 2030 Agenda for Sustainable Development" adopted by the General Assembly on 25 September 2015. [49]

SDG1: No Poverty

If no action is taken, the global economic cost of AMR in terms of lost production between now and 2050 would be US$ 100 trillion. [50] Low and middle-income countries would be more negatively impacted, widening the inequality gap within countries [2]. Moreover, in low-income countries, rates of resistant bacteria are higher and affordable treatment options are usually not available, especially as many pay for medicines out-of-pocket. Besides that, in some of these countries, the spread of diseases is enabled by weak sanitary systems. [48]

Treating drug-resistant infections is more expensive, takes longer, and has lower chances of success than treating drug-susceptible infections which could ultimately contribute to slowing down progress towards SDG 1. [48]

SDG2: Zero Hunger

Global consumption of antimicrobials in food/animal production was estimated at 63 000 tonnes in 2010 and is projected to rise by 70% by 2030 [50]. The increased demand for animal protein has led to

a rapid growth of intensive production systems which has been estimated to increase the consumption of antimicrobials in the food animal sector. [48]

Two of the indicators for the SGD2 are the duplication of agricultural productivity by 2030 and ensure the implementation of sustainable food production systems and resilient agricultural practices which creates a conflict with the AMR problem. It is crucial to develop sustainable animal production practices with high productivity without inadequate use of antimicrobials.[48]

There are several examples of high productivity being reached without the use of antibiotics for growth promotion or routine mass-medication, and without severe economic losses where the most important factors are sustainable animal husbandry practices that prevent disease, combined with a legal framework that regulates the use of antibiotics in the animal sector.[48]

SDG3: Good Health and Well-being

AMR threatens the progress made so far in the health and well-being of populations globally. It affects health outcomes such as maternal, children, and newborn mortality rates. [51] A study in Vietnam found that newborn mortality rates thirty days after infection were almost 32%, with a possibility that this percentage would increase by 27% with each added resistance to an antibiotics class. [52]
To stress the magnitude and complexity of AMR, sometimes they are compared to that of other global health problems. [53][54] Despite that, there is no specific mention of the AMR in the targets or indicators of SDG 3. [55] The UN Inter-Agency and Expert Group on the SDG Indicators (IAEG-SDGs) on its 10th meeting approved a proposal to add a specific indicator for the AMR to the SDG 3d; to "reduce the percentage of bloodstream infections due to selected antimicrobial-resistant organisms". [56]

SDG-4: Quality Education

Community involvement raises awareness and helps develop approaches in which people view themselves as advocates of their own health. This can be an effective way to reduce antibiotic use. Designing of special markers on the packaging of antimicrobials can also help in curbing the spread of AMR. Internet sales of antimicrobials pose a threat as they run internationally and without effective regulations. Therefore, consumers should be made aware of the risks of using non-licensed drugs. [57]

The importance of Antimicrobial resistance should also be addressed through certain training within the farmers as they have financial consequences when animals are in a poor state. Nevertheless, primary care providers should be informed about the agricultural use of antimicrobials through specific training or educational materials. [58] Awareness should be raised on certainly applicable advisories on each level, as without basic water, sanitation and hygiene, there is an increased chance of spreading infections and this can lead to AMR transmission. Hand hygiene stations, sanitary toilets and water treatment improve the way of life in which people live and also reduces the burden of healthcare facilities to use antimicrobials to treat infections. Raising awareness on proper waste management for companies and communities, in addition to dissemination of the proper storage information is vital as a means to reduce AMR. Training health workers is essential to rational antibiotic use including implementation of interprofessional education for future healthcare workers. [59] Currently, many private practitioners receive incentives from pharmaceutical representatives in order to prescribe the medications produced by these companies so there is an increased chance of AMR. Thus, more advocacy on AMR, in addition to spreading education materials and formulating guidelines based on proven facts and information, would improve adherence to rational prescription and consumption of antimicrobials. [60]

SDG-9: Industry, Innovation and Infrastructure

The need for evolution in the field of antibiotics is constantly rising due to the decrease of effective drugs. [61] This inhibits innovation, as antimicrobials have a poor return on investment and blur markets for vaccinations and diagnoses. [62] Innovation in the field of AMR is also not effectively funded and clinical trials for antibiotics are done by smaller units. In addition to this, there are a lot of voids in the current pathways, making the approval and licensing of antimicrobials more tedious and time taking. Development of vaccines, as an option to drugs, also lacks awareness they cannot be effective in all species, study of genomics is still rarely leading to decreased researches. [61]

Another major challenge while innovating a plan to tackle AMR is the lack of research and data available. The interlinkage between human and environment have not been understood/ established clearly so innovations and infrastructure for diagnostic procedures have always been difficult. [61][62]

SDG-12: Responsible Consumption and Production

Manufacturing and industry units have a key role to play in handling waste. The manufactures have to minimize the production of wastes while production and prevent them from accumulating in the environment. [63][64] Due to decreased costs, the companies often ignore their responsibilities and the local companies are severely hit. Moreover, labelling of levels for antibiotic use, where AMR could arise is not scientifically structured. [65]

The handling of effective antimicrobials should be done in collaboration with all the interested and relevant stakeholders and plans for a target to be achieved, within the next few years, need to be developed. These plans should be, necessarily, followed by every country. Lack of global consensus on policies defining the critical antibiotics in human use at different levels has hampered the efforts to improve antimicrobial manufacturer waste management. [65][66]

Lack of regulations leads to improper handling and misuse of antibiotics. Defining guidelines and improving them while monitoring the results should be done in order to have a check on proper handling. Furthermore, community engagement plays a major role in persuading the manufacturers in reducing the AMR by forcing them to focus on the risks involved with increasing cases of resistance. [65]

SDG13: Climate Action

Some research studies and reports tried to answer the questions regarding the interlinkage between climate change and AMR by “Thinking outside the box”. [67][68] Hani et al. conducted a study covering 30 countries across Europe that linked climate change and three resistant strains from the WHO Global Priority List of Antibiotic-Resistant Bacteria. They described an almost one-fold increase in carbapenem-resistant Pseudomonas aeruginosa (CRPA) prevalence because of a 0.5 °C increase in year-wise temperature. [67] While another study in the USA reported a two-fold increase in CRPA prevalence for the same temperature rise. They also compared regional temperature variations and found that an increase in temperature by 10 °C resulted in a 4.2% increase in antibiotic resistance in Escherichia *coli.* [69]

SDG17: Partnerships for the Goals

The AMR problem requires partnerships between governments, civil society, and the private sector as called for in SDG 17. [48] In September 2016, heads of state at the United Nations General Assembly recognized the need for stronger systems to monitor drug-resistant infections and the volume of

antimicrobial agents used in humans, animals, and crops, as well as the need for increased international cooperation and funding. [70]

Achievements in finance, technology and innovation, capacity-building, fair trade, policy and institutional coherence, stakeholder partnerships and data monitoring and accountability would strengthen the regulation of antimicrobial usage and improve knowledge and awareness. Besides that, there would be better promotion of best practices, new innovative approaches using alternatives to antimicrobial agents and more support for the development of new technologies for diagnosis and vaccines. [70]

AMR and Health in All Policies

The 8th Global Conference on Health Promotion, organized jointly by the WHO and the Ministry of Social Affairs and Health issued a statement in which it called on governments for the inclusion of Health in All Policies. The statement mentioned that governments fortify the ministries of Health to create incentives with the aim of joining forces with other sectors. [71]

A study done by Van Katwyk et al. suggests that the already set policies to regulate AMR tend to be regional, and that policy approaches should be more broad and available to all governments and stakeholders. [72] One of the steps towards incorporating AMR in All Policies that were mentioned was committee development through the formation of expert teams on stewardship (e.g: The Swedish Strategic Programme). [73] Many key policies were suggested for AMR control, an example of the role of governments was to coordinate stakeholders to provide help for firms seeking to bring new tests to market. This strategy was studied and was found to be cost-effective but it poses a problem which is the difficulty of stakeholder coordination. [74]

AMR efforts on Global and National levels

AMR Global Action Plan

The Global Action Plan on antimicrobial resistance (GAP) aims to ensure, for as long as possible, 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. [75]

This global plan focused on combating the emergence and spread of AMR which was adopted by members of WHO, the Food and Agriculture Organization of United Nations (FAO) and the World Organization for Animal Health (OIE) in 2015. The GAP was further endorsed by political leaders in 2016 when heads of state issued a high-level political declaration on AMR during the 75th session of the UN General Assembly, committing to implement the GAP at global, regional and national levels. [76]

The GAP articulates five major goals to combat AMR:

- Improve awareness and understanding of antimicrobial resistance through effective communication, education and training;
- Strengthen the evidence base and knowledge through research and surveillance;
- Decrease the incidence of infection through effective hygiene, sanitation and infection prevention measures;
- Optimize the usage of antimicrobial medicines in animal and human health;

- Develop the economic case for sustainable investment that takes account of the needs of all countries, increasing investment in new medicines, diagnostic tools, vaccines and other interventions. [76]

The plan sets out the tasks required to achieve them, highlighting the roles and responsibilities of country governments, the tripartite One Health organizations (FAO, OIE and WHO) and other national and international partners. To ensure that all stakeholders are fulfilling their roles and responsibilities, and to assess whether they are collectively bringing about the necessary change in AMR, the implementation of the GAP needs to be routinely monitored and evaluated. [76]

Outcomes

There has been sustained progress in the development of national action plans even if the initial target of having national AMR action plans for every country by 2017 was not achieved. [77]

Based on the Monitoring Global Progress on Addressing AMR analysis report survey 2020 most countries have developed National Action Plans (NAPs) but many failed to identify funding sources for them. A total of 88.2% of responding countries reported a developed NAP on AMR, whereas only 19.9% of countries reported funding their NAPs in 2019–2020. Based on the latest World Bank population data, 90.0% of the global population is covered by countries that have developed NAPs on AMR. [78]

Besides that, the number of countries with ongoing multi sectoral working groups on AMR has increased from previous years, with 76 countries reporting a functional multi sectoral working group and over 90% of responding countries had human and animal health sector representatives in their working groups. Regarding the goal for nationwide awareness campaigns, only 44.9% of reporting countries had nationwide awareness campaigns targeting priority stakeholder groups, highlighting the need for additional investments in campaigns with targeted messaging. [78]

Moreover, 75.6% of responding countries offer at least some level of training on AMR for human health professionals, of which only 9.6% of countries have systematically incorporated AMR into training curricula for these professionals. Besides that, 57.1% of countries have some level of training on AMR for professionals in the veterinary sector and only 24.2% of countries have training for professionals in the farming and environment sector. The trend analysis shows the levels of training in AMR have increased across the human health, animal health and farming sectors over the past three years, with the most rapid rise being in the veterinary sector.[78]

Furthermore, 75.4% of countries reported having national AMR surveillance activities in human health, 92 of those countries are currently enrolled in WHO's Global Antimicrobial Resistance Surveillance System (GLASS). Over two-thirds of countries collect at least some AMR data on animals, and 41.7% of countries have systematic data collection on resistance in animals. Countries reported national monitoring systems for antimicrobial sale and use in the human health sector and 83 countries in animal health. Around 40% of responding countries do not have a national plan or system to monitor the use of antimicrobial pesticides, such as bactericides and fungicides.[78]

Regarding the goal of optimizing the use of antimicrobial medicines in human and animal health, 91.9% of countries reported having laws or regulations on the prescription and sale of antimicrobials for human use and 71.8% reported having policies for the optimization of the usage of antimicrobials in human health, such as guidelines for treatment and practices to ensure proper antimicrobial use.

Regarding the animal sector, 62.8% of countries reported having laws that prohibit the use of antibiotics for growth promotion. Over half (56.4%) of countries reported having policies to optimize the use of antimicrobials in animal health, including national legislation that covers all aspects of the national manufacture, import and marketing of antimicrobials. [78]

National Action Plans

While reflecting on the principles identified in the GAP, the WHO urges the member nations to involve all the related sectors contributing to the implementation of the action plans and give increased importance to prevention than mitigation. It has also been advised to prevent the access and at the same time facilitate adequate access to the antimicrobials which are mandatorily required. In addition, particular targets should be set and met while framing and implementation of the concerned strategies. [79]

The development of National Action Plans includes steps like establishing a governance mechanism where multisectorial coordinated groups can be established, agreeing on a time frame and establishing a technical working group. Moreover, conducting situational analysis, to understand the prevailing conditions and hurdles aggravating the problem and might prevent proper implementation of the action plan needs to be considered. [79]

Once a systematic, transparent multi stakeholder process has been established and various analyses and assessments have been done, proper planning and implementation become crucial through the National Action Plans. [79]

Current Global Efforts

In addition to the AMR Global Action Plan, several stakeholders are joining forces to fight this public health threat. The WHO issued an AMR report in 2014 describing the status of AMR at the time with the recent data and the further steps to be taken. [80] One year later, the Global Antimicrobial Resistance Surveillance System was shared in 4 languages to increase its reach with further details on the research to ensure an evidence-based approach in tackling AMR. [81]

While the work done by the CDC on the AMR challenge was limited to one year (September 2018 - September 2019), it is evident how it encouraged the One Health approach and connected efforts from 30+ countries with more than 300 commitments made to the challenge. [82]

On top of that, the University of Oxford Big Data Institute partnered with the Institute for Health Metrics and Evaluation (IHME) to launch the Global Research on Antimicrobial Resistance project that aims to promote policymakers interventions on the local level and to consolidate, review and analyse all available data and surveillance systems on AMR worldwide, while disseminating results to the public by June 2021. [83]

As for the United Nations, the 2016 General Assembly adopted the topic of AMR, as did the High-level Interactive Dialogue in April 2021. The UN also included AMR in the Sustainable Development Goals of the 2030 global as discussed in this document. [84]

AMR and Universal Health Coverage

Universal Health Coverage (UHC) strives for the existence of health services available for all individuals and communities when needed, without causing financial hardship. This concept includes quality

health services, from health promotion to prevention, treatment, rehabilitation, and palliative care across the entire life course. [85] One of the major challenges in fighting AMR is improving access to antimicrobial agents to vulnerable populations and UHC can be a strategy to achieve that. [86]

In many health systems, widespread inappropriate use of antimicrobials is accompanied by inadequate access to them. An effective antimicrobial resistance strategy must ensure both access to effective therapy and reduce the risk of resistance emerging. There is a need for action at national and global levels to ensure that there is an integrated approach to making progress towards UHC and addressing AMR. [87] This being said, actions to fight AMR should go hand in hand with actions to strengthen the attributes of health systems that contribute to progress towards UHC, ensuring equity, quality, efficiency, accountability, sustainability and resilience. [87]

The building blocks of health systems and AMR

- **Health Workforce**

Training the health workforce in antimicrobial stewardship is crucial to capacitate communities and hospitals in curbing the consequences of AMR. However, according to WHO, updates and continuing medical education are being provided by pharmaceutical companies to healthcare workers. This can be problematic because these companies may have incentives to increase drug sales, specifically more expensive antimicrobial drugs, which defeats the purpose of antimicrobial stewardship. [60]

The WHO Competency framework for health workers' education and training on AMR suggests that there should be a deep understanding of the development and main causes of AMR. This also includes principles of infection prevention and control and the choice of antimicrobial therapy. Knowledge on the economic threat of AMR to human health and optimizing the use of antimicrobials would complement the overall knowledge of the basic principles of AMR. It was also mentioned that skills in the ability to interpret and communicate policy guidelines on AMR will also be essential. And lastly, healthcare workers should also advocate awareness amongst all healthcare workers, communities, and the general public. And efforts to protect the effectiveness of antimicrobials are an ethical imperative. [88]

Ultimately, even with information awareness, there may be a circumstance when health workers prescribe antimicrobials unnecessarily if there is not enough time to diagnose or follow-up care is provided. Therefore, it is important to address the fundamental weakness in primary care, rather than restricting antibiotic access, as a long-term solution for AMR. [60]

- **Leadership and Governance**

Leadership and Governance to tackle AMR and develop agenda is key to ensure strategic policy frameworks are created and implemented. This should be complemented with coalition building, regulation, and accountability. [89] Well-defined national strategy and regulatory systems should support sustained development of Antimicrobial Stewardship (AMS) policies. According to Dyar et al., including regulatory requirements of institutions should include AMS in the criteria for quality evaluation, which can bring a positive impact on Antimicrobial Stewardship Programs (ASP). [90]

Evidence shows that implementation of Antimicrobial Stewardship Programs is high in countries with the most developed regulatory systems. However, rigorous assessment across many different settings including the impact of regulatory requirements on responsible antimicrobial use is still needed. [90]

At a global level, governance and accountability are also essential. In 2016, there were discussions of antimicrobial resistance at the United Nations and a Conscience of Antimicrobial Resistance Accountability (CARA) was created after the meeting, to create and coordinate an alliance of organizations, in order to monitor and report progress on the containment of AMR across the globe. [90]

- **Service Delivery**

Effective, safe, quality personal and non-personal health interventions provided to those that need that are the qualities of good service delivery. [89] In the AMR context, UHC programs such as clean water and sanitation, immunization, and infection prevention and control should be emphasized as prevention. Another entry-point, to integrate AMR in the service delivery building block of the health system, is increased opportunities and facilities for better diagnosis; It should focus on people-centered primary care and increase access to diagnostics. [91]

Implementation of behavior change strategies that target both the individual and healthcare system more broadly could also be effective. For instance, changing the organization of service delivery or the culture surrounding prescribing within an institution could greatly improve Antimicrobial Stewardship. However, changing the culture could be challenging as it usually requires buy-in from top-level governance, as well as leadership across all healthcare worker groups. [90]

Preventing the spread of resistant infections and lowering the use of antimicrobials through infection prevention and control is the best and most affordable intervention. But it should also be complemented with antimicrobial stewardship programs in all healthcare settings, and strengthening of immunization programs to have a significant impact. [91]

- **Health information systems**

Well-made health information systems provide decision-makers with reliable, timely, and easy to understand data. Health information systems generate, compile, analyze, deliver and use data. They vary according to the needs of the health planners and decision-makers; they could provide information about the determinants of health, monitor health infrastructure, or monitor health outcomes. While most developed countries have effective national health information systems, few developing countries have effective health information systems. [92]

An example of a global antimicrobial resistance information system is the Global Antimicrobial Resistance Surveillance System (GLASS), launched in October 2015. It aims to guide decision-makers on global, regional, and national levels to take evidence-based actions towards AMR. It was also developed to support the global action plan on AMR. It does so by providing standardized, analyzed, and validated data from participating WHO member states. Then share this data with countries to drive local, regional and national action. Using GLASS could potentially improve patient safety by providing standardized, validated data to healthcare providers to base their diagnosis and treatment on it. Thus promoting Antimicrobial Stewardship Programs (ASP). [93]

Stewardship can be defined as "the careful and responsible management of something entrusted to one's care". In the context of AMR, this means the rational use of antimicrobials to improve human, animal, and plant health while avoiding the spread of AMR. Its goal is to efficiently use antimicrobials while decreasing the spread of AMR. [94] To do so, it is important to innovate and use technological advancement for efficient ASPs; technological advancements such as electronic medical record (EMR), clinical decision support systems (CDSS), and mobile applications. [95]
Two studies demonstrated that by using EMR, there was an increase in chart reviews and a 27% decrease in broad-spectrum antimicrobial use. [95][96] Another technology, the CDSS, monitors patients and provides timely alerts and reports to help ASPs identify proper interventions. [95] The majority of health professionals include mobile devices in their workflow and it showed improvement to their clinical decisions. [97]

- **Access to essential medicines**

As time passes, the spread of AMR renders more antibiotic drugs ineffective. Many people in low and middle-income countries (LMICs) lack access to essential, quality antibiotics. [98] Equitable access to quality, safe, and efficient medical products, vaccines, and technologies is the fourth building block of a well-functioning health system. [99] The UN defined the indicator to measure access to essential medicine as the proportion of the population that has "essential medicines continuously available and affordable at public or private health facilities or medicine outlets that are within one hour walk from the homes of the population." [100]

5.7 million people die each year from treatable infectious diseases, most of which are in LMICs; most of these infections are susceptible to existing antimicrobials if they are accessible. [101] The WHO report on antibiotic surveillance and consumption describes differences in the consumption rates of antibiotics among countries; the rate drops as low as 4 Defined Daily Doses (DDD)/inhabitant and rises as high as 64 DDD/inhabitant. Indicating that some countries are overusing antibiotics, while others may lack access to these antibiotics. [102]

The Center for Disease Dynamics, Economics & Policy (CDDEP) released a report identifying key access barriers to antibiotics in LMICs and high-income countries (HICs). The barriers they identified are in three main categories: drug discovery and development; funding, costs, and affordability; and health systems supply chains and quality controls. [98]

- **Health systems financing**

The basis of a well-functioning health system is to ensure that no one is left behind and that all individuals have access to the quality health services they need. Health system financing should be built on that basis. It is defined as the "function of a health system concerned with the mobilization, accumulation, and allocation of money to cover the health needs of the people, individually and collectively, in the health system". [92]
Objective five of the global action plan for AMR aims to "Develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines, and other interventions". [76]

While public investment in researching and developing new antibiotics increased, the private sector has been continuously decreasing its investment and funding. Current investments are mainly driven by

small to medium companies that are mostly developing antibiotic agents with limited clinical benefits. [103]

AMR and Research

Research is considered an important pillar for tackling Antimicrobial Resistance. This has been highlighted by the actions of many key stakeholders such as the WHO. In 2017, in order to ensure guidance for research and development into new antimicrobials, diagnostics and vaccines, WHO created the WHO priority pathogens list, which is compared with the annual WHO reviewal of the pre-clinical and clinical antibacterial pipelines, in order to see how the pipeline is progressing with respect to the list. This has shown the urgent need for research and development, in particular for antibacterial targeting of the gram-negative carbapenem-resistant bacteria. In addition to that, a joint initiative of WHO and the Drugs for Neglected Diseases Initiative (DNDi) called "Global Antibiotic Research and Development Partnership" (GARDP) was created to encourage research and development through public-private partnerships. By 2025, the partnership is looking forward to developing and delivering five new treatments that target drug-resistant bacteria identified as posing the greatest threat, by the WHO. [104]

According to the latest 2020 report by the WHO, it showed that none of the 43 antibiotics that are currently in the process of clinical development adequately address the global health issue of drug resistance in the world's most dangerous bacteria. Furthermore, the report has shown that, at the moment, the pipeline is near static with only a few antibiotics being approved by regulatory agencies in recent past years. Most of these agents in development are offering limited clinical benefit over existing treatments, with 82% of the recently approved antibiotics being derived from already existing antibiotic classes with well-established drug resistance. This led to the report including 27 non-traditional antibacterial agents in the pipeline including but not limited to antibodies, bacteriophages and therapies that support the patient's immune response and decrease the effect of the bacteria. [104][105]

Unfortunately, it has been decades since the latest new original class of antibiotics was introduced in the late 1980s. Pharmaceutical companies have been decreasing and neglecting investment in new antibiotics, which are considered, for them, not cost-effective enough and instead are focusing on other drugs such as cancer drugs. This issue is even increasing the need for research and development in the antimicrobials and antimicrobial resistance arena. [106]

The WHO 2020 annual review of the clinical and preclinical antibacterial pipelines agrees with the financial and investment issues regarding research and development as a means of tackling antimicrobial resistance. Therefore, in addition to the GARDP, WHO has been working with other non-profit funding partners to accelerate and push forward the antibacterial research. Moreover, the "AMR Action Fund" initiative has been developed as a collaborative initiative between philanthropies, pharmaceutical companies, the European Investment Bank, with the support of the WHO, aiming to strengthen and accelerate antibiotic development through global pooled funding, in addition to ensuring that the most innovative and promising products receive the required funding. [104]

One Health

One Health is a concept based on the collective effort of various health and science fields to attain optimal health for people, domestic animals, wildlife, plants, and our environment, recognizing that our

health is intertwined with the health of animals and with the environment. Many factors of animal and people's health but also plants and environment have changed, bringing even more importance to the concept in the past few years. [107][108]

AMR and Animal Health

Most classes of antimicrobials used to treat bacterial infections in humans are also used in animals. There are two main concerns in animal health and agriculture: the mass medication of animals with antimicrobials of critical importance to humans - such as third-generation cephalosporins and fluoroquinolones, and the long-term use of medically important antimicrobials in feed - such as colistin, tetracyclines, and macrolides - to promote growth. [107]

In veterinary medicine, there are notable differences in the ways that antimicrobials are used in companion animals compared to food-producing animals. Antimicrobial use in companion animals is similar to those in humans, where the drugs are mostly administered on an individual animal basis for the treatment of clinical infection, with some use for prophylaxis in individual animals, such as post-surgery. In food animals, if some animals in a group are clinically infected and require antimicrobial therapy, the drugs are often administered to the entire group through feed or water, even if the majority of the animals show no signs of infection. The most controversial type of group treatment in food animals is long-term, low-dose mass medication for growth promotion. The controversy is rooted partly in the tendency of this practice to select for antimicrobial resistance and partly in its justification on economic grounds rather than to treat clinical infections. [107]

WHO advocates ending the use of antimicrobials for growth promotion, and the practice has been banned in Europe and elsewhere and phased out in some other countries, such as the United States and Canada. In 2018, the World Organization for Animal Health reported that 41% of the 146 countries reporting the use of antimicrobials in animals allow the use of antimicrobial growth promoters. This represents a decrease from 51% of the 151 reporting countries in 2012. . All countries in Europe and the Middle East have a regulatory framework for the use of antimicrobial agents on animals but there is a lack of policies on this matter in countries in the Americas. [65][107][109]

Some countries like the Netherlands and Denmark, are being considered case studies on this matter, implementing policies focused on diminishing antibiotic use in agriculture with good results, showing that it is possible to have low antibiotic use, maintaining production rates and being competitive in multiple international commercial markets. [65]

AMR and environmental health

It has been shown how the misuse of antimicrobials in different sectors can contribute to the negative impact on environmental health through the transmission of large amounts of biocides including but not limited to pesticides, antimicrobials and heavy metals, from various sources such as livestock agriculture, pharmaceutics, aquaculture, urban activities and hospital waste. The selective pressure applied on the government by these biocides leads to the spread of antimicrobial resistance by horizontal gene transfer with the aid of mobile genetic elements that confer resistance to these compounds and get easily shared among bacterial species.[110]

This linked issue between antimicrobial resistance and environmental health can be further explained in the animal production system, that uses high levels of antimicrobials in the animals for the sake of

growth promotion, prophylaxis and treatment and since it is is difficult to give carefully calculated amounts to the animals according to their needs, huge amongst of antimicrobials are added to the food and drink and then transferred to the environment through the animal waste. In addition to that, huge amounts of sewage waste from antimicrobials' loaded sources are transferred to the water and thus increasing the spread of antimicrobial resistance through the use of water as a vehicle to transmit it between humans, animals and the environment, causing an imbalance in the aquatic system. [111]

In conclusion, the impact of antimicrobial misuse of environmental health and antimicrobial resistance is very much underestimated in spite of the fact that the environment is considered a very important reservoir for the spread of antimicrobial resistance. Moreover, several studies have shown that the release of antimicrobials to the environment, combined with direct contact between discharged resistant bacteria and the natural bacterial community, are pushing bacterial evolution and the rise of more resistant strains forward. [112]

Interprofessional Collaboration

Interprofessional collaboration can be defined as "when multiple health workers from different professional backgrounds work together with patients, families, carers (caregivers), and communities to deliver the highest quality of care." It is built upon the idea that when caregivers work together they understand and consider each other's perspectives providing the best possible care for the patients. Interprofessional collaborations are especially needed in the case of AMR in order to promote optimal healthcare, curb financial burdens and improve patient satisfaction. [113]

Doctors

Health care providers, being constantly working with their patients, are key stakeholders who can be related both with the spread and control of infections and AMR. Thus, raising awareness among doctors is extremely necessary. Educating health care providers about the AMR and aseptic practices may help in the control of the spread of infections. [114] The healthcare workforce must guarantee that the advantages of simply prescribing antimicrobials, to cure patients, do not exceed the potential hazards posed by AMR. It is important to ensure that the benefits of merely prescribing the antimicrobials curing the patients don't outweigh the possible threats arising due to AMR. Doctors need to make sure that the existing efforts to ensure rational drug prescriptions are well adhered to and modified accordingly, maintaining the local needs. Also, doctors are responsible for not "over-" prescribing "antimicrobial medications" and informing patients about the hazards associated with self-medication. [60]

Along with treating the diseases, the doctors have to comply with controlling infections locally in order to timely report the resistant cases. Doctors also play a major role in screening and surveillance of possible infections and resistance seen in microbes. In addition, the doctors need to be vigilant about WHO categorized antibiotics, ensure optimum supplies of drugs, and restrain the use of antibiotics from the Watch and Reserve drugs. [60]

Mobile applications provide a worldwide reach, and cater to a wide range of needs. The use of the Internet provides access to a wide range of information, but also promotes misinformation simultaneously. As the levels of literacy among people are rising across the world, more and more people with Internet access are educating themselves to manage their own health. Hence, in addition

to self--education, healthcare workers should work to educate the public in regards to health promotion, correct antibiotic use, and cleanliness habits at public levels.[60]

Veterinarians

According to the American College of Veterinary Internal Medicine, there is a need for improved antimicrobial use practices in veterinary medicine, human medicine, and animal production to reduce the prevalence and impact of AMR. Veterinarians must consider the impact of antimicrobial use in animals and take steps to optimize antimicrobial use to maximize health benefits to animals while minimizing the likelihood of antimicrobial resistance and other adverse effects. [115]

All sectors must be included in this matter and it is important that veterinarians focus their efforts on the areas where they have greater impact, antimicrobial use in animals, working mainly on 3 approaches:

- Preventing disease occurrence in animals is a critical aspect of antimicrobial stewardship, if disease occurrence can be reduced, the pressure to use antimicrobials therapeutically can be similarly reduced. This requires appropriate animal care and husbandry, proper vaccines usage, and implementation of infection control measures on farms and in veterinary hospitals
- Reducing overall antimicrobial drug use;
- Improving antimicrobial drug use. [115]

Reducing and improving antimicrobial drug use are receiving increasing attention, particularly in human healthcare. However, in animal care, this association is not absolute. There is a need for more studies in the area, especially regarding unintended consequences. For example, high levels of dietary zinc as an alternative to antimicrobials for the prevention of postweaning diarrhea in pigs can result in as strong selection pressure for MRSA as administration of tetracycline. If reduced prophylactic use of antimicrobials results in increased disease rates and subsequently in the use of newer antimicrobials with more impact on the commensal microbiota, the benefit of overall antimicrobial reduction can be lost. [115]

The American College of Veterinary Internal Medicine recommends that most of the antimicrobials used in animals should be available only by prescription by a veterinarian with a valid veterinarian/client/patient relationship; it does not recommend over-the-counter access to antimicrobials. Besides that, non-prescription use of some drugs can increase the risk of resistance, resulting in ineffective therapy, unnecessary animal suffering, and increase the risk of drug residues in food animals. [115]

In conclusion, although antimicrobial drug usage for the treatment of animal diseases will continue, it must be sustainable, within the One Health concept and should develop into a more prudent and rationally based prescription process [116]

Dentists

In the dental practice, antibiotics are used on several occasions including odontogenic and non-odontogenic infections, local infections, focal infections, and prophylaxis. In addition, they are used for certain groups including those with infective endocarditis, prosthetic joints, metabolic disorders and immunosuppressed conditions. However, some studies have shown that only about 12% of dentists prescribe antibiotics wisely, resulting in a higher incidence of antibiotics complications including but

not limited to allergic and dermatological disorders and hypersensitivity reactions, in addition to antimicrobial resistance, and diversion of bacterial microbiota. The use of antibiotics after dental surgical interventions has been proven useful in many cases, but the unwise prescription of antibiotics can produce adverse results, as mentioned earlier. [117]

Moreover, some studies also indicated that 10% of antibiotic prescriptions are made by dentists and that the use of antibiotics in dental practice is characterized by empirical prescription on the basis of clinical and bacteriological epidemiological factors, while using broad-spectrum antibiotics for short periods of time, and the application of a very narrow range of antibiotics. [118]

Examples of the misuse of antibiotics by dentists include: overuse of antibiotics for prophylaxis for infectious diseases more than treatment of the infections themselves; usage of antibiotics for acute and chronic infections of the oral cavity, which can otherwise be treated by other methods; and antibiotics therapy to prevent local infection and systemic spread among those patients undergoing surgery for treatment, in spite of the fact that surgical devices and implants may result in infections that are resistant to systemic antibiotics. [119]

Pharmacists

Pharmacists play a role in the fight against AMR primarily through adequate selection of antimicrobials in their practice. According to a study done by Saha et Al, the role of pharmacists is deeply understood by first identifying their role in the context of infectious diseases. [120] Pharmacists have proven a contribution to disease management, especially in the context of COVID-19, where they ensured the adoption of prevention methods, established rapid diagnosis, and performed tests. [121] According to the aforementioned, there is a huge overlap between the fields of work of both pharmacists and physicians. Both are the first contact between a patient and infections; hence they have a role in making optimal choices while selecting antimicrobials and promoting stewardship. [120]

A certain concern that rises while highlighting the importance of the collaboration between pharmacists and other healthcare professionals in their readiness. *Khan et al.* tackled the roots of it all, which is education. According to a study done in 2018, a strategic plan was put into practice in 2004 to implement interprofessional education. The challenges faced by these programs were mainly cultural and resulting from the unpreparedness and lack of promotion of a collaborative approach in healthcare. [122] In addition, according to several studies, not only do they contribute to educational levels through for example educating patients on antibiotic therapy [123], but also contributed to a decreased time of appropriate therapy which emphasizes the importance of pharmacy presence in emergency departments. [124]

Other healthcare professionals

The misuse and overuse of antimicrobials have increased the acceleration of resistance to antimicrobial drugs. Other healthcare workers such as nurses, and midwives play a significant role in antimicrobial stewardship and infection prevention and control. They can advocate for rational antibiotic use, and increase the awareness of patients on the responsible use of antimicrobial medications. [125]

Substantial efforts are needed to ensure behavior change in healthcare workers and patients, with little training on AMR and rational antibiotic use, most of which are focused on infectious disease specialists or pharmacists, which will be lacking in addressing AMR. So other healthcare workers should be

included in training because the lack of a coordinated approach to AMR education will become a challenge. [125] Another threat to AMR includes a high rate of healthcare-associated infections which is needed to address alongside with prescription of antimicrobials. [2] According to Hayat et al., 49.6% of nurses view AMR to be a serious threat. And with regards to patient care and eradication of AMR 58.4% agree that improving prescribing of antimicrobials could decrease AMR. This difference of views among healthcare professionals towards AMR could affect guidelines to treat resistant infections. [126]

To combat AMR in hospitals, healthcare professionals should have adequate awareness and training in AMR, its triggering factors, and strategies on how to cope with it. Because these hospital-based antimicrobial stewardship programs will be affected by the different views of the healthcare professionals. In addition, its successful implementation is highly dependent on the joint efforts which include nurses, and midwives as the stakeholders. [126]

References

1. Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline, including tuberculosis. Geneva: World Health Organization; 2017 (WHO/EMP/IAU/2017.12). Licence: CC BY-NC-SA 3.0 IGO.
2. Antimicrobial resistance [Internet]. World Health Organization. World Health Organization; [cited 2021Jun5]. Available from: https://www.who.int/news-room/q-a-detail/antimicrobial-resistance
3. Antimicrobial resistance [Internet]. World Health Organization. World Health Organization; [cited 2021Jun5]. Available from: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance
4. Antimicrobial Resistance [Internet]. OECD. [cited 2021Jun5]. Available from: https://www.oecd.org/health/health-systems/antimicrobial-resistance.htm
5. Prestinaci F, Pezzotti P, Pantosti A. Antimicrobial resistance: a global multifaceted phenomenon [Internet]. Pathogens and global health. Taylor & Francis; 2015 [cited 2021Jun5]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4768623/
6. Development process of the global action plan on antimicrobial resistance [Internet]. World Health Organization. World Health Organization; 2016 [cited 2021Jun5]. Available from: http://www.emro.who.int/health-topics/drug-resistance/global-action-plan.html
7. Determinants of health [Internet]. World Health Organization. World Health Organization; [cited 2021Jun6]. Available from: https://www.who.int/news-room/q-a-detail/determinants-of-health
8. Donkin A, Goldblatt P, Allen J, et al. Global action on the social determinants of health. BMJ Glob Health 2017;3:e000603. doi:10.1136/bmjgh-2017-000603
9. Antimicrobial Resistance Determinants and Future Control - Volume 11, Number 6-June 2005 - Emerging Infectious Diseases journal - CDC [Internet]. Centers for Disease Control and Prevention. Centers for Disease Control and Prevention; [cited 2021Jun6]. Available from: https://wwwnc.cdc.gov/eid/article/11/6/05-0167_article
10. A. Radyowijati, H. Haak, Determinants of antimicrobial use in the developing world. Child Health Research Project Special Report, vol 4, n°1, February 2002, 36 p.

11. Wang D, Liu C, Zhang X, Liu C. Does diagnostic uncertainty increase antibiotic prescribing in primary care? [Internet]. Nature News. Nature Publishing Group; 2021 [cited 2021Jun6]. Available from: https://www.nature.com/articles/s41533-021-00229-9
12. Sarkar U, Bonacum D, Strull W, Spitzmueller C, Jin N, López A, et al. Challenges of making a diagnosis in the outpatient setting: a multi-site survey of primary care physicians [Internet]. BMJ Quality & Safety. BMJ Publishing Group Ltd; 2012 [cited 2021Jun6]. Available from: https://qualitysafety.bmj.com/content/21/8/641
13. Machowska A, Stålsby Lundborg C. Drivers of Irrational Use of Antibiotics in Europe [Internet]. MDPI. Multidisciplinary Digital Publishing Institute; 2018 [cited 2021Jun6]. Available from: https://www.mdpi.com/1660-4601/16/1/27/htm
14. Cilloniz C, Martin-Loeches I, Garcia-Vidal C, San Jose A, Torres A. Microbial Etiology of Pneumonia: Epidemiology, Diagnosis and Resistance Patterns [Internet]. MDPI. Multidisciplinary Digital Publishing Institute; 2016 [cited 2021Jun6]. Available from: https://www.mdpi.com/1422-0067/17/12/2120/htm
15. Global Health Estimates: Life expectancy and leading causes of death and disability [Internet]. World Health Organization. World Health Organization; [cited 2021Jun6]. Available from: https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates
16. Vincent J-L, Brealey D, Libert N, Abidi NE, O'Dwyer M, Zacharowski K, et al. Rapid Diagnosis of Infection in the Critically Ill, a Multicenter Study of Molecular Detection in Bloodstream Infections, Pneumonia, and Sterile Site Infections [Internet]. Critical care medicine. Lippincott Williams & Wilkins; 2015 [cited 2021Jun6]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4603364/
17. Banerjee R, Teng CB, Cunningham SA, Ihde SM, Steckelberg JM, Moriarty JP, et al. Randomized Trial of Rapid Multiplex Polymerase Chain Reaction–Based Blood Culture Identification and Susceptibility Testing [Internet]. OUP Academic. Oxford University Press; 2015 [cited 2021Jun6]. Available from: https://academic.oup.com/cid/article/61/7/1071/289120?login=true
18. Cole A. GPs feel pressurised to prescribe unnecessary antibiotics, survey finds [Internet]. The BMJ. British Medical Journal Publishing Group; 2014 [cited 2021Jun6]. Available from: https://www.bmj.com/content/349/bmj.g5238.full
19. A; RJCMS. A qualitative literature review exploring the drivers influencing antibiotic over-prescribing by GPs in primary care and recommendations to reduce unnecessary prescribing [Internet]. Perspectives in public health. U.S. National Library of Medicine; [cited 2021Jun6]. Available from: https://pubmed.ncbi.nlm.nih.gov/31633458/
20. Kohut MR, Keller SC, Linder JA, Tamma PD, Cosgrove SE, Speck K, et al. inconvincible patient: how clinicians perceive demand for antibiotics in the outpatient setting [Internet]. OUP Academic. Oxford University Press; 2019 [cited 2021Jun6]. Available from: https://academic.oup.com/fampra/article-abstract/37/2/276/5613669?redirectedFrom=fulltext
21. Barker AK, Brown K, Ahsan M, Sengupta S, Safdar N. Social determinants of antibiotic misuse: a qualitative study of community members in Haryana, India [Internet]. BMC Public Health. BioMed Central; 2017 [cited 2021Jun6]. Available from: https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-017-4261-4
22. Frost I, Van Boeckel TP, Pires J, Craig J, Laxminarayan R. Global geographic trends in antimicrobial resistance: the role of international travel [Internet]. OUP Academic. Oxford University Press; 2019 [cited 2021Jun6]. Available from: https://academic.oup.com/jtm/article-abstract/26/8/taz036/5496989?redirectedFrom=fulltext

23. Kamata K, Tokuda Y, Gu Y, Ohmagari N, Yanagihara K. Public knowledge and perception about antimicrobials and antimicrobial resistance in Japan: A national questionnaire survey in 2017 [Internet]. PLOS ONE. Public Library of Science; [cited 2021Jun6]. Available from: https://journals.plos.org/plosone/article?id=10.1371%2Fjournal.pone.0207017
24. Planta MB. The Role of Poverty in Antimicrobial Resistance [Internet]. American Board of Family Medicine. American Board of Family Medicine; 2007 [cited 2021Jun6]. Available from: https://www.jabfm.org/content/20/6/533
25. Dadgostar P. Antimicrobial Resistance: Implications and Costs [Internet]. Infection and drug resistance. Dove; 2019 [cited 2021Jun6]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6929930/
26. Michael CA, Dominey-Howes D, Labbate M. The antimicrobial resistance crisis: causes, consequences, and management [Internet]. Frontiers in public health. Frontiers Media S.A.; 2014 [cited 2021Jun6]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4165128/
27. Bhatia R. Antimicrobial Resistance: Threat, consequences and options. Natl Med J India [serial online] 2018 [cited 2021 Jun 6];31:133-5. Available from: http://www.nmji.in/text.asp?2018/31/3/133/255752
28. World Health Organization. Regional Office for South-East Asia. (2014). A brief guide to emerging infectious diseases and zoonoses. WHO Regional Office for South-East Asia. https://apps.who.int/iris/handle/10665/204722
29. RK; AGVK. Emerging Infectious Diseases, Antimicrobial Resistance and Millennium Development Goals: Resolving the Challenges through One Health [Internet]. Central Asian journal of global health. U.S. National Library of Medicine; [cited 2021Jun6]. Available from: https://pubmed.ncbi.nlm.nih.gov/29755885/
30. European Observatory on Health Systems and Policies, van Hecke, Oliver, Tonkin-Crine, Sarah, Abel, Lucy, Wang, Kay. et al. (2020). Tackling antimicrobial resistance in the community. Eurohealth, 26 (1), 12 - 15. World Health Organization. Regional Office for Europe. https://apps.who.int/iris/handle/10665/332479
31. Getahun H, Smith I, Trivedi K, Paulin S, Balkhy HH. Tackling antimicrobial resistance in the COVID-19 pandemic. Bull World Health Organ. 2020 Jul 1;98(7):442-442A. doi: 10.2471/BLT.20.268573. PMID: 32742026; PMCID: PMC7375214.
32. THE POTENTIAL OF VACCINES TO PREVENT AMR. Padmini Srikantiah, MD MPH. Bill & Melinda Gates Foundation. PDVAC Meeting, June 27, 2018.
33. Jansen KU, Anderson AS. The role of vaccines in fighting antimicrobial resistance (AMR) [Internet]. Human vaccines & immunotherapeutics. Taylor & Francis; 2018 [cited 2021Jun7]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6183139/#CIT0035
34. Kwong JC;Maaten S;Upshur RE;Patrick DM;Marra F; The effect of universal influenza immunization on antibiotic prescriptions: an ecological study [Internet]. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. U.S. National Library of Medicine; [cited 2021Jun7]. Available from: https://pubmed.ncbi.nlm.nih.gov/19624280/
35. Micoli F, Bagnoli F, Rappuoli R, Serruto D. The role of vaccines in combatting antimicrobial resistance [Internet]. Nature News. Nature Publishing Group; 2021 [cited 2021Jun7]. Available from: https://www.nature.com/articles/s41579-020-00506-3
36. Guidelines on sanitation and health. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.

37. Antimicrobial resistance: An emerging water, sanitation and hygiene issue [Internet]. World Health Organization. World Health Organization; 2016 [cited 2021Jun7]. Available from: https://www.who.int/water_sanitation_health/publications/antimicrobial-resistance/en/
38. Rathnayake I, Hargreaves M, Huygens F. SNP diversity of Enterococcus faecalis and Enterococcus faecium in a South East Queensland waterway, Australia, and associated antibiotic resistance gene profiles [Internet]. BMC microbiology. BioMed Central; 2011 [cited 2021Jun7]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3179957/
39. Technical brief on water, sanitation, hygiene (WASH) and wastewater management to prevent infections and reduce the spread of antimicrobial resistance (AMR) [Internet]. World Health Organization. World Health Organization; 2020 [cited 2021Jun7]. Available from: https://www.who.int/water_sanitation_health/publications/wash-wastewater-management-to-prevent-infections-and-reduce-amr/en/
40. International Health Regulations (2005) Third Edition [Internet]. World Health Organization. World Health Organization; [cited 2021Jun7]. Available from: https://www.who.int/publications/i/item/9789241580496
41. World Health Assembly, 72. (2019). Public health emergencies: preparedness and response: WHO's work in health emergencies: report by the Director-General. World Health Organization. https://apps.who.int/iris/handle/10665/328553
42. Operations [Internet]. World Health Organization. World Health Organization; [cited 2021Jun7]. Available from: https://www.who.int/emergencies/operations
43. MacIntyre CR, Bui CM. Pandemics, public health emergencies and antimicrobial resistance - putting the threat in an epidemiologic and risk analysis context [Internet]. Archives of Public Health. BioMed Central; 2017 [cited 2021Jun7]. Available from: https://archpublichealth.biomedcentral.com/articles/10.1186/s13690-017-0223-7
44. Knight GM, Glover RE, McQuaid CF, Olaru ID, Gallandat K, Leclerc QJ, et al. Antimicrobial resistance and COVID-19: Intersections and implications [Internet]. eLife. eLife Sciences Publications, Ltd; 2021 [cited 2021Jun8]. Available from: https://elifesciences.org/articles/64139
45. J; AFANPCS. Why inequality could spread COVID-19 [Internet]. The Lancet. Public health. U.S. National Library of Medicine; [cited 2021Jun8]. Available from: https://pubmed.ncbi.nlm.nih.gov/32247329/
46. Lucien MAB, Canarie MF, Kilgore PE, Jean-Denis G, Fénélon N, Pierre M, et al. Antibiotics and antimicrobial resistance in the COVID-19 era: Perspective from resource-limited settings [Internet]. International Journal of Infectious Diseases. Elsevier; 2021 [cited 2021Jun8]. Available from: https://www.sciencedirect.com/science/article/pii/S1201971221000163
47. Afshinnekoo E;Bhattacharya C;Burguete-García A;Castro-Nallar E;Deng Y;Desnues C;Dias-Neto E;Elhaik E;Iraola G;Jang S;Łabaj PP;Mason CE;Nagarajan N;Poulsen M;Prithiviraj B;Siam R;Shi T;Suzuki H;Werner J;Zambrano MM;Bhattacharyya M; ; COVID-19 drug practices risk antimicrobial resistance evolution [Internet]. The Lancet. Microbe. U.S. National Library of Medicine; [cited 2021Jun8]. Available from: https://pubmed.ncbi.nlm.nih.gov/33655229/
48. Jasovský D, Littmann J, Zorzet A, Cars O. Antimicrobial resistance-a threat to the world's sustainable development [Internet]. Upsala journal of medical sciences. Taylor & Francis; 2016 [cited 2021Jun8]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4967260/
49. SDGs have been adopted and the issue of AMR is in it – 2015 [Internet]. ReAct. 2017 [cited 2021Jun8]. Available from: https://www.reactgroup.org/news-and-views/news-and-opinions/year-2015/sdgs-have-been-adopted-and-the-issue-of-amr-is-in-it/

50. Fact sheet on the SDGs: Antimicrobial resistance (2017) [Internet]. World Health Organization. World Health Organization; 2020 [cited 2021Jun8]. Available from: https://www.euro.who.int/en/health-topics/health-policy/sustainable-development-goals/publications/2017/fact-sheets-on-the-sustainable-development-goals-sdgs-health-targets/fact-sheet-on-the-sdgs-antimicrobial-resistance-2017
51. ANTIMICROBIAL-RESISTANCE THREATENS SUCCESSFUL ACHIEVEMENT OF THE SDG TARGETS. [Internet] Centers for Disease Control and Prevention. [cited 2021 Jun8]. Available from: https://www.cdc.gov/drugresistance/pdf/amr-sdg-pamphlet.pdf
52. Peters L, Olson L, Khu DTK, Linnros S, Le NK, Hanberger H, et al. Multiple antibiotic resistance as a risk factor for mortality and prolonged hospital stay: A cohort study among neonatal intensive care patients with hospital-acquired infections caused by gram-negative bacteria in Vietnam [Internet]. PLOS ONE. Public Library of Science; [cited 2021Jun8]. Available from: https://journals.plos.org/plosone/article?id=10.1371%2Fjournal.pone.0215666
53. Harring N, Krockow EM. The social dilemmas of climate change and antibiotic resistance: an analytic comparison and discussion of policy implications [Internet]. Nature News. Nature Publishing Group; 2021 [cited 2021Jun8]. Available from: https://www.nature.com/articles/s41599-021-00800-2
54. Antimicrobial resistance and climate change: Two wicked problems [Internet]. The Economist. The Economist Newspaper; [cited 2021Jun8]. Available from: https://eiuperspectives.economist.com/healthcare/antimicrobial-resistance-and-climate-change-two-wicked-problems
55. Goal 3 | Department of Economic and Social Affairs [Internet]. United Nations. United Nations; [cited 2021Jun8]. Available from: https://sdgs.un.org/goals/goal3
56. Hub IISDSDGK. New Indicators on AMR, Dispute Resolution, GHG Emissions Agreed for SDG Framework: News: SDG Knowledge Hub: IISD [Internet]. SDG Knowledge Hub. [cited 2021Jun8]. Available from: https://sdg.iisd.org/news/new-indicators-on-amr-dispute-resolution-ghg-emissions-agreed-for-sdg-framework/
57. Lavorgna A. The online trade in counterfeit pharmaceuticals: New criminal opportunities, trends and challenges - Anita Lavorgna, 2015 [Internet]. SAGE Journals. [cited 2021Jun8]. Available from: https://journals.sagepub.com/doi/abs/10.1177/1477370814554722?journalCode=euca
58. India is Training 'Quacks' to Do Real Medicine. This is Why. [Internet]. The Wire. [cited 2021Jun8]. Available from: http://thewire.in/government/india-is-training-quacks-to-do-real-medicine-this-is-why
59. Hallsworth M, Chadborn T, Sallis A, Sanders M, Berry D, Greaves F, et al. Provision of social norm feedback to high prescribers of antibiotics in general practice: a pragmatic national randomised controlled trial [Internet]. The Lancet. Elsevier; 2016 [cited 2021Jun8]. Available from: https://www.sciencedirect.com/science/article/pii/S0140673616002154
60. World Health Organization. (2018). Antimicrobial resistance and primary health care. World Health Organization. https://apps.who.int/iris/handle/10665/326454. License: CC BY-NC-SA 3.0 IGO
61. Antimicrobial resistance: Invest in innovation and research, and boost R&D and access. IACG discussion paper. June 2018. [cited 2021 Jun8]. Available from: https://www.who.int/antimicrobial-resistance/interagency-coordination-group/IACG_AMR_Invest_innovation_research_boost_RD_and_access_110618.pdf
62. Van den Bruel A, Turner P. Forecast diagnostics for antimicrobial resistance (AMR) [Internet]. [cited 2021 Jun8]. Available from: https://amr-review.org/sites/default/files/Forecast%20diagnostics_AMR_1%200.pdf

63. Joakim LDG, D. G. Joakim Larsson D. G. Joakim Larsson Google Scholar Find this author on PubMed Search for more papers by this author, Larsson DGJ, D. G. Joakim Larsson Google Scholar Find this author on PubMed Search for more papers by this author, One contribution of 18 to a Theme Issue 'Assessing risks and impacts of pharmaceuticals in the environment on wildlife and ecosystems'., Al. E. Pollution from drug manufacturing: review and perspectives [Internet]. Philosophical Transactions of the Royal Society B: Biological Sciences. 2014 [cited 2021Jun8]. Available from: https://royalsocietypublishing.org/doi/10.1098/rstb.2013.0571
64. Ågerstrand M;Berg C;Björlenius B;Breitholtz M;Brunström B;Fick J;Gunnarsson L;Larsson DG;Sumpter JP;Tysklind M;Rudén C; Improving environmental risk assessment of human pharmaceuticals [Internet]. Environmental science & technology. U.S. National Library of Medicine; [cited 2021Jun8]. Available from: https://pubmed.ncbi.nlm.nih.gov/25844810/
65. Antimicrobials in agriculture and the environment : reducing unnecessary use and waste / the Review on Antimicrobial Resistance chaired by Jim O'Neill. [Internet]. Wellcome Collection. [cited 2021Jun8]. Available from: https://wellcomecollection.org/works/x88ast2u
66. Bengtsson-Palme J, Larsson DGJ. Concentrations of antibiotics predicted to select for resistant bacteria: Proposed limits for environmental regulation [Internet]. Environment International. Pergamon; 2015 [cited 2021Jun8]. Available from: https://www.sciencedirect.com/science/article/pii/S0160412015300817
67. Kaba HEJ, Kuhlmann E, Scheithauer S. Thinking outside the box: Association of antimicrobial resistance with climate warming in Europe – A 30 country observational study [Internet]. International Journal of Hygiene and Environmental Health. Urban & Fischer; 2019 [cited 2021Jun8]. Available from: https://www.sciencedirect.com/science/article/abs/pii/S1438463919303128
68. Burnham JP. Climate change and antibiotic resistance: a deadly combination - Jason P. Burnham, 2021 [Internet]. SAGE Journals. [cited 2021Jun8]. Available from: https://journals.sagepub.com/doi/10.1177/2049936121991374?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed
69. MacFadden DR, McGough SF, Fisman D, Santillana M, Brownstein JS. Antibiotic resistance increases with local temperature [Internet]. Nature News. Nature Publishing Group; 2018 [cited 2021Jun8]. Available from: https://www.nature.com/articles/s41558-018-0161-6
70. At UN, global leaders commit to act on antimicrobial resistance | | UN News [Internet]. United Nations. United Nations; [cited 2021Jun8]. Available from: https://news.un.org/en/story/2016/09/539912-un-global-leaders-commit-act-antimicrobial-resistance
71. Health in All Policies: Framework for Country Action [Internet]. World Health Organization. World Health Organization; 2016 [cited 2021Jun8]. Available from: https://www.who.int/healthpromotion/frameworkforcountryaction/en/
72. Rogers Van Katwyk S, Grimshaw JM, Nkangu M, Nagi R, Mendelson M, Taljaard M, et al. Government policy interventions to reduce human antimicrobial use: A systematic review and evidence map [Internet]. PLoS medicine. Public Library of Science; 2019 [cited 2021Jun8]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6559631/
73. O; MSC. Major change in the use of antibiotics following a national programme: Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance (STRAMA) [Internet]. Scandinavian journal of infectious diseases. U.S. National Library of Medicine; [cited 2021Jun8]. Available from: https://pubmed.ncbi.nlm.nih.gov/10447331/

74. Coburn J, Bone F, Hopkins MM, Stirling A, Mestre-Ferrandiz J, Arapostathis S, et al. Appraising research policy instrument mixes: a multicriteria mapping study in six European countries of diagnostic innovation to manage antimicrobial resistance [Internet]. Research policy. Elsevier, North-Holland Pub. Co; 2021 [cited 2021Jun8]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8039188/
75. Bloom G, Merrett GB, Wilkinson A, et al. Antimicrobial resistance and universal health coverage. BMJ Glob Health 2017;2:e000518. doi:10.1136/bmjgh-2017-000518
76. Global action plan on AMR [Internet]. World Health Organization. World Health Organization; 2016 [cited 2021Jun8]. Available from: https://www.who.int/antimicrobial-resistance/global-action-plan/en/
77. World Health Organization, Food and Agriculture Organization of the United Nations & World Organisation for Animal Health. (2019). Monitoring and evaluation of the global action plan on antimicrobial resistance: framework and recommended indicators. World Health Organization. https://apps.who.int/iris/handle/10665/325006
78. Monitoring global progress on antimicrobial resistance: Tripartite AMR country self-assessment survey (TrACSS) 2019-2020 [Internet]. World Health Organization. World Health Organization; [cited 2021Jun8]. Available from: https://www.who.int/publications/i/item/monitoring-global-progress-on-antimicrobial-resistance-tripartite-amr-country-self-assessment-survey-(tracss)-2019-2020
79. National action plans [Internet]. World Health Organization. World Health Organization; 2019 [cited 2021Jun8]. Available from: https://www.who.int/antimicrobial-resistance/national-action-plans/en/
80. Antimicrobial resistance: global report on surveillance 2014 [Internet]. World Health Organization. World Health Organization; 2016 [cited 2021Jun8]. Available from: https://www.who.int/drugresistance/documents/surveillancereport/en/
81. Global Antimicrobial Resistance Surveillance System [Internet]. World Health Organization. World Health Organization; 2017 [cited 2021Jun8]. Available from: https://www.who.int/antimicrobial-resistance/publications/surveillance-system-manual/en/
82. The AMR Challenge [Internet]. Centers for Disease Control and Prevention. Centers for Disease Control and Prevention; 2021 [cited 2021Jun8]. Available from: https://www.cdc.gov/drugresistance/intl-activities/amr-challenge.html#
83. Global Research on Antimicrobial Resistance (GRAM) [Internet]. Fleming Fund. 2020 [cited 2021Jun8]. Available from: https://www.flemingfund.org/grants/global-research-on-antimicrobial-research-gram/
84. High-Level Interactive Dialogue on Antimicrobial Resistance (29 April 2021) | General Assembly of the United Nations [Internet]. United Nations. United Nations; [cited 2021Jun8]. Available from: https://www.un.org/pga/75/antimicrobial-resistance/
85. Universal health coverage (UHC) [Internet]. World Health Organization. World Health Organization; [cited 2021Jun8]. Available from: https://www.who.int/news-room/fact-sheets/detail/universal-health-coverage-(uhc)
86. Bhatia R. Universal health coverage framework to combat antimicrobial resistance [Internet]. The Indian journal of medical research. Medknow Publications & Media Pvt Ltd; 2018 [cited 2021Jun8]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6022393/
87. Bloom G, Merrett GB, Wilkinson A, et al. Antimicrobial resistance and universal health coverage. BMJ Glob Health 2017;2:e000518. doi:10.1136/bmjgh-2017-000518
88. WHO Competency Framework for Health Workers' Education and Training on Antimicrobial Resistance [Internet]. World Health Organization. World Health Organization; 2018 [cited

2021Jun8]. Available from: https://www.who.int/hrh/resources/WHO-HIS-HWF-AMR-2018.1/en/

89. Manyazewal T. Using the World Health Organization health system building blocks through survey of healthcare professionals to determine the performance of public healthcare facilities [Internet]. Archives of public health = Archives belges de sante publique. BioMed Central; 2017 [cited 2021Jun8]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5651704/
90. Dyar OJ, Tebano G, Pulcini C. Managing responsible antimicrobial use: perspectives across the healthcare system [Internet]. Clinical Microbiology and Infection. Elsevier; 2017 [cited 2021Jun8]. Available from: https://www.sciencedirect.com/science/article/pii/S1198743X17302276
91. New ReAct policy brief: Antimicrobial resistance and universal health coverage – What's the deal? – 2019 [Internet]. ReAct. 2019 [cited 2021Jun8]. Available from: https://www.reactgroup.org/news-and-views/news-and-opinions/year-2019/new-react-policy-brief-antimicrobial-resistance-and-universal-health-coverage-whats-the-deal/
92. Monitoring the building blocks of health systems: a handbook of indicators and their measurement strategies [Internet]. World Health Organization. World Health Organization; 2014 [cited 2021Jun8]. Available from: https://www.who.int/healthinfo/systems/monitoring/en/
93. GLASS | Global Antimicrobial Resistance Surveillance System (GLASS) [Internet]. World Health Organization. World Health Organization; 2020 [cited 2021Jun8]. Available from: https://www.who.int/glass/en/
94. Global Framework for Development & Stewardship to Combat Antimicrobial Resistance: Draft [Internet]. World Health Organization. World Health Organization; [cited 2021Jun8]. Available from: https://www.who.int/publications/m/item/global-framework-for-development-stewardship-to-combat-antimicrobial-resistance-draft
95. Bremmer DN, Trienski TL, Walsh TL, Moffa MA. Role of Technology in Antimicrobial Stewardship [Internet]. Medical Clinics of North America. Elsevier; 2018 [cited 2021Jun8]. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0025712518300452?via%3Dihub
96. Cook PP, Rizzo S, Gooch M, Jordan M, Fang X, Hudson S. Sustained reduction in antimicrobial use and decrease in methicillin-resistant Staphylococcus aureus and Clostridium difficile infections following implementation of an electronic medical record at a tertiary-care teaching hospital [Internet]. OUP Academic. Oxford University Press; 2010 [cited 2021Jun8]. Available from: https://academic.oup.com/jac/article/66/1/205/724918
97. Tuon FF, Gasparetto J, Wollmann LC, Moraes TPde. Mobile health application to assist doctors in antibiotic prescription – an approach for antibiotic stewardship [Internet]. The Brazilian Journal of Infectious Diseases. Elsevier; 2017 [cited 2021Jun8]. Available from: https://www.sciencedirect.com/science/article/pii/S1413867017305627
98. Access Barriers to Antibiotics [Internet]. Center for Disease Dynamics, Economics & Policy (CDDEP). 2021 [cited 2021Jun8]. Available from: https://cddep.org/publications/access-barriers-to-antibiotics/
99. Everybody's Business: Strengthening Health Systems to Improve Health Outcomes [Internet]. dokumen.tips. [cited 2021Jun8]. Available from: https://dokumen.tips/documents/everybodys-business-strengthening-health-systems-to-improve-health-outcomes.html
100. 8.13 Proportion of population with access to affordable essential drugs on a sustainable basis - ScrewTurn Wiki [Internet]. United Nations. United Nations; [cited 2021Jun8].

Available from: http://mdgs.un.org/unsd/mi/wiki/8-13-Proportion-of-population-with-access-to-affordable-essential-drugs-on-a-sustainable-basis.ashx

101. Nils Daulaire AB. Universal Access to Effective Antibiotics is Essential for Tackling Antibiotic Resistance - Nils Daulaire, Abhay Bang, Göran Tomson, Joan N. Kalyango, Otto Cars, 2015 [Internet]. SAGE Journals. [cited 2021Jun8]. Available from: https://journals.sagepub.com/doi/10.1111/jlme.12269
102. WHO report on surveillance of antibiotic consumption [Internet]. World Health Organization. World Health Organization; [cited 2021Jun8]. Available from: https://www.who.int/publications/i/item/who-report-on-surveillance-of-antibiotic-consumption
103. 2019 antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline [Internet]. World Health Organization. World Health Organization; [cited 2021Jun8]. Available from: https://www.who.int/publications/i/item/9789240000193
104. Global shortage of innovative antibiotics fuels emergence and spread of drug-resistance [Internet]. World Health Organization. World Health Organization; [cited 2021Jun8]. Available from: https://www.who.int/news/item/15-04-2021-global-shortage-of-innovative-antibiotics-fuels-emergence-and-spread-of-drug-resistance
105. 2020 antibacterial agents in clinical and preclinical development: an overview and analysis [Internet]. World Health Organization. World Health Organization; [cited 2021Jun8]. Available from: https://www.who.int/publications/i/item/9789240021303
106. Plackett B. Why big pharma has abandoned antibiotics [Internet]. Nature News. Nature Publishing Group; 2020 [cited 2021Jun8]. Available from: https://www.nature.com/articles/d41586-020-02884-3
107. McEwen SA, Collignon PJ, Scott A. McEwenDepartment of Population Medicine Uof G, Peter J. CollignonInfectious Diseases and Microbiology CH. Antimicrobial Resistance: a One Health Perspective [Internet]. Microbiology Spectrum. 2018 [cited 2021Jun8]. Available from: https://journals.asm.org/doi/10.1128/microbiolspec.ARBA-0009-2017
108. One Health Basics [Internet]. Centers for Disease Control and Prevention. Centers for Disease Control and Prevention; 2018 [cited 2021Jun8]. Available from: https://www.cdc.gov/onehealth/basics/index.html
109. Góchez D, Raicek M, Pinto Ferreira J, Jeannin M, Moulin G, Erlacher-Vindel E. OIE Annual Report on Antimicrobial Agents Intended for Use in Animals: Methods Used [Internet]. Frontiers. Frontiers; 2019 [cited 2021Jun8]. Available from: https://www.frontiersin.org/articles/10.3389/fvets.2019.00317/full
110. Tamhankar AJ, Stålsby Lundborg C. Antimicrobials and Antimicrobial Resistance in the Environment and Its Remediation: A Global One Health Perspective [Internet]. International journal of environmental research and public health. MDPI; 2019 [cited 2021Jun8]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6926838/
111. Martins AF, Rabinowitz P. The impact of antimicrobial resistance in the environment on public health. Future Microbiology. 2020;15(9):699–702.
112. Antimicrobial resistance: a global threat. [Internet]. UNEP. [cited 2021 Jun9]. Available from: https://www.unep.org/explore-topics/chemicals-waste/what-we-do/emerging-issues/antimicrobial-resistance-global-threat
113. WHO: Framework for Action on Interprofessional Education & Collaborative Practice [Internet]. WHO: Framework for Action on Interprofessional Education & Collaborative Practice :: Interprofessional Education | The University of New Mexico. 2020 [cited 2021Jun8]. Available from: https://hsc.unm.edu/ipe/resources/who.html

114. Uchil RR, Kohli GS, Katekhaye VM, Swami OC. Strategies to combat antimicrobial resistance [Internet]. Journal of clinical and diagnostic research : JCDR. JCDR Research and Publications (P) Limited; 2014 [cited 2021Jun8]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4149102/#b24
115. Weese JS, Giguère S, Guardabassi L, Morley PS, Papich M, Ricciuto DR, et al. ACVIM consensus statement on therapeutic antimicrobial use in animals and antimicrobial resistance [Internet]. Journal of veterinary internal medicine. John Wiley and Sons Inc.; 2015 [cited 2021Jun8]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4895515/
116. Lees P, Pelligand L, Giraud E, Toutain PL. A history of antimicrobial drugs in animals: Evolution and revolution. Journal of Veterinary Pharmacology and Therapeutics. 2020;44(2):137–71.
117. Ahmadi H, Ebrahimi A, Ahmadi F. Antibiotic Therapy in Dentistry [Internet]. International Journal of Dentistry. Hindawi; 2021 [cited 2021Jun8]. Available from: https://www.hindawi.com/journals/ijd/2021/6667624/
118. Poveda-Roda R, Bagán JV, Sanchis-Bielsa JM, Carbonell-Pastor E. Antibiotic use in dental practice. A review. Med Oral Patol Oral Cir Bucal 2007;12:E186-92.
119. Montero-Aguilar M. Antimicrobial Resistance: What Should Dentists be Doing? [Internet]. Odovtos - International Journal of Dental Sciences. 2017 [cited 2021Jun8]. Available from: https://www.medigraphic.com/cgi-bin/new/resumenI.cgi?IDARTICULO=70041#
120. Saha SK, Kong DCM, Thursky K, Mazza D. Development of an antimicrobial stewardship implementation model involving collaboration between general practitioners and pharmacists: GPPAS study in Australian primary care [Internet]. Primary health care research & development. Cambridge University Press; 2021 [cited 2021Jun8]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8057431/
121. Community Pharmacists' Contributions to Disease Management During the COVID-19 Pandemic [Internet]. Centers for Disease Control and Prevention. Centers for Disease Control and Prevention; 2020 [cited 2021Jun8]. Available from: https://www.cdc.gov/pcd/issues/2020/20_0317.htm
122. Khan TM, Bukhsh A. Interprofessional Education in Pharmacy: Review of Case Studies [Internet]. Pharmacy Education in the Twenty First Century and Beyond. Academic Press; 2018 [cited 2021Jun8]. Available from: https://www.sciencedirect.com/science/article/pii/B9780128119099000198
123. FM; MEBDMFGJEM. The effect of an educational intervention to improve patient antibiotic adherence during dispensing in a community pharmacy [Internet]. Atencion primaria. U.S. National Library of Medicine; [cited 2021Jun8]. Available from: https://pubmed.ncbi.nlm.nih.gov/24581680/
124. Baker SN;Acquisto NM;Ashley ED;Fairbanks RJ;Beamish SE;Haas CE; Pharmacist-managed antimicrobial stewardship program for patients discharged from the emergency department [Internet]. Journal of pharmacy practice. U.S. National Library of Medicine; [cited 2021Jun8]. Available from: https://pubmed.ncbi.nlm.nih.gov/22095578/
125. Katwyk SRV, Jones SL, Hoffman SJ. Mapping educational opportunities for healthcare workers on antimicrobial resistance and stewardship around the world [Internet]. Human Resources for Health. BioMed Central; 2018 [cited 2021Jun8]. Available from: https://human-resources-health.biomedcentral.com/articles/10.1186/s12960-018-0270-3
126. Hayat K, Rosenthal M, Gillani AH, Chang J, Ji W, Yang C, et al. Perspective of Key Healthcare Professionals on Antimicrobial Resistance and Stewardship Programs: A Multicenter Cross-Sectional Study From Pakistan [Internet]. Frontiers in pharmacology.

Frontiers Media S.A.; 2020 [cited 2021Jun8]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6967405/