Ceftaroline

Is a parenteral advanced-generation cephalosporin. It's FDA-approved for MRSA SSTs infection and community-acquired pneumonia (MRSA pneumonia excluded from a clinical trial). Demonstrates greater affinity for penicillin-binding protein 2a (PBP2a), may be effective against vancomycin-intermediate *Staphylococcus aureus* (VISA), hetero-VISA, VRSA, as well as for *Streptococcus pneumoniae* strains that are intermediate or resistant to penicillin or ceftriaxone.
As a time-dependent antibiotic, the percentage of a dosing interval in which free drug concentrations exceed the minimum inhibitory concentration (MIC) of the target bacteria (% fT > MIC) is considered the pharmacodynamic index most closely associated with clinical efficacy. Prolonged or continuous infusion is the most studied strategy for beta-lactams, especially for critically ill patients or pathogens with high MICs. Administration every 8 hours has also been shown to be an alternative, but larger studies are still needed to demonstrate the effects of these strategies on clinical outcomes.

Ceftobiprole

Is an advanced-generation parenteral cephalosporin with activity against both Gram-positive and Gram-negative bacteria, including MRSA. Like ceftaroline, it is also able to bind to PBP2a. As a beta-lactam antibiotic, the primary strategy to optimize efficacy involves prolonged infusion. There are also reports of the development of methods for quantifying serum levels for the application of therapeutic drug monitoring in clinical practice. However, more PK/PD studies are needed to determine the therapeutic target.

Other alternative drugs for resistant Gram-positive bacteria

There are other antibiotics from the lipoglycopeptide class that can be used as therapeutic alternatives for the treatment of MRSA, like telavancin, dalbavancin, oritavancin. The PK/PD index is the 24-hour AUC/MIC; however, serum monitoring has not yet been incorporated into clinical practice, and further studies are needed for this application.
Delafloxacin, is the first fluoroquinolone with activity against MRSA, approved for skin and skin structure infections (SSSIs). The PK/PD index is the 24-hour AUC/MIC, more studies are still needed in this area to determine the desired therapeutic targets.

Conclusion

Resistant Gram-positive bacterial infections represent an impactful problem worldwide. Strategies for dose optimization based on PK/PD principles and the use of TDM are important to maximize the efficacy of antibiotics, reduce toxicity, and prevent the emergence of resistance. This is a field of study that requires investment so that these resources are not limited to research alone but can be expanded to the routine practice of healthcare institutions worldwide.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 19

Global burden of invasive fungal infections in hospital settings

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Introduction

Invasive fungal infections (IFIs) are severe, life-threatening conditions that occur when fungi invade typically sterile sites such as the bloodstream, lungs or central nervous system. These infections are particularly dangerous for immune-compromised individuals, such as those undergoing chemotherapy, solid organ transplants, living with HIV/AIDS, or on immune-suppressive drugs. Unlike superficial fungal infections such as those affecting the skin, nails, and mucous membranes, IFIs involve deep tissue invasion, typically more challenging to manage clinically. Often, it necessitates prolonged systemic antifungal therapy which is usually complicated by the high toxicity of available antifungals and the emerging resistance of fungal pathogens to antifungal agents. IFIs carry a significant mortality risk, with rates exceeding 50% in some high-risk populations, such as patients with hematologic malignancies or those in intensive care. The rising global incidence of IFIs is driven by an aging population and increased use of immunosuppressive therapies.

The economic burden is substantial, driven by prolonged hospital stays, the high cost of systemic antifungal treatments, intensive infection control measures, and long-term rehabilitation for survivors. IFIs are frequently underdiagnosed, largely due to non-specific symptoms that resemble bacterial or viral infections, and the limitations of current diagnostic tools, especially in low- and middle-income countries (LMICs). In these regions, limited access to advanced diagnostics and antifungal therapies exacerbates the problem. In this chapter, we examine the global burden of IFIs, focusing on epidemiological trends, clinical challenges, antifungal resistance, and prevention strategies across different world regions.

Epidemiology and burden of invasive fungal infections by region

Global epidemiology and burden of invasive fungal infections

The global burden of IFIs has significantly increased over the past decade, with more than 6.55 million people affected annually. This includes over 2.1 million cases of invasive aspergillosis, 1.8 million cases of chronic pulmonary aspergillosis, 1.5 million cases of *Candida* bloodstream infections, and 500,000 cases of *Pneumocystis* pneumonia. The mortality burden is also striking, with over 3.75 million deaths attributed to fungal infections, of which 2.55 million are directly caused by the disease.

The rising burden of IFIs is driven not only by an increasing number of immunocompromised individuals, but also by patients with chronic conditions like chronic obstructive pulmonary disease (COPD) and tuberculosis. Recent estimates suggest that up to one-third of the 3.23 million annual deaths from COPD and 28% of the more than 1.2 million tuberculosis deaths may be attributable to fungal co-infections, particularly chronic pulmonary aspergillosis.

Common pathogens causing IFIs include *Candida* species (particularly *Candida albicans* and *Candida auris*), *Aspergillus fumigatus*, and *Cryptococcus neoformans*. There is a changing global pattern toward decreasing rates of *Candida albicans* infections and increasing rates of non-*albicans Candida* species, which are often more resistant to antifungal treatments. *Candida auris* has recently emerged as a multidrug-resistant pathogen, posing challenges in infection control within healthcare settings. The burden of IFIs varies by region, influenced by healthcare infrastructure, environmental factors, and population vulnerability.

Epidemiology and burden of invasive fungal infections in Africa

Invasive fungal infections (IFIs) represent a significant health burden across Africa. Despite the severity of these infections, their true burden remains underreported due to diagnostic challenges and limited healthcare resources.

The most prevalent IFI in Africa is cryptococcal meningitis (CM), caused by *Cryptococcus neoformans*. Sub-Saharan Africa accounts for 73% of the estimated 223,100 global cases of CM and 75% of the estimated 181,000 deaths annually. An annual incidence rate of 41 per 100,000 people, amounting to 6,086 cases has been reported in Zimbabwe. Nigeria alone experiences more than 57,866 cases each year. The high mortality rate is exacerbated by limited access to the cryptococcal antigen (CrAg) assay and the absence of critical antifungal treatments, such as amphotericin B and liposomal amphotericin B, in most healthcare settings.

Other IFIs, such as *Candida auris*, invasive aspergillosis, candidemia, histoplasmosis, and pneumocystis pneumonia (PCP), are increasingly recognized but often misdiagnosed due to their overlapping symptoms with endemic diseases like tuberculosis and malaria. *Candida auris*, a multidrug-resistant pathogen, has been identified in over 100 hospitals in South Africa, where it accounts for a significant proportion of candidemia cases. In Zimbabwe, candidemia has an incidence of 5 per 100,000 people, with 743 cases reported annually. The COVID-19 pandemic has heightened the risk for fungal infections, particularly in patients receiving corticosteroids, and opportunistic infections like *Mucorales* and *Aspergillus* are of rising concern. Additionally, overlapping infections with endemic diseases like tuberculosis and HIV continue to complicate diagnosis and treatment.

Invasive aspergillosis, for instance, affects between 0.3 to 16 per 100,000 people, though this figure likely underestimates its true prevalence due to diagnostic limitations. Histoplasmosis, particularly in West and Central Africa, is frequently mistaken for tuberculosis, further complicating its detection. Emerging studies show that it is a major cause of illness, especially in HIV-positive individuals.

Pneumocystis pneumonia (PCP) also poses a significant threat, particularly in people living with HIV, with prevalence rates as high as 24% among inpatients with respiratory symptoms.

Epidemiology and burden of invasive fungal infections in Asia

The incidences of invasive fungal infections (IFIs) are increasing across Asia. Advanced age, diabetes, exposure to immunosuppressants, neutropenia, and catheter usage have been recognized as major risk factors for IFIs. Patients with pre-existing respiratory conditions such as COPD and tuberculosis are particularly vulnerable to invasive aspergillosis, and COVID-19 has further amplified the risk of fungal infections across the region.

India, the most populous country in South Asia, reports an estimated 4.1% of its 1.39 billion population (approximately 57.25 million people) suffering from serious fungal diseases. This includes recurrent vulvovaginal candidiasis (24.3 million), allergic bronchopulmonary aspergillosis (2 million), tinea capitis in school-age children (25 million), severe asthma with fungal sensitization (1.36 million), chronic pulmonary aspergillosis (1.74 million), and chronic fungal rhinosinusitis (1.52 million). The annual incidence rates for certain conditions are staggering, with mucormycosis (195,000 cases), invasive aspergillosis (250,900 cases), *Pneumocystis* pneumonia (58,400 cases), esophageal candidiasis in HIV (266,600 cases), candidemia (188,000 cases), fungal keratitis (1,017,100 cases), and cryptococcal meningitis (11,500 cases) also posing significant public health challenges. Less frequent conditions such as histoplasmosis, talaromycosis, mycetoma, and chromoblastomycosis are also present.

The COVID-19 pandemic exacerbated the burden of IFIs in India, particularly during the second wave when there was a dramatic surge in mucormycosis cases. This COVID-19-associated mucormycosis (CAM) was largely attributed to the widespread use of corticosteroids in treating severe COVID-19 and the high prevalence of diabetes in the region. Mortality rates for mucormycosis often exceed 50% due to diagnostic delays, limited availability of antifungal treatments, and the role of comorbidities like diabetes.

In the Arab world, invasive candidiasis (IC) is the most studied fungal infection. *Candida albicans* remains the predominant species, although non-*albicans* species like *Candida tropicalis*, *C. glabrata*, and *C. parapsilosis* are on the rise. In Saudi Arabia, IC incidence rates have been reported as high as 1.65 cases per 1,000 hospital discharges. A multicenter study from Lebanon and Saudi Arabia revealed that between 2011 and 2012, 102 cases of IFIs were caused by *Candida* and *Aspergillus* species. Invasive aspergillosis (IA) is emerging as a major concern across Asian countries, particularly in immunocompromised patients. This is being exacerbated by the dry, dusty climate in many parts of the region which contributes to the inhalation of *Aspergillus* spores, and consequently invasive aspergillosis. *Aspergillus flavus* and *Aspergillus fumigatus* are the most commonly isolated species, with invasive fungal rhinosinusitis frequently reported in Saudi Arabia and other Gulf states. In Iran, invasive *Aspergillus* infections were found in 8.3% of patients with haematological malignancies. Mucormycosis, although less frequently reported in the Arab world compared to South Asia, is still a critical issue. In Qatar, the mucormycosis rate is 1.23 per 100,000 inhabitants, while Iraq, Jordan, and Algeria report lower rates of about 0.2 per 100,000. High mortality rates in these regions are linked to delays in diagnosis and limited access to life-saving treatments such as liposomal amphotericin B. Hospital construction and renovation projects in this region have been linked with significant IFIs outbreaks through the release of spores from disturbed dust and soil.

Epidemiology and burden of invasive fungal infections in Europe

The rise of invasive fungal infections (IFIs) in Europe is primarily due to an increase in immunosuppressive therapies and invasive medical procedures. A prevalence of 7.8% has been reported among pediatric patients with hematological malignancies in Greece. Invasive pulmonary aspergillosis (IPA) and candidemia were the most common infections, with breakthrough infections frequently occurring despite antifungal prophylaxis. The emergence of azole-resistant *Aspergillus* strains and cryptic species has further complicated treatment efforts in the region.

In the Netherlands, the estimated annual burden of serious invasive fungal infections is 3,185 cases, which includes 1,283 cases of invasive aspergillosis, 445 cases of candidemia, and 15 cases of mucormycosis. Mortality rates for these infections are high, particularly for azole-resistant aspergillosis, which has been reported in 145 cases. The mortality rate for invasive aspergillosis can reach 30-50%, depending on resistance patterns and underlying conditions.

In the United Kingdom (UK), the burden of invasive fungal infections is also substantial. According to estimates, there are around 3,185 serious IFIs annually, including 1,283 cases of invasive aspergillosis, 445 cases of candidemia, and 15 cases of mucormycosis. Mortality rates for these infections are high, with invasive aspergillosis reaching up to 50% in certain populations. Furthermore, the rise of azole-resistant *Aspergillus* strains and the increasing prevalence of multidrug-resistant *Candida auris* pose significant challenges in treatment. The incidence of *Pneumocystis jirovecii* pneumonia (PCP) in solid organ transplant recipients has also been rising in the UK, with the incidence in lung and heart transplant recipients reported to be as high as 5.8%, while kidney transplant recipients showed an incidence of 0.3%.

The burden of invasive candidiasis (IC) is especially concerning. Invasive candidiasis is primarily caused by *Candida albicans*, though there has been a global shift toward infections caused by non-*albicans Candida* species, such as *Candida glabrata*, which exhibit increased resistance to antifungals. A recent study reported that candidemia increases 90-day mortality rates by over 28%, and candidemia remains a leading cause of healthcare-associated bloodstream infections. The emergence of *Candida auris*, a multidrug-resistant pathogen, is particularly worrisome due to its rapid spread in healthcare settings and its resistance to multiple antifungal agents. A meta-analysis of European studies found a pooled candidemia incidence of 3.9 per 100,000 population. IC in Europe is also marked by geographic differences in the prevalence of *Candida* species. While *Candida albicans* remains the dominant pathogen in Northern and Middle Europe, there has been a noticeable shift toward non-*albicans Candida* species, such as *Candida glabrata* and *Candida parapsilosis*, especially in Southern Europe. Mortality rates for IC in Europe range between 38-42%, reflecting the severity of the condition. *Candida* bloodstream infections alone cause an estimated 20-40% mortality in ICU settings across Europe. The cost impact of IFIs in Europe is substantial, particularly for healthcare systems dealing with prolonged hospital stays, ICU admissions, and expensive antifungal treatments.

In Germany, a 10-year single-center retrospective study highlighted the growing concern over candidemia in critically ill patients. The incidence of candidemia was 4.8 per 1,000 ICU admissions, with mortality rates of 47% at 28 days and almost 60% at 180 days, underscoring the severity of the condition. The study found that *Candida albicans* was the most prevalent species (60.9%), but there was also a significant presence of non-*albicans* species such as *Candida glabrata* (19.4%). Despite early antifungal intervention, high mortality rates persisted, emphasizing the importance of timely treatment and source control. Germany's findings reflect trends across Europe, where invasive candidiasis (IC) remains a significant cause of healthcare-associated bloodstream infections, contributing to high ICU mortality rates.

Epidemiology and burden of invasive fungal infections in North America

In the United States, the burden of IFIs has grown substantially, with 666,235 fungal infections diagnosed during inpatient visits in 2018, of which 20% were invasive infections. *Aspergillus*, *Candida*, and *Pneumocystis jirovecii* are the most prevalent pathogens, with invasive infections accounting for more than 80% of the associated healthcare costs. Similar to findings across Europe, cancer patients, diabetics, and those undergoing organ transplants are at significantly higher risk of contracting IFIs.

The United States Centre for Disease Control and Prevention has declared *Candida auris*, an emerging fungus and urgent antimicrobial resistance threat, spread rapidly in U.S. healthcare facilities between 2020 and 2021, with clinical cases rising from 476 in 2019 to 1,471 in 2021. The fungus, often resistant to multiple antifungal drugs, poses a high risk to severely ill patients, particularly those with invasive medical devices or prolonged hospital stays.

In 2017, the estimated burden of candidemia in the United States was substantial, with 22,660 cases and a national incidence rate of 7.0 per 100,000 persons. The highest rates were observed in adults aged 65 and older (20.1 per 100,000) and among black individuals (12.3 per 100,000). Candidemia led to significant mortality, with an estimated 3,380 deaths occurring within 7 days of diagnosis and 5,628 deaths during hospitalization. Although candidemia is a leading cause of invasive fungal infections, it represents only a portion of the overall burden of invasive candidiasis, which includes other severe forms of infection not always detected through blood cultures. In the United States, candidemia remains a major healthcare concern, causing approximately 22,000 infections annually and being the second most common cause of healthcare-associated bloodstream infections. Candidemia incidence has decreased over time due to improved infection control practices, though there has been a rise in non-blood invasive candidiasis from sterile sites, such as intra-abdominal candidiasis (IAC), particularly in ICU settings. The incidence of candidemia increased during the COVID-19 pandemic, with higher rates reported among patients with severe COVID-19 infections. The economic burden of invasive candidiasis (IC) in the US is significant, with an estimated annual cost of $1.8 billion and high associated mortality rates (36%). The average hospital stay for a patient with candidemia is approximately 28 days in the US.

The incidence of invasive fungal infections (IFI) among solid organ transplant (SOT) recipients in Canada was 8.3 per 1000 person-years, with lung transplant recipients experiencing the highest incidence at 43.0 per 1000 person-years. IFI significantly increased the risk of mortality in SOT recipients, with a 1-year mortality rate of 34.3% following IFI.

Epidemiology and burden of invasive fungal infections in South America

In South America, invasive fungal infections (IFIs) are a growing concern, with a notable rise in non-*albicans Candida* species, particularly *Candida parapsilosis* and *Candida tropicalis*. The incidence of candidemia in the region is higher than in other parts of the world, ranging from 0.6 to 6.0 per 1000 hospital admissions. Mortality rates for invasive candidiasis vary widely, from 30% to 70%, largely due to disparities in healthcare resources. The burden is particularly heavy in regions with widespread HIV/AIDS, where late diagnosis and limited access to treatment contribute to high mortality.

Presentation and diagnostic challenges

Invasive fungal infections (IFIs) can present with a broad range of non-specific symptoms, including fever, cough, respiratory distress, and sometimes more specific signs such as haemoptysis or cutaneous lesions. This clinical variability, combined with the limitations of traditional diagnostic methods—microscopy, culture, and antigen detection—poses significant challenges for early and accurate diagnosis. While these methods remain foundational, they are often slow and exhibit low sensitivity for certain fungal pathogens, particularly in resource-limited settings where access to advanced tools is scarce.

Recent advances in molecular diagnostics, such as PCR, next-generation sequencing (NGS), matrix-assisted laser desorption ionisation-time of flight mass spectrometry (MALDI-TOF MS), and biosensor technologies, have shown great promise in addressing these diagnostic challenges. MALDI-TOF MS, for instance, enables rapid and accurate identification of fungal pathogens through protein profile analysis. However, its effectiveness relies on the availability of comprehensive fungal databases, which can be a limiting factor, particularly in under-resourced regions. In such settings, more affordable point-of-care tools, such as lateral flow assays (LFA) for detecting fungal antigens, have proven highly valuable.

Furthermore, rapid diagnostic platforms like T2Candida and antigen detection assays provide improved accuracy and speed. Despite these advancements, their accessibility in resource-limited areas remains limited, and traditional methods, such as microscopy and culture, continue to play a crucial role. Enhanced clinical awareness, combined with the integration of both traditional and advanced diagnostics, is essential to reduce the significant number of preventable deaths from IFIs.

Recent advances in diagnostic technologies, such as PCR, next-generation sequencing (NGS), and biomarkers like galactomannan and beta-D-glucan, have improved the ability to diagnose IFIs with greater speed and precision. These emerging techniques are especially important in high-risk populations but are still not widely accessible in many LMICs, where diagnostic capabilities remain limited.

Infection control and environmental measures

Preventing IFIs in hospital settings requires stringent infection control practices. Proper hand hygiene, environmental cleaning, and isolation protocols for infected patients are crucial. In addition, regular monitoring of hospital environments for fungal spores, especially in areas undergoing construction or renovation, is necessary to prevent outbreaks. Improving hospital ventilation and maintaining heating, ventilation, and air conditioning (HVAC) systems are also important steps in reducing the risk of airborne fungal infections.

Conclusion

Invasive fungal infections represent a significant global health burden, especially in hospital settings where immunocompromised patients are most vulnerable. The incidence of IFIs continues to rise due to the increasing use of immunosuppressive therapies, invasive procedures, and the emergence of multidrug-resistant fungal pathogens.

Geographical variation in the prevalence of IFIs reflects differences in healthcare infrastructure, environmental factors, and population vulnerability. High-risk groups, including cancer patients, transplant recipients, and individuals with HIV/AIDS, are particularly susceptible to these infections, which often result in high mortality rates.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 20

Candida auris: a global threat, in the fight against antimicrobial resistance

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Introduction

C. auris is a species of fungus first identified in 2009. It is part of the diverse phylum Ascomycota, including yeasts, molds, and mildews found in various environments. Within this phylum, the class *Saccharomycetes*, known for sugar fermentation, and the genus *Candida*, which includes various yeast-like fungi. The genus *Candida* comprises over 150 species, some of which are harmless commensals, while others are pathogens. Unlike many other species in this genus, *C. auris* is challenging to diagnose using standard laboratory methods and is typically prone to misidentification, resulting in inappropriate management. *C. auris* can cause severe infections in humans, particularly in immunocompromised individuals. *C. auris* has gained significant attention due to its multidrug-resistant properties, high mortality rates, and propensity to cause outbreaks in healthcare settings. This pathogen is known for its resilience and ability to persist on surfaces in hospitals, contributing to its rapid spread and difficulty in eradication.

Emergence and spread of *Candida auris*

The first reported case of *C. auris* was in 2009 isolated from the external ear canal of an inpatient in Japan. In the same year, *C. auris* was also isolated from ear canal specimens in South Korea. By 2014, 5 years later, *C. auris* had been identified in South Korea, India, and South Africa, where it caused outbreaks of bloodstream infections.

A meta-analysis showed that at least 742 *C. auris* isolates have been reported in 16 countries, with most of these being from India (≥243), USA (≥232) and UK (≥103) between 2013–2017. Since its initial discovery, *C. auris* has spread to over 40 countries across six continents, including North America, Europe, and Asia. Its global dissemination has been facilitated by international travel.

The emergence of *C. auris* in India was first noted in sporadic outbreaks and documented in a multicentre study of candidemia across 27 ICUs in 2011. In this study, *C. auris* was identified as the causative agent in

5.3% (74 out of 1400) of candidemia episodes, making it the fifth most common cause of this condition. The isolates from India were found to be clonal and genotypically distinct from those in Japan and South Korea. Significant risk factors for *C. auris* candidemia included admissions to overburdened public hospitals, previous exposure to antifungal treatments, respiratory illnesses, and vascular surgery. The high rate of disease, even in patients with relatively fewer comorbidities, may be attributed to the extensive medical interventions in ICU patients.

Candida auris in healthcare settings

C. auris has become a significant concern in healthcare settings due to its association with high morbidity and mortality rates among hospitalized patients. It is particularly prevalent in intensive care units (ICUs) and long-term care facilities, where patients with weakened immune systems or invasive devices, such as catheters and ventilators, are at increased risk of infection. The majority of reported cases involve invasive infections, such as bloodstream infections (candidemia). Additionally, *C. auris* has been implicated in urinary tract infections, otitis, and deep-seated infections including osteomyelitis, myocarditis, wound infections, skin abscesses, and meningitis.

C. auris colonizes various body sites including the nares, palms, fingertips, axillae, inguinal creases, and toe webs. It disrupts the normal mycobiome of patients in healthcare settings, increasing the risk of developing fungal bloodstream infections (candidemia) by up to 25% within 60 days of the first detection of colonization. The crude in-hospital mortality rate for *C. auris* candidemia ranges from 25% to 70%. The pathogen spreads through various routes, contaminating hospital surfaces such as floors, bed rails, bedsheets, trolleys, chairs, bed trays, air conditioning units, and sinks. Medical equipment, including temperature probes, blood pressure cuffs, glucometers, intravenous poles, oxygen masks, carts, dialysis equipment, ultrasound machines, computer monitors, and keypads, also shows significant contamination. *C. auris* can survive up to 28 days on plastic surfaces and up to 7 days on both wet and dry steel surfaces. In its biofilm form, it can persist on surfaces for more than a week and withstand recommended concentrations of disinfectants like sodium hypochlorite, while quaternary ammonium compounds prove ineffective. This ability of *C. auris* to colonize the skin and persist on environmental surfaces makes it a formidable pathogen in hospitals, contributing to difficult-to-control outbreaks.

Types of infections caused by *Candida auris* and their severity

Bloodstream infections (BSI)

Bloodstream infections caused by *C. auris* are severe, especially for critically ill patients in intensive care units (ICUs). These infections have high death rates, ranging from 30% to 72%. In Russia, a study found that 55.3% of patients with these infections died, and 39.5% died within 30 days. In Colombia, 41% of children with these infections died in the hospital. In the United States, about 40% of patients died within 30 days during outbreaks. These high death rates show the need for better ways to detect, treat, and prevent these infections.

Intra-abdominal infections

Although less commonly reported, *C. auris* can cause intra-abdominal infections, particularly in patients with predisposing factors such as abdominal surgery or invasive procedures. These infections are challenging to manage due to the pathogen's resistance profile and the need for aggressive and prolonged treatment protocols.

Surgical site infections

Post-surgical infections caused by *C. auris* are a significant concern, particularly in healthcare settings where the pathogen can persist on surfaces and spread between patients. These infections can result in severe complications, including prolonged hospital stays, increased morbidity, and higher healthcare costs.

Osteomyelitis and endophthalmitis

Infections such as osteomyelitis and endophthalmitis caused by *C. auris* are notably severe and challenging to treat, frequently leading to long-term morbidity. Globally, cases have been reported in diverse regions highlighting the widespread impact of these difficult-to-manage infections. These conditions require extensive medical intervention and often have poor prognoses, underscoring the critical need for effective treatment strategies.

Neonatal infections

Neonatal infections caused by *C. auris* exhibit high case fatality rates, especially among premature and immunocompromised infants, with mortality rates in neonatal intensive care units (NICUs) exceeding 50%. An outbreak in a large referral centre in Colombia highlighted significant diagnostic and treatment challenges, resulting in multiple fatalities. This underscores the critical need for improved diagnostic tools and therapeutic strategies to manage *C. auris* infections in this vulnerable population.

Urinary tract infections (UTIs)

Urinary tract infections (UTIs) caused by *C. auris* are notably persistent and challenging to eradicate due to the pathogen's resistance to commonly used antifungal medications. Reports from healthcare settings in the United States and India have highlighted the prevalence of *C. auris* UTIs, particularly among patients with indwelling catheters and those in long-term care facilities. These findings underscore the need for enhanced infection control measures and novel therapeutic approaches to manage *C. auris* in these high-risk populations.

Respiratory infections

Respiratory infections caused by *C. auris* can significantly complicate pre-existing conditions, particularly in patients who require mechanical ventilation. Documented cases in intensive care units (ICUs) have demonstrated that respiratory tract colonization by *C. auris* can result in severe pneumonia and other respiratory complications, thereby worsening patient outcomes. This underscores the critical need for vigilant monitoring and effective management strategies to address the risks associated with *C. auris* in vulnerable respiratory patients.

The most vulnerable population to *Candida auris* infections

Hospitalised patients, especially those in intensive care units (ICUs) and those with central venous catheters (CVCs), are at high risk due to invasive procedures and prolonged antibiotic use. Long-term care facility residents, particularly those on mechanical ventilation, also face heightened risk. Immunocompromised individuals, including those with hematologic malignancies, transplant recipients, and patients on immunosuppressive therapy, are especially susceptible. Neonates, particularly preterm and low birth weight infants in neonatal intensive care units (NICUs), are highly vulnerable, often experiencing high mortality rates. Additionally, individuals with chronic conditions such as diabetes or renal failure are more prone to *C. auris* infections due to frequent hospitalisations. Effective infection control measures are crucial to protect these high-risk groups and prevent the spread of *C. auris* in healthcare settings.

Screening and diagnosing *Candida auris* infections

Screening and diagnosing *C. auris* infections typically involve screening asymptomatic patients in healthcare settings with known transmission or close contacts of confirmed cases. Swabs from the axillae and groin are collected using flocked swabs for higher yield, transported in Amies transport medium, and processed for either culture-based or molecular testing. Culture methods, such as Sabouraud Dextrose Agar (SDA) or chromogenic media, are used to isolate *C. auris*, with selective enrichment broths improving recovery. Molecular techniques, like PCR assays targeting the ITS and 28S rRNA regions, enable rapid and specific identification. Advanced methods like MALDI-TOF mass spectrometry distinguish *C. auris* from related species, while Whole Genome Sequencing (WGS) provides detailed epidemiological insights and helps understand antifungal resistance mechanisms. These combined approaches are critical for accurate diagnosis and effective outbreak management (**Table 1**, **Figure 1**).

Table 1. Screening and diagnosing *Candida auris* infections.

Step	Description
Screening	Identify asymptomatic patients in healthcare settings where transmission is known or in close contact with confirmed cases for screening.
Sample collection	Collect swabs from recommended sites such as the axillae and groin using superficial swabs immersed in Amies transport medium. Use flocked swabs for higher yield potential.
Transport to laboratory	Promptly transport the collected swabs to the laboratory to maintain organism viability.
Initial screening	Process the swabs for either culture-based or molecular testing depending on the clinical scenario and urgency of results.
Culture-based methods	**Media:** Sabouraud dextrose agar or chromogenic media like CHROMagar Candida Plus. **Purpose:** facilitates growth and identification of *C. auris* based on distinctive colony characteristics.
Selective enrichment broth	**Broth:** 10% salt Sabouraud Dulcitol broth. **Purpose:** enhances recovery rates of *C. auris*, useful given its ability to thrive under saline and elevated temperature conditions.
Molecular techniques	**Methods:** PCR assays targeting ITS and 28S rRNA regions. **Purpose:** offers rapid and specific identification, valuable in outbreak investigations and high-risk scenarios.
Phenotypic and biochemical identification	**Techniques:** fermentation profiles of sugars like sucrose, mannitol, and dulcitol. **Purpose:** helps distinguish *C. auris* from related species like the *C. haemulonii* complex.

(cont.)

Table 1. Screening and diagnosing *Candida auris* infections *(cont.)*

Step	Description
Advanced identification techni-ques	**Method:** MALDI-TOF mass spectrometry. **Purpose:** achieves accurate species differentiation, overcoming challenges of conven-tional methods.
Comprehensive genomic analy-sis	**Method:** Whole Genome Sequencing (WGS). **Purpose:** provides superior discriminative power, aids in phylogenetic analysis, and helps understand virulence factors and antifungal resistance. **Application:** epidemiological studies.

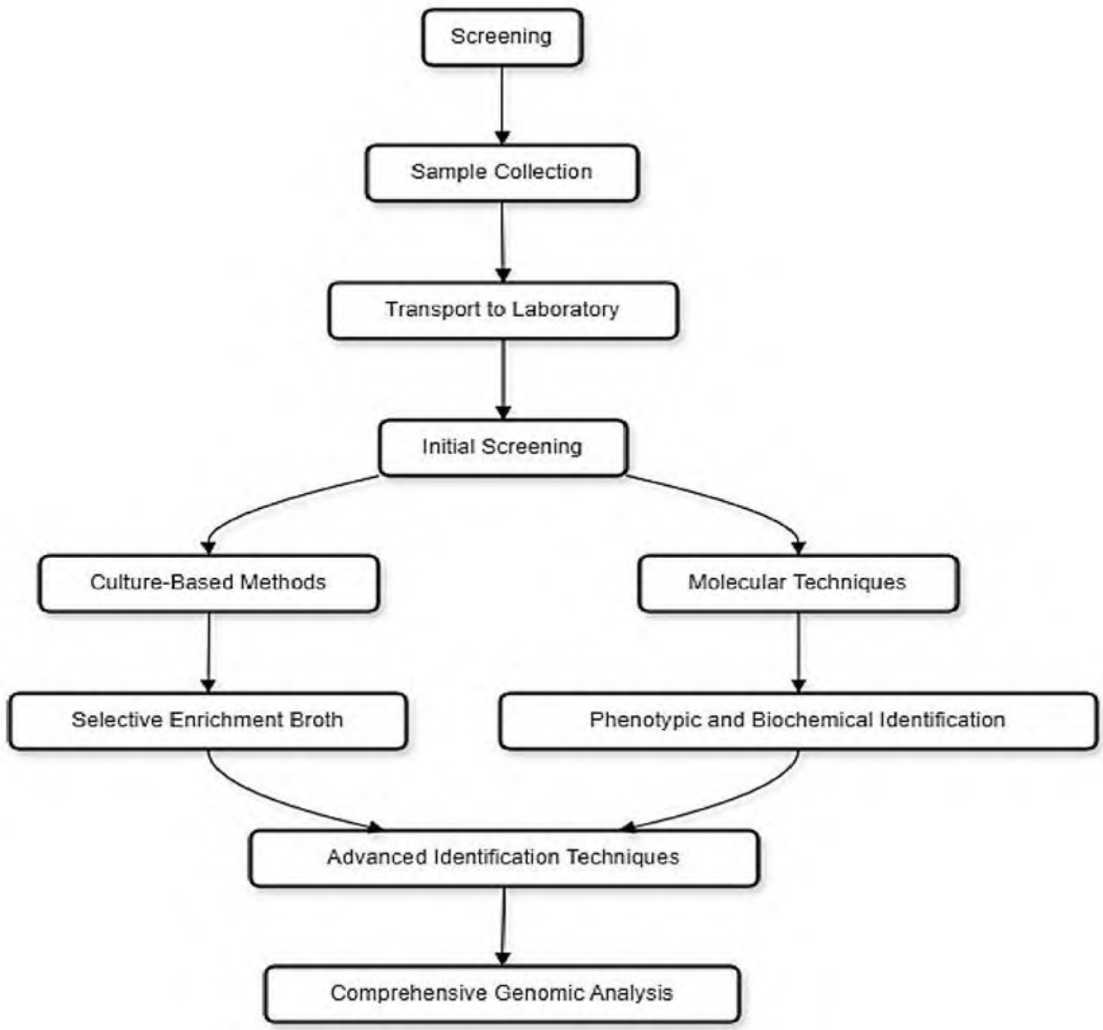

Figure 1. Diagnostic pathways for identifying *Candida auris* in healthcare settings.

The Impact of *Candida auris* infections: morbidity, mortality (CFR), DALY

C. auris is an emerging multidrug-resistant fungal pathogen that poses a significant global health threat, particularly in critical care settings. Infections caused by *C. auris* have high morbidity and mortality rates, with studies reporting mortality rates ranging from 30% to 72%. For instance, in Russia, the overall all-cause mortality rate for *C. auris* bloodstream infections is 55.3%, with a 30-day mortality rate of 39.5%. In Colombia, a study found a 38.1% crude mortality rate for *C. auris* candidemia compared to 51.1% for non-*auris Candida* species. These infections significantly contribute to the global burden of disease, measured in Disability-Adjusted Life Years (DALYs), and lead to prolonged hospital stays and increased healthcare costs. A systematic review and meta-analysis highlighted a crude mortality rate of 39% for *C. auris* infections, with bloodstream infections having a mortality rate of 45%. The persistent and widespread nature of *C. auris* necessitates urgent and effective prevention and control measures to mitigate its impact on global health.

The economic burden due to *Candida auris*

C. auris is a multidrug-resistant fungal pathogen that imposes a significant economic burden on global healthcare systems due to its severe infections, resistance to multiple antifungal treatments, and persistence in healthcare environments. Outbreaks necessitate extensive infection control measures, such as patient isolation, environmental decontamination, and staff education, costing over £1 million in a single London outbreak, with ongoing monthly expenses of £58,000. In the United States, these costs are compounded by extended hospital stays and ICU admissions. The pathogen's resistance increases treatment costs, while its persistence requires continuous and costly environmental cleaning and enhanced surveillance efforts. Addressing the economic burden of *C. auris* demands improved diagnostics, effective infection control, and advanced treatment strategies.

Mechanisms of antifungal resistance in *Candida auris*

The fungus *C. auris* is a growing threat in hospitals because it can quickly become resistant to many antifungal drugs. This resistance comes from two main sources: the natural defenses of the fungus itself and the adaptations it develops over time. Intrinsic resistance in *C. auris* is rooted in its unique cell wall composition, which limits the penetration of antifungal agents, and the presence of efflux pumps such as ATP-binding cassette (ABC) transporters and major facilitator superfamily (MFS) proteins. These pumps actively expel antifungal drugs from within the fungal cell, reducing their intracellular concentration and effectiveness.

Acquired resistance mechanisms further complicate treatment efficacy and can emerge through various pathways. Genetic mutations in key genes like ERG11, which encodes lanosterol 14-alpha-demethylase, alter the structure or expression of drug targets, thereby reducing the binding affinity of antifungal agents. *C. auris* can also upregulate efflux pumps in response to drug exposure, increasing the expulsion of drugs and contributing to resistance. Additionally, the formation of biofilms—a protective matrix of extracellular polymeric substances—enhances resistance by shielding fungal cells from antifungal drugs and the host immune system. Furthermore, *C. auris* exhibits metabolic flexibility, allowing it to activate alternative pathways or detoxification mechanisms in response to drug stress. Epigenetic changes, such as alterations in chromatin structure and gene expression patterns, can also influence resistance development. Horizontal gene transfer, where resistance genes are acquired from other microorganisms, further diversifies its resistance profile. Of particular concern is the emergence of multidrug-resistant (MDR) strains of *C. auris*, which severely limits treatment options and underscores the urgent need for effective infection control measures and novel antifungal therapies.

Factors contributing to resistance development in *Candida auris* and its consequences

The development of resistance in *C. auris* is driven by several interconnected factors. Inappropriate antifungal use in healthcare is a major contributor, as antifungals are often prescribed empirically before identifying the specific pathogen, leading to the use of broad-spectrum agents. This practice encourages the survival and proliferation of resistant *C. auris* strains, compromising treatment efficacy and complicating patient care. Environmental contamination plays a significant role as well, with *C. auris* persisting and spreading in healthcare environments despite routine cleaning protocols, making it difficult to eradicate the pathogen. Poor infection control practices exacerbate the issue; inadequate measures, such as improper handwashing or ineffective disinfection, contribute to the persistence and transmission of resistant strains among patients.

The agricultural use of antifungal agents further complicates the situation by leading to environmental contamination with these chemicals, creating selective pressure on fungal populations, including *C. auris*, and promoting resistance development. Host-related factors are also significant, as immunocompromised individuals and those in long-term care settings are particularly vulnerable to infections. Prolonged or repeated exposure to antifungal treatments in these populations can select resistant strains, making treatment more complex and increasing transmission risk. Genetic adaptation in *C. auris* occurs through mutations in drug target genes or horizontal gene transfer, allowing the pathogen to evade antifungal treatments. Finally, global spread and transmission dynamics facilitate the dissemination of resistant strains across regions. International travel and healthcare-associated transmission contribute to the cross-regional spread, complicating control efforts and exacerbating the global challenge of resistant *C. auris* infections.

Resistance to *C. auris* can have extensive short- and long-term consequences. Patient impact includes prolonged illness, higher mortality rates, and extended hospital stays due to ineffective treatments. The healthcare system burden involves increased costs from longer hospitalisations, specialised care, and outbreak management. Transmission risks are elevated by *C. auris*'s persistence in the environment, complicating infection control.

AMR in surgical settings

C. auris highlights the broader problem of antimicrobial resistance (AMR) in surgical settings, where extensive use of antibiotics and antifungals can lead to the development of resistant pathogens. Surgical patients are especially vulnerable to infections due to invasive procedures and frequent use of prophylactic antimicrobials. The rise of *C. auris* emphasises the need for strict infection control, careful use of antimicrobials, and strong surveillance systems. Tackling AMR requires improving antimicrobial stewardship, enhancing diagnostic tools to quickly identify resistant infections, and ongoing research for new treatments.

Resistance profiles of *C. auris* against antifungal agents have revealed significant challenges in treatment across global regions between 2006 and 2017. Fluconazole (FLZ) resistance was prevalent, with MIC values frequently exceeding 64 µg/ml in multiple countries including Canada, Colombia, Germany, India, Israel, Kuwait, Oman, South Africa, South Korea, Spain, the UK, USA, and Venezuela. Amphotericin B (AMB) resistance also posed a substantial issue, with MIC values equal to or greater than 2 µg/ml observed in these same regions. Voriconazole (VRZ), itraconazole (ITZ), posaconazole (PSZ), and isavuconazole (ISA) exhibited varied resistance levels among isolates, ranging from susceptibility to higher MIC values. Echinocandins such as micafungin (MCF), caspofungin (CFG), and anidulafungin (ANF) generally showed lower MIC values but resistance was still reported in specific cases. Flucytosine (FCN) resistance was noted particularly in isolates from India and South Korea.

Potential solutions and recommendations

Enhanced surveillance for *Candida auris* infections in healthcare settings

Enhanced surveillance is crucial for early detection and control of *C. auris* infections. This involves regular screening of high-risk patients, such as those in intensive care units (ICUs) and long-term care facilities, to identify colonization and implement timely infection control measures. For example, routine swabbing of patients admitted from facilities with known outbreaks and employing advanced diagnostic tools like PCR for rapid identification can help in early containment.

Adherence to infection prevention and control measures to prevent transmission

Strict adherence to infection prevention and control measures is essential to prevent the spread of *C. auris*. This includes isolating colonized or infected patients, using personal protective equipment (PPE), and implementing contact precautions. Regular cleaning and disinfection of patient environments with sporicidal agents are also critical. Education and training of healthcare staff on proper hygiene practices and infection control protocols are necessary to ensure compliance.

Specific recommended practices

1. **Hand hygiene**
   Rigorous hand hygiene practices are fundamental in controlling the spread of *C. auris*. This includes the use of alcohol-based hand rubs and handwashing with soap and water. Effective hand hygiene is critical in preventing healthcare-associated infections.
2. **Use of personal protective equipment (PPE)**
   Appropriate use of PPE, including gloves and gowns, is necessary when caring for patients with *C. auris* infections. PPE plays a vital role in protecting healthcare workers and preventing the transmission of this pathogen in healthcare settings.
3. **Environmental disinfection protocols**
   Regular and thorough cleaning of patient environments with effective disinfectants is crucial. Advanced disinfection methods, such as the use of hydrogen peroxide vapor and ultraviolet light, have proven effective in eliminating *C. auris* from surfaces, which is essential for controlling its spread in healthcare settings.

Development of new diagnostics and therapeutics

The development of new diagnostic tools and therapeutic options is vital for effective management of *C. auris* infections. Rapid and accurate diagnostic methods, such as molecular-based DNA amplification assays, can identify *C. auris* directly from patient samples, reducing the time to diagnosis. Research into novel antifungal agents and treatment combinations is necessary to overcome the high levels of drug resistance observed in *C. auris.*

Role of antimicrobial stewardship programs in healthcare settings

Antimicrobial stewardship programs play a crucial role in managing *C. auris* by optimizing the use of antifungal medications to minimize the development of resistance. These programs should promote the judicious use of antifungals, monitor antifungal prescribing patterns, and ensure adherence to treatment guidelines. Regular training and education of healthcare providers on the importance of antimicrobial stewardship are essential components of these programs.

Strategies for optimizing antibiotic use to minimize the emergence of resistant pathogens like *Candida auris*

Strategies to optimize antibiotic use include implementing guidelines for appropriate antifungal use, conducting regular audits of antifungal prescriptions, and providing feedback to prescribers. Ensuring timely de-escalation of antifungal therapy based on culture results and susceptibility patterns can also help in reducing unnecessary antifungal exposure. Additionally, integrating antimicrobial stewardship with infection control practices can enhance the overall effectiveness of efforts to combat resistant pathogens like *C. auris*.

One Health approach

The One Health approach is critical for managing *C. auris*, a multidrug-resistant fungal pathogen that poses significant global health risks due to its rapid spread, environmental persistence, and resistance to multiple antifungal treatments. This approach emphasizes the interconnectedness of human, animal, and environmental health, requiring collaborative efforts across sectors. *C. auris* has been found in healthcare settings and natural environments, such as marine habitats, highlighting its broad ecological presence and potential for cross-sectoral transmission. Effective management necessitates enhanced surveillance, accurate diagnostics, stringent infection control measures, and environmental decontamination strategies. Collaborative efforts among public health officials, veterinarians, environmental scientists, and policymakers are essential to monitor and control *C. auris*, study its genetic diversity and resistance mechanisms, and develop targeted interventions to reduce its impact and improve patient outcomes.

Conclusion

C. auris has emerged as a formidable pathogen in healthcare settings worldwide, posing unique challenges due to its multidrug-resistant nature and the difficulty of accurate identification. Its rapid spread and potential for causing outbreaks, particularly in hospital environments, make effective management strategies crucial for public health. The pathogen's ability to resist common antifungal agents, combined with its tenacity in colonizing patients and healthcare surfaces, underscores the need for enhanced diagnostic tools, infection control measures, and a comprehensive understanding of its epidemiology and resistance mechanisms.

Advanced diagnostic techniques, such as MALDI-TOF mass spectrometry and Whole Genome Sequencing (WGS), have revolutionized the way *C. auris* is identified and studied. These technologies offer more reliable identification methods than conventional approaches, which often fail to differentiate between *C. auris* and related species. The integration of molecular and genomic techniques allows for rapid detection and better management of outbreaks, improving patient outcomes and mitigating the risk of transmission.

Equally important are the strategies aimed at preventing *C. auris* infections. Infection control measures, such as strict hand hygiene practices, regular environmental cleaning, and patient screening protocols, play a vital role in limiting its spread. Early identification of asymptomatic carriers and swift isolation of infected individuals are essential in preventing further transmission within healthcare facilities. In addition, the development of new antifungal therapies that can overcome the inherent and acquired resistance of *C. auris* is a pressing need.

Overall, the fight against *C. auris* requires a multifaceted approach involving robust surveillance, early diagnosis, rigorous infection control measures, and continued research into the pathogen's resistance mechanisms. As this fungal pathogen continues to evolve, healthcare systems must adapt and employ cutting-edge technologies and best practices to safeguard patients and reduce the threat posed by this emerging superbug. Without these efforts, *C. auris* will remain a persistent and dangerous challenge in modern healthcare.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 21

Lessons from global health advocacy: strengthening collective action and strategies to combat antimicrobial resistance

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Introduction

Antimicrobial Resistance (AMR) is an urgent global health threat that compromises the usefulness of antimicrobials and threatens human, animal, and environmental health. AMR reduces the effectiveness of antimicrobials, leading to prolonged illness, higher mortality rates, and increased healthcare costs. The World Health Organization (WHO) has described AMR as one of the top ten global public health threats facing humanity. Effective advocacy campaigns are crucial for raising awareness, driving policy change, and promoting interventions to address this escalating issue.

Global health advocacy has historically played a pivotal role in improving health outcomes and expanding healthcare access. Advocacy efforts have often involved influencing policy, mobilizing resources, and raising awareness about critical health issues. The evolution of global health advocacy—ranging from responses to pandemics to broader campaigns for universal health coverage, and climate action—demonstrates its importance in shaping public health. Various actors including governments, international organizations, civil society, and grassroots movements, employing strategies from activism to high-level policy engagement drive advocacy. Lessons from past advocacy efforts can guide future AMR advocacy, emphasizing the need for inclusive, multi-sectoral approaches that draw on the voices and needs of underrepresented communities and those most at risk of AMR.

This chapter explores the importance of advocacy in combating AMR and how it has gained momentum and evolved through the years. It reviews current players and activities and highlights how historical campaigns have influenced its policies and outcomes. By drawing parallels with other large-scale global health campaigns, we aim to identify strategies that can enhance AMR advocacy and action, leveraging innovative strategies to improve global health outcomes.

Comparative insights for AMR advocacy: origins of global health advocacy

Understanding AMR advocacy benefits from examining successful strategies from other global health campaigns that have tackled diverse challenges.

The origins of global health advocacy can be traced back to the 19th century, spurred by cholera pandemics that necessitated international collaboration. Early efforts focused on communicable diseases, with the recognition of health as a human right emerging in the early 20th century.

Global health advocacy has a rich history of driving significant improvements. By examining successful advocacy efforts for other health issues such as smallpox, HIV/AIDS, climate change, and COVID-19, we can identify strategies and lessons applicable to AMR advocacy.

Smallpox eradication: a case study in global health success

One of the most significant achievements in global health advocacy is the eradication of smallpox. WHO launched the Intensified Smallpox Eradication Programme in 1967, building on earlier efforts. At the start of the program, an estimated 10 to 15 million people contracted smallpox annually, with approximately 2 million deaths each year. Over the course of the campaign, more than 200 million vaccinations were administered globally. The last naturally occurring case of smallpox was reported in 1977, and the disease was declared eradicated in 1980. This success demonstrated the power of coordinated international action and set a precedent for AMR health initiatives.

Global coordination. The smallpox eradication campaign showcased the power of a coordinated international response. The establishment of a global network for surveillance and vaccination was crucial to its success. However, the challenge posed by AMR is far greater in scope. Unlike smallpox, which is caused by a single virus, AMR affects a wide array of microorganisms, including bacteria, viruses, fungi, and parasites. This means that AMR has the potential to impact every aspect of healthcare, agriculture, and the environment. Given the complexity and scale, the need for extensive global collaboration, innovation, and sustained effort is even more critical. Addressing AMR will require a level of coordination that surpasses even that of the smallpox eradication campaign. This underscores the need for a unified global strategy to address AMR, involving international cooperation with globally accepted goals/milestones and clear roles for various stakeholders, including governments, health organizations, and the private sector.

Surveillance and monitoring. Surveillance was a cornerstone of the smallpox eradication strategy. Developing robust monitoring systems enabled timely identification and containment of outbreaks. For AMR, similar surveillance systems are essential for tracking resistance patterns and guiding interventions and everyday prescribing decisions between clinicians and patients. Comprehensive monitoring networks that collect AMR data on humans, animals, food systems, and the environment and are supported by advanced data analytics and real-time reporting are crucial for responding to emerging resistance threats.

Community engagement. The success of the smallpox campaign was also due to its emphasis on community engagement. Local health workers and communities were integral to vaccination efforts, highlighting the importance of involving grassroots actors in health initiatives. AMR advocacy should similarly engage communities and ensure the availability of dedicated funding for community-based efforts, leveraging local knowledge and networks to promote responsible antimicrobial use and support infection prevention measures.

HIV/AIDS movement: advocacy and activism in health crises

The HIV/AIDS epidemic of the 1980s marked a pivotal moment in global health advocacy. During this crisis, grassroots organizations like AIDS Coalition to Unleash Power (ACT UP) were some of the first organizations to play a vital role in demanding access to treatments, combating stigma, and influencing policy changes (Reilly, 2016). The declaration of December 1st, as World AIDS Day in 1988, the establishment of UNAIDS in 1996 and the creation of the Global Fund to Fight AIDS, Tuberculosis, and Malaria in 2002, demonstrated the power of global cooperation and resource mobilization. The lessons learned from the HIV/AIDS movement offer valuable insights for AMR advocacy.

Grassroots mobilization. The HIV/AIDS epidemic demonstrated the critical role of grassroots and patient activism. Organizations like ACT UP, which is considered a political group, used activism to demand action from governments and pharmaceutical companies, leading to increased funding, accelerated research, and improved access to treatment. AMR advocacy can benefit from similar grassroots mobilization, empowering affected communities and patients to drive change.

Policy advocacy. The establishment of UNAIDS and the Global Fund to Fight AIDS, Tuberculosis and Malaria highlighted the impact of policy advocacy and international funding. For AMR, securing funding and policy support at both national and international levels is crucial. Advocacy should focus on integrating AMR into broader health policies and ensuring sustained financial support for research, diagnostics, vaccination, and treatment.

Addressing stigma. The HIV/AIDS movement made strides in addressing stigma, in particular by highlighting patients' stories, giving people the tools and information to prevent infections, involving artists and musicians in community advocacy efforts, creating community systems for care and dignity in death, and giving a voice to affected communities to foster supportive environments. Combating stigma related to AMR—such as misconceptions about antimicrobial use and resistance—is vital for effective advocacy. Public awareness campaigns and policies should aim to reduce stigma, promote accurate information, and encourage supportive behaviors.

Climate change advocacy: integrating health and environmental policies

Climate change has emerged as a pressing global health issue, threatening health through increased risks of the spread of infectious diseases, malnutrition, and displacement. Advocacy efforts have sought to integrate health considerations into climate policies and promote sustainable practices. International agreements, such as the Paris Agreement and heightened recognition of the connection between climate and health in general, have been central to these campaigns and creating systems of global and national accountability.

The lessons from climate change advocacy are pertinent to AMR advocacy.

Integrated approach. Climate change campaigns demonstrated the need to integrate health considerations into environmental policies, while also recognizing that systemic and industrial change must occur along with individual action Similarly, AMR advocacy should incorporate AMR concerns into broader health and environmental strategies through a One Health approach and create systems of accountability and mitigation for antimicrobial pollution in the environment.

International agreements. The Paris Agreement represents a significant global commitment to climate change, showing the effectiveness of international agreements in advancing health and sustainability goals. AMR advocacy can benefit from aligning with international frameworks on pandemics to enhance support and mobilize resources.

Public awareness. Efforts to raise awareness about climate change and its health impacts have successfully engaged the public and policymakers in creating a critical mass of people who have come together to demand change. AMR campaigns should similarly focus on increasing public "buy-in" and understanding of AMR, using diverse communication channels and strategies to reach various audiences and empowering them to take action.

COVID-19 pandemic: lessons from a global health emergency

The COVID-19 pandemic highlighted the critical need for resilient health systems, effective pandemic response mechanisms, and equitable access to and distribution of treatments and vaccines. It emphasized the importance of international collaboration and the urgent need to combat health misinformation. The swift development and distribution of vaccines illustrated the power of coordinated global efforts in addressing significant health threats, which are valuable characteristics for AMR campaigns.

Rapid innovation. The rapid development and distribution of COVID-19 vaccines demonstrated the importance of innovation and speed in health crises. For AMR, promoting research and development of new antibiotics, diagnostics, and alternative treatments is crucial. Ensuring rapid innovation and accessibility to all regions will be key in the fight against AMR.

Global collaboration and basic health system strengthening. The pandemic highlighted the importance of international collaboration and data sharing. Strengthening global AMR surveillance and data sharing efforts, as well as recognizing the importance of basic public health systems, will enhance our ability to tackle resistance challenges effectively.

Managing misinformation. The spread of misinformation about COVID-19 vaccines and treatments underscored the need for accurate communication. Addressing misinformation about AMR and antimicrobials' use is essential for successful advocacy. Public health campaigns should focus on providing reliable information, countering false claims, and engaging trusted sources to build confidence in AMR measures.

The following table (**Table 1**) summarizes key lessons and impacts of campaigns related to Smallpox, Climate Change, COVID-19 and HIV/AIDS along with lessons applicable to AMR advocacy.

Table 1. Historical lessons for AMR.

Health campaign	Key lessons	Relevance to AMR advocacy
Smallpox eradication	● Global coordination ● Effective surveillance ● Community engagement	● Need for a unified international strategy ● Robust monitoring systems ● Community involvement
HIV/AIDS movement	● Grassroots mobilization ● Policy advocacy ● Addressing stigma	● Importance of community and patients' involvement ● Securing funding ● Combating stigma related to AMR
Climate change	● Integrated approach ● International agreements ● Public awareness	● Incorporating AMR into broader policies ● Leveraging global agreements ● Increasing public engagement
COVID-19 pandemic	● Rapid innovation ● Global collaboration ● Managing misinformation	● Promoting research and innovation ● Strengthening health systems, access to basic healthcare provisions and data sharing ● Addressing misinformation about AMR

Progress and evolution of AMR advocacy

AMR advocacy has evolved significantly over time, reflecting a growing recognition of AMR as a critical global health threat. Initially, it was a concern mostly within the medical community with limited public and political awareness. Early advocacy efforts focused on scientific research and the clinical aspects of AMR to demonstrate the impact of overuse and misuse of antimicrobials in human medicine and only marginally in agriculture.

By the early 2000s, the WHO's Global Strategy for Containment of Antimicrobial Resistance, set the stage for a more structured approach. This was followed by the launch of the WHO Global Action Plan on Antimicrobial Resistance and the adoption of the One Health approach, integrating human, animal, and environmental health into AMR strategies. This period also marked the initiation of global campaigns like World Antibiotic Awareness Week (now called World AMR Awareness Week or WAAW), enhancing public and professional engagement. Recently, the COVID-19 pandemic has further highlighted the importance of addressing AMR, particularly with the increased use of antibiotics during the pandemic, leading to renewed advocacy and integration of AMR into broader health security agendas. The reasons driving this evolution include:

- Increased global mobility, which has facilitated the spread of resistant pathogens and emphasizes the need for a cross-border focus rather than regional responses.
- The One Health approach, which promotes a holistic view of health that recognizes the impact of antimicrobial use and pollution on animals and the environment.
- Heightened public awareness driven by media and advocacy campaigns, which is increasingly highlighting patients' stories.
- Technological advancements in diagnostics and research of new treatments.
- Stronger regulatory and policy measures to regulate the supply and distribution of antimicrobials and reduce the circulation of substandard and counterfeit medicines, especially in low-resource settings.
- The COVID-19 pandemic's impact, which has amplified the urgency of AMR issues.

These trends illustrate the growing recognition of AMR as a multifaceted and urgent challenge, necessitating a comprehensive and collaborative response.

Challenges in raising AMR awareness

Raising awareness about AMR is challenging because resistance is not limited to one pathogen as to other global health issues. Additionally, AMR is spread across diverse systems and regions. Access to basic public health provisions, such as clean water sanitation, and vaccinations, compounds the issue, making low-resource settings especially vulnerable. As addressing AMR requires a multifaceted approach, key challenges include:

1. *Awareness and understanding.* A major challenge in AMR advocacy is the lack of awareness and understanding. Many individuals and policymakers are not fully informed about AMR's complexity and consequences, often perceiving it as a distant threat rather than an immediate issue. The complexity of AMR, including its scientific intricacies and the multifaceted drivers behind it, makes it harder to communicate and raise awareness. Other health priorities, like HIV/AIDS, have benefited from more straightforward messaging and visible symptoms that enable clearer advocacy.
2. *Behavior change.* Changing behaviors related to antimicrobial use is crucial. AMR advocacy requires significant behavior change across multiple sectors, including healthcare, agriculture, and the general public. Encouraging the prudent use of antimicrobials, for example, involves changing long-established practices in both clinical settings and daily life. Inappropriate use, such as over-prescription and self-medication, significantly contributes to resistance. Education, antimicrobial stewardship programs, and improved communication between healthcare providers and patients are essential for behavior change. In contrast, other health campaigns, such as the HPV vaccination campaign, often have more direct calls to action, like receiving a vaccine, and a clearly defined target audience that can be easier to reach with health promotion messaging.

3. *Policy and legislation.* Securing sustained policy and financial support for AMR is challenging due to competing health priorities. Unlike diseases with immediate and visible impacts, AMR's effects are often long-term and diffuse, leading to difficulties in prioritizing it over more urgent health crises. Moreover, economic incentives for developing new antibiotics are weaker compared to more profitable pharmaceuticals, making it harder to drive innovation in this area.
4. *Global coordination*. AMR requires a highly coordinated global response, integrating efforts across human health, animal health, and environmental sectors (One Health approach). This is more complex than other health priorities, where actions can be more localized or sector-specific. For example, the global response to HIV/AIDS, while also requiring coordination, has been more straightforward in terms of targeting interventions like treatment and prevention programs.
5. *Stigma and public perception.* Unlike HIV/AIDS, which has a history of stigma that advocacy campaigns have actively worked to combat, AMR faces the challenge of being an "invisible" threat. The lack of immediate personal impact for many individuals leads to complacency and difficulty in generating the same level of public concern and action that more immediately impactful diseases might inspire.

In summary, while AMR advocacy shares some challenges with other health campaigns, its unique complexities—particularly in terms of behavior change, economic incentives, and global coordination—present significant barriers that require tailored strategies to overcome.

Thematic analysis of AMR advocacy efforts

To analyze AMR advocacy efforts, we can categorize them into several key themes. Each theme represents a different aspect of AMR advocacy, with examples illustrating the type of work being done in each area.

1. **Global coordination and policy development.** This theme involves efforts to create and implement global strategies, frameworks, and policies to address AMR. It focuses on international collaboration and policy-making to drive coordinated actions against AMR.
2. **Public and patient awareness and education.** This theme encompasses efforts aimed at increasing public understanding of AMR, promoting responsible antibiotic use, and reducing the stigma associated with resistance.
3. **Surveillance and data collection.** Efforts under this theme focus on monitoring and tracking antibiotic resistance patterns, as well as gathering data to inform policies and interventions.
4. **Research and development.** This theme involves initiatives aimed at advancing research on AMR, developing new antibiotics, and fostering innovation in diagnostics and treatment.
5. **Healthcare professional training and stewardship.** This theme covers efforts to educate healthcare providers about AMR, promote best practices in antibiotic stewardship, and enhance prescribing practices.

6. **One Health approach.** This theme integrates human, animal, and environmental health to address AMR, recognizing the interconnected nature of these domains.

A diverse range of organizations and initiatives have emerged to address this challenge, each contributing to advocacy, research, policy influence, and public awareness. These organizations work across different levels—from global partnerships to grassroots youth movements—to address the spread of AMR and ensure sustainable access to effective antimicrobials.

The following tables (**Table 2A** and **Table 2B**) provide an overview of key organizations currently involved in AMR advocacy, highlighting their specific roles and contributions. We recognize that there are many other local, national and international organizations spread across several countries, which are currently investing considerable efforts to raise AMR awareness. Providing an exhaustive list of organizations involved in AMR advocacy is out of the scope of this chapter.

Table 2A. Key organizations involved in AMR advocacy.

Theme	Organization	Description of advocacy work	Link(s)
Global coordination and policy development	World Health Organization (WHO)	WHO routinely develops advocacy briefs for member states to explain the health impact of AMR urging action across different sectors. It has recently launched a Taskforce of AMR Survivors and a working group on Youth Engagement for AMR.	https://www.who.int/health-topics/antimicrobial-resistance
	Global Leaders Group on Antimicrobial Resistance	The group advises and advocates for action documenting global efforts to curb AMR.	https://www.amrleaders.org/resources
	World Organisation for Animal Health (WOAH)	WHOA advocates for coordinated global action on AMR with a One Health approach, integrating human, animal, plant, and environmental health routinely publishing advocacy briefs for members states.	https://www.woah.org/en/who-we-are/advocacy/
	REACT	ReAct advocates for global engagement on AMR by collaborating with a broad range of organizations, individuals and stakeholders to advocate on a wide range of topics related to AMR.	https://www.react-group.org/about-us/
	Wellcome	Wellcome advocates for global action on AMR on a wide range of topics publishing advocacy and policy briefs targeting a wide range of stakeholders	https://wellcome.org/what-we-do/infectious-disease/antimicrobial-resistance

Table 2B. Key organizations involved in AMR advocacy.

Theme	Organization	Description of advocacy work	Link(s)
Public and patient awareness	Students Against Superbugs Africa (SAS)	SAS Africa raises AMR awareness across universities and students based in Africa through campaigns, workshops, and advocacy events.	https://www.studentsagainstsuper-bugs.org/
	The AMR Narra-tive	The AMR Narrative is a patient-led charity highlighting AMR patient sto-ries and providing access to key AMR information to support and enable patient-led advocacy efforts.	https://amrnarrative.org/#
	African Youth AMR Alliance Task Force	The Alliance was launched to better represent the role of youth in curbing AMR across the African continent.	https://www.reactgroup.org/af-rica/youth-enagement/
Research, development and access	GARDP	GARDP encourages the development and access to treatments for resistant infections. The organization collabo-rates with public, private, and non-profit stakeholders addressing gaps in access to effective treatments.	https://gardp.org/about-gardp/
	AMR Industry Alli-ance	A coalition driving progress in AMR across research, appropriate use, ac-cess, and environmental impact working with industry to drive policy change.	https://www.amrindustryalli-ance.org/
Healthcare professional training and stewardship	National Institute of Antimicrobial Resistance Re-search and Educa-tion (NIAMRRE)	NIAMRRE collaborates with academia and industry to advocate for AMR across human, animal, and environ-mental health, focusing on funding and education.	https://www.niamrre.org/home/our-work/advocacy-3/
	GASPH	GASPH provides support and educa-tion to the scientific and medical community working on AMR to sup-port proper antibiotic use.	https://global-asp-hub.com/
One Health approach	One Health Trust	OHT works in multiple sectors in par-ticular promoting the collection of AMR surveillance data and their use to promote responsible antimicrobial use in the human and agriculture sec-tors. It advocates for vaccination and infection prevention control to re-duce demand for antibiotics.	https://onehealthtrust.org/research-areas/antimicrobial-resistance/

Practical recommendations for building AMR advocacy capacity

Drawing on historical advocacy successes and challenges and on the insights from the various organizations and initiatives provides valuable insights for strengthening AMR advocacy. Effective AMR campaigns must integrate lessons from past health movements, embrace a One Health approach, and address barriers related to awareness, behavior change, policy, and economic incentives. By employing a multifaceted strategy that includes public education, healthcare professional and patients' engagement, community involvement, policy advocacy, and industry collaboration, we can enhance our efforts to combat AMR and safeguard global health.

The following recommendations can enhance the effectiveness of AMR advocacy and action globally:

1. **Strengthen multisectoral collaboration.**
   - *Broaden partnerships.* Encourage more robust collaboration between healthcare, agriculture, veterinary medicine, and environmental sectors. This collaboration should extend beyond established organizations to include grassroots movements, youth networks, and private-sector stakeholders
   - *Integrate AMR into other health agendas.* Leverage existing health initiatives, such as those focused on universal health coverage (UHC), climate change, and pandemic preparedness, to integrate AMR considerations and ensure a more holistic approach to health and well-being.
2. **Enhance public awareness, patient groups representations and education.**
   - *Targeted campaigns.* Develop and disseminate tailored public education campaigns that address specific population groups, such as healthcare workers, farmers, patients, and young people, to increase awareness and understanding of AMR.
   - *Utilize digital platforms.* Harness the power of social media, online educational resources, and webinars to reach a broader audience, especially in regions with limited access to traditional media. Engage influencers and thought leaders to amplify messages about AMR and responsible antibiotic use.
3. **Support youth engagement and leadership.**
   - *Empower youth networks.* Provide funding, resources, and platforms for youth organizations, like Students Against Superbugs Africa (SASA) and the World Healthcare Students' Alliance (WHSA), to take a leading role in AMR advocacy. Encourage youth-driven initiatives and leadership in policy dialogues.
   - *Incorporate AMR education in curricula.* Advocate for the inclusion of AMR education in the curricula of schools, universities, and professional training programs for healthcare providers, veterinarians, and agricultural professionals.
4. **Increase policy influence and integration.**
   - *Advocate for comprehensive policies.* Push for the integration of AMR action plans into broader national and international health, agricultural, and environmental policies. Ensure that AMR remains a priority in global health discussions and is reflected in funding allocations and policy frameworks.
   - *Leverage international agreements.* Utilize international agreements, such as the Paris Agreement on climate change or global pandemic response frameworks, to align AMR action with broader global health and sustainability goals.
5. **Promote research and innovation.**
   - *Support the development of new therapies.* Encourage investment in research and development (R&D) for new antibiotics, vaccines, and diagnostic tools through initiatives like CARB-X and the AMR Action Fund. Ensure that new treatments are accessible and affordable, particularly in low- and middle-income countries.
   - *Foster collaborative research.* Promote collaborative research efforts between public, private, and academic institutions to address gaps in AMR knowledge and innovation. Encourage open data sharing and the dissemination of research findings to accelerate progress.
6. **Improve global coordination and accountability.**
   - *Establish clear metrics.* Develop clear metrics and indicators to measure the progress of AMR action plans and advocacy efforts. This should include tracking the implementation of national action plans, the impact of public awareness campaigns, and the success of new treatment development.

- *Enhance accountability.* Advocate for stronger accountability mechanisms at the global level, ensuring that countries and organizations adhere to their commitments to combat AMR. This could involve regular reporting, peer reviews, and international assessments of progress.

7. **Combat stigma and misinformation.**
   - *Address stigma in communication.* Design public health campaigns that specifically address the stigma associated with AMR and antibiotic use, promoting more open discussions about the issue. Ensure that communication strategies are culturally sensitive and inclusive.
   - *Counteract misinformation.* Develop strategies to effectively combat misinformation about antibiotics and AMR, particularly on social media and other online platforms. Collaborate with trusted community leaders, healthcare professionals, and educators to disseminate accurate information.
8. **Ensure equitable access to interventions.**
   - *Focus on low-resource settings.* Prioritize the needs of low- and middle-income countries in AMR advocacy and action plans. Ensure that these regions have access to the necessary resources, including new antibiotics, vaccines, and diagnostic tools.
   - *Promote access to quality care.* Advocate for policies that ensure equitable access to quality healthcare, including the availability of essential antimicrobials and the implementation of effective infection prevention and control measures.

By implementing these recommendations, stakeholders can enhance the global response to AMR, making it more effective, inclusive, and sustainable. These actions will help safeguard the effectiveness of antimicrobials for future generations and protect global health security.

Conclusion

AMR poses a significant threat to global health, requiring comprehensive advocacy efforts to raise awareness, influence policy, and drive behavior change. By drawing on lessons from successful health campaigns, such as those addressing smallpox, HIV/AIDS, climate change, and COVID-19, AMR advocacy can employ effective strategies to combat resistance.

Key components of successful AMR advocacy include public education campaigns, healthcare professional engagement, community involvement, policy advocacy, and industry collaboration. A One Health approach that recognizes the interconnectedness of human, animal, and environmental health is essential for developing holistic and sustainable solutions.

Addressing the challenges and barriers in AMR advocacy requires targeted communication, innovative incentives for research and development, and the integration of AMR considerations into broader health and policy agendas. By fostering collaboration across sectors and engaging diverse stakeholders, AMR advocacy can drive meaningful change and protect the efficacy of life-saving antimicrobials for future generations.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 22

Health inequalities and antimicrobial resistance in Africa

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Introduction

Antimicrobial resistance (AMR) represents one of the most pressing challenges in global public health today. AMR occurs when microorganisms such as bacteria, viruses, fungi, and parasites evolve to resist the effects of medications that were previously effective against them, rendering standard treatments ineffective. The primary drivers of AMR include the overuse and misuse of antibiotics in both human medicine and agriculture, inadequate infection prevention and control practices, and insufficient investment in the development of new antimicrobial agents. The consequences of AMR are dire: infections become harder and sometimes impossible to treat, leading to prolonged illness, increased mortality, and escalating healthcare costs. Globally, AMR threatens to reverse decades of medical progress, turning once-treatable diseases into deadly threats. Without urgent action, it is estimated that by 2050, AMR could cause 10 million deaths annually, surpassing cancer as a leading cause of death worldwide. In 2019, the World Health Organization (WHO) estimated that bacterial AMR directly caused 1.27 million deaths globally and contributed to an additional 4.95 million deaths, prompting the WHO to declare AMR a top global public health threat. The WHO African region experienced the largest burden, with an estimated 1.05 million deaths associated with bacterial AMR and 250,000 deaths directly attributable to it, representing the highest fatal and non-fatal AMR impact of any WHO region.

This significant burden of AMR in Africa is deeply intertwined with the continent's persistent health inequalities. Africa, home to over a billion people, is a continent marked by significant health disparities, particularly in access to healthcare services, which are shaped by an interplay of socioeconomic, geographical, and political factors. In many African countries, healthcare infrastructure is underdeveloped, particularly in rural and remote areas, where access to even basic medical care can be limited or non-existent. This urban-rural divide

means that people living in cities are more likely to receive timely and effective healthcare than those in rural communities. Socioeconomic factors further exacerbate health inequalities, with poverty being a significant barrier to accessing quality healthcare. In many parts of Africa, out-of-pocket payments for medical services are common, making healthcare unaffordable for a large portion of the population. Additionally, educational disparities contribute to poor health outcomes, as individuals with limited education may lack the knowledge necessary to make informed health decisions, including the appropriate use of antibiotics. Geographical differences also play a key role in health disparities. In some regions, conflict and political instability have disrupted healthcare systems, leading to shortages of essential medicines and trained healthcare workers. Furthermore, cultural beliefs and practices can influence healthcare utilisation, sometimes leading to delays in seeking treatment or reliance on traditional medicine instead of modern healthcare services.
This chapter aims to explore the intersection of health inequalities and AMR in Africa, shedding light on how these inequalities contribute to the spread and impact of AMR on the continent.

The intersection of health inequalities and antimicrobial resistance

The interplay between health inequalities and AMR is complex (**Table 1**), with disparities in access to healthcare, education, and infrastructure playing a significant role in the spread and impact of AMR in Africa. These inequalities create environments where the misuse of antibiotics is prevalent, leading to the acceleration of resistance. Understanding how these factors contribute to AMR is key to developing effective strategies to combat this growing threat.

Access to healthcare

Limited access to quality healthcare is a significant driver of AMR in Africa, particularly in rural and low-income areas. In these regions, people often face substantial barriers, such as long distances to clinics, high out-of-pocket costs, and a shortage of healthcare professionals. For instance, nearly 50% of the population in Sub-Saharan Africa lacks access to essential health services, with up to 70% of rural residents needing to travel more than 5 kilometres to reach the nearest health facility. Additionally, in some African countries, out-of-pocket expenses account for over 40% of total health expenditure, forcing many individuals to avoid formal healthcare and resort to self-medication or seek care from informal providers who may lack the proper training to prescribe antibiotics appropriately. The shortage of healthcare professionals is also critical, with some countries having as few as 1 physician per 10,000 people, leading to rushed consultations and potentially inappropriate antibiotic prescriptions. The absence of adequate diagnostic tools in many healthcare facilities further exacerbates this issue, with less than 10% of health facilities in some countries having access to reliable diagnostics for infectious diseases. As a result, providers may prescribe antibiotics as a precautionary measure, even when unnecessary. This practice is especially prevalent in areas with high poverty rates and low health literacy, where patients often view antibiotics as a cure-all and may pressure healthcare providers into prescribing them. Consequently, the overuse and misuse of antibiotics in these settings accelerate the development of resistance, making future infections harder to treat and posing a severe threat to public health.

Table 1. Multidimensional intersection of health inequalities and antimicrobial resistance (AMR).

Health inequality dimension	Key determinants	Mechanisms of influence on AMR	Resulting AMR dynamics	Implications for public health policy
Healthcare access inequities	Urban-rural divide, workforce distribution, accessibility of essential medicines.	Inequitable healthcare access leads to increased self-medication, delayed treatment, and inappropriate antibiotic use.	Localised outbreaks of resistant infections in underserved areas; amplification of resistance due to inconsistent treatment.	Focus on decentralised health care models; improve access to essential medicines in rural/remote areas to reduce self-medication.
Socioeconomic disparities	Poverty and income inequality, out-of-pocket expenditures, social safety nets.	Economic barriers limit access to quality healthcare, resulting in higher reliance on informal providers and unregulated antibiotic sales.	Higher AMR prevalence in low-income populations; delayed treatment and overuse of broad-spectrum antibiotics in the absence of affordable care.	Implement subsidy programs for essential antibiotics; strengthen regulation of antibiotic sales in low-income regions.
Educational and health literacy gaps	General education levels, public awareness of AMR, cultural perceptions of medicine.	Low health literacy fosters misconceptions about antibiotics, leading to misuse such as treating viral infections with antibiotics.	Increased selection pressure for resistant strains due to improper antibiotic usage and incomplete treatment courses.	Enhance AMR-focused health education campaigns; integrate AMR education into school curricula and community outreach programs.
Healthcare infrastructure disparities	Diagnostic capabilities, hospital infection control, availability of trained personnel.	Poor infrastructure results in empirical, broad-spectrum antibiotic prescriptions and inadequate infection control, fostering resistance.	Spread of resistant strains within healthcare facilities, particularly in low-resource settings; failure to contain outbreaks.	Invest in diagnostic technologies and infection control measures; prioritise training for healthcare workers in AMR management.
Geographical and environmental inequalities	Geographic barriers, environmental sanitation, impact of conflict on healthcare systems.	Geographical isolation and poor sanitation exacerbate infection rates and complicate timely access to effective antibiotics.	Hotspots of AMR in environmentally compromised or conflict-affected regions; transnational spread of resistance due to migration.	Develop regional AMR surveillance systems; strengthen cross-border collaboration to monitor and address AMR in conflict zones.

(cont.)

Table 1. Multidimensional intersection of health inequalities and antimicrobial resistance (AMR) *(cont.)*

Health inequality dimension	Key determinants	Mechanisms of influence on AMR	Resulting AMR dynamics	Implications for public health policy
Cultural and behavioural practices	Traditional medicine use, trust in informal healthcare providers, antibiotic sharing practices.	Cultural reliance on traditional medicine and informal providers delays appropriate treatment, increasing AMR risk.	Cultural practices contribute to uneven antibiotic use, resulting in varied resistance patterns and challenges in public health messaging.	Culturally sensitive AMR interventions; engage traditional healers in AMR education efforts and develop trust-based community health programs.
Population vulnerability	Age (children, elderly), immunocompromised (HIV, chronic diseases), gender inequalities.	Vulnerable populations face higher exposure to resistant infections due to weakened immunity and poor healthcare access.	Disproportionate AMR impact on vulnerable groups, leading to higher morbidity and mortality rates; potential for resistant strains to spread in communities.	Targeted interventions for vulnerable groups; integrate AMR considerations into broader health equity and social protection policies.

Education and awareness

Low health literacy is another critical factor driving AMR in Africa. In many communities, there is a widespread lack of understanding about the appropriate use of antibiotics and the dangers of resistance. For example, it is not uncommon for people to wrongly believe antibiotics are effective against viral infections like the common cold, leading to their misuse. This lack of awareness leads to the misuse of antibiotics, with people often using them to treat viral infections, such as the common cold, for which they are ineffective. In communities with low health literacy, individuals may also fail to complete prescribed antibiotic courses. This practice allows surviving bacteria to develop resistance to the antibiotic, increasing the likelihood of treatment failure in the future. Additionally, the use of leftover antibiotics or sharing them with others is common in areas where access to healthcare is limited, with studies showing that in some African countries, over 50% of individuals reported using antibiotics without a prescription, further contributing to the spread of resistant strains. For instance, in some African countries, efforts to improve health literacy have highlighted the challenges of combating AMR in low-resource settings. Despite campaigns to raise awareness about the dangers of antibiotic misuse, many people in rural areas continue to use antibiotics inappropriately, often due to misconceptions about their effectiveness. For example, it is common for individuals to purchase antibiotics over the counter without a prescription, with surveys showing that in certain regions, up to 62% of antibiotics are purchased without any medical guidance, using them to treat symptoms that may not require antibiotic therapy. These practices are fuelled by a lack of understanding about how antibiotics work and the importance of using them correctly.

Healthcare infrastructure

The state of healthcare infrastructure in Africa significantly contributes to the misuse of antibiotics and the spread of AMR. Many healthcare facilities, particularly in rural and underserved areas, lack the resources necessary to provide quality care. For example, in Sub-Saharan Africa, it is estimated that 60% of health facilities do not have access to basic diagnostic equipment, and in some countries, less than 20% of facilities have reliable electricity, which is crucial for maintaining the cold chain for medications and operating diagnostic tools. This includes a shortage of trained healthcare professionals, inadequate diagnostic tools, and limited access to essential medicines. In poorly resourced healthcare settings, antibiotics are often used as a substitute for proper medical care. Healthcare providers may prescribe antibiotics broadly due to the absence of diagnostic capabilities or as a means of compensating for the lack of other treatment options. The over-reliance on antibiotics in these settings not only drives the development of resistance but also leads to the spread of resistant infections within healthcare facilities, where infection control measures are often inadequate. In many parts of African countries, healthcare facilities are underfunded and understaffed, leading to a reliance on antibiotics as a first-line treatment for a wide range of conditions. The lack of diagnostic tools means that healthcare providers often have to make treatment decisions based on clinical judgment alone, resulting in the over-prescription of antibiotics. Moreover, the scarcity of resources for infection control in hospitals and clinics contributes to the spread of resistant bacteria, particularly among vulnerable patients.

Vulnerable populations

The impact of AMR is not evenly distributed across populations; certain groups, including children, women, the elderly, and immunocompromised individuals, are particularly vulnerable. These populations face unique challenges related to health inequalities that make them more susceptible to the consequences of AMR.

Children, especially infants, are highly vulnerable to the effects of AMR, particularly in settings with high health inequalities. In many African countries, childhood infections, such as pneumonia and diarrhoea, are the leading causes of morbidity and mortality. The rise of resistant bacteria makes it increasingly difficult to treat these infections effectively, leading to higher rates of complications and death. In areas with poor healthcare infrastructure and limited access to essential medicines, the treatment of paediatric infections becomes even more challenging. The lack of access to timely and appropriate care means that children are often treated with broad-spectrum antibiotics, which may contribute to the development of resistance. Additionally, malnutrition and other underlying health conditions common in low-income settings weaken children's immune systems, making them more susceptible to severe infections and less likely to respond to treatment.

In the DRC, the burden of childhood infections is exacerbated by the rise of AMR. In conflict-affected regions, healthcare services are often disrupted, leading to a lack of access to essential medicines and trained healthcare professionals. As a result, children suffering from common infections are frequently treated with inappropriate or substandard antibiotics, contributing to the development of resistance. The high prevalence of malnutrition further complicates treatment, making it difficult for children to recover from infections that have become resistant to standard therapies.

Furthermore, women, particularly during pregnancy and childbirth, face significant challenges related to AMR. In many parts of Africa, access to maternal healthcare is limited, and complications during pregnancy or childbirth can lead to infections that require antibiotic treatment. The rise of AMR increases the risk of treatment failure, which can have devastating consequences for both mothers and newborns. In settings with high health inequalities, women are often at a greater risk of contracting infections due to poor sanitation, inadequate access to clean water, and limited access to healthcare services. These factors, combined with the overuse and misuse of antibiotics, contribute to the spread of resistant infections among pregnant women and new mothers. Sierra Leone, which has one of the highest maternal mortality rates in the world, illustrates the challenges women face in the context of AMR. The country's healthcare system is severely under-resourced, and many women lack access to skilled birth attendants and emergency obstetric care. Infections during pregnancy and childbirth are common, and the overuse of antibiotics, often inappropriately

prescribed, has led to the emergence of resistant bacteria. This situation poses a significant risk to maternal and neonatal health, as infections that were once treatable become increasingly difficult to manage.
The elderly and immunocompromised individuals are also particularly at risk from the effects of AMR, as they are more likely to develop severe infections and less likely to respond to treatment. In Africa, where healthcare services for these populations are often limited, the rise of AMR presents a significant threat to their health and well-being. The lack of specialised care for the elderly and those with compromised immune systems, such as individuals living with HIV, means that these populations are often treated with broad-spectrum antibiotics without proper diagnosis. This practice not only increases the risk of resistance but also exposes these vulnerable groups to potentially harmful side effects from inappropriate antibiotic use. In South Africa, where a significant portion of the population is living with HIV, the impact of AMR is particularly acute. Many individuals with HIV are immunocompromised, making them more susceptible to infections. The rise of resistant bacteria complicates the treatment of these infections, leading to higher mortality rates and prolonged hospital stays. The situation is further exacerbated by the lack of access to advanced diagnostics and the overuse of antibiotics in treating opportunistic infections in HIV-positive patients.
Lastly, people living with disabilities, refugees, and other marginalised groups face compounded challenges in accessing healthcare, making them particularly vulnerable to the impacts of AMR. These populations often reside in environments with limited healthcare infrastructure, poor sanitation, and inadequate access to essential medicines, which increases their risk of infection and reliance on antibiotics. For people with disabilities, barriers such as physical inaccessibility to healthcare facilities, stigmatisation, and a lack of tailored healthcare services further exacerbate their vulnerability to infections and their complications. Refugees, often living in overcrowded camps with inadequate sanitation and healthcare services, are at heightened risk of contracting infections that may be treated inappropriately with antibiotics, contributing to the spread of AMR. These conditions are worsened by the high mobility of refugee populations, which can facilitate the spread of resistant bacteria across regions. For both groups, the lack of consistent and appropriate healthcare means that infections are frequently mismanaged, leading to higher rates of resistance and poorer health outcomes. For example, in regions like the Sahel, where conflict and displacement are prevalent, refugees and internally displaced persons (IDPs) are often treated in under-resourced facilities where antibiotics are overprescribed due to a lack of diagnostic tools and trained healthcare workers. This not only endangers the health of these vulnerable populations but also accelerates the development and spread of resistant strains of bacteria, posing a significant threat to public health at large.

The vicious cycle of inequality and AMR in Africa

The relationship between health inequalities and AMR in Africa is a deeply entrenched and self-perpetuating cycle. Health inequalities, driven by socioeconomic disparities, limited access to healthcare, and inadequate infrastructure, contribute significantly to the spread of AMR (**Table 2**). Conversely, the rise of AMR further exacerbates these inequalities, creating a vicious cycle that traps vulnerable populations in a state of persistent poverty and poor health.

Table 2. Bidirectional impact of AMR and health inequalities.

Dimension	AMR exacerbating health inequalities	Health inequalities fuelling AMR
Access to healthcare	*Increased costs:* AMR leads to more expensive, less effective treatments, pushing quality healthcare out of reach for poorer populations.	*Limited access:* Inequitable healthcare access leads to improper use of antibiotics, fostering AMR due to self-medication and incomplete treatments.
Economic impact	*Decreased productivity:* AMR-driven illnesses reduce workforce productivity, further deepening poverty and inequality.	*Economic barriers:* Poverty limits the ability to afford proper medications, leading to the use of counterfeit or substandard antibiotics, contributing to resistance.
Healthcare infrastructure	*Strain on resources:* AMR increases the burden on already fragile healthcare systems, reducing their ability to serve disadvantaged populations effectively.	*Inadequate infrastructure:* Poor healthcare infrastructure in low-income areas fosters the spread of infections, increasing antibiotic use and resistance.
Morbidity and mortality	*Higher mortality rates:* AMR increases death rates among vulnerable populations, where the burden of disease is already high, exacerbating inequalities.	*High disease burden:* Vulnerable populations experience higher infection rates, leading to more frequent antibiotic use and accelerated AMR development.
Social determinants of health	*Widening health gaps:* AMR disproportionately affects the poor, widening existing health disparities and entrenching poverty.	*Poor living conditions:* Poor sanitation and crowded living conditions in marginalised communities contribute to the spread of resistant infections.
Education and awareness	*Lack of awareness:* The complexity of AMR and its management is not well understood, particularly in impoverished areas, leading to misuse of antibiotics.	*Low health literacy:* Low levels of education and awareness among disadvantaged groups result in the misuse and overuse of antibiotics, accelerating AMR.
Global and local policy response	*Insufficient policy response:* AMR diverts resources from other critical health needs, disproportionately affecting the poorest.	*Policy neglect:* Lack of targeted policies for disadvantaged populations leads to unchecked antibiotic use and the rise of AMR.
Healthcare quality	*Deterioration in care:* As AMR renders standard treatments ineffective, healthcare quality declines, particularly in low-resource settings.	*Low-quality care:* Inadequate training and resources in underfunded healthcare facilities lead to poor prescription practices, driving AMR.

Health inequalities fuelling AMR

In many African countries, the combination of poverty, lack of education, and limited healthcare access creates an environment where AMR can thrive. Poor living conditions, such as overcrowding, inadequate sanitation, and the absence of clean water, lead to higher rates of infections, which are often treated with antibiotics. However, due to the widespread availability of antibiotics without prescriptions and a lack of public awareness about the proper use of these drugs, misuse is rampant. Antibiotics are frequently used to treat viral infections or taken in incorrect dosages, fostering the development of resistant strains of bacteria. Additionally, in resource-poor settings, where healthcare services are scarce, individuals may turn to informal healthcare providers who lack proper training in antibiotic stewardship. This often results in inappropriate prescriptions, further driving the emergence of AMR. The lack of diagnostic tools in many healthcare facilities also means that antibiotics are often prescribed empirically, rather than based on confirmed diagnoses, increasing the likelihood of resistance.

AMR exacerbating health inequalities

As AMR becomes more prevalent, it deepens existing health inequalities in Africa. Resistant infections are harder to treat, requiring second- or third-line antibiotics, which are often more expensive and less accessible in low-income settings. For individuals in poverty, the cost of these treatments can be prohibitive, leading to untreated infections, prolonged illness, and, in many cases, death. The economic impact of AMR is particularly devastating for already disadvantaged communities. When individuals are unable to work due to prolonged illness, they lose income, which can push families further into poverty. This loss of productivity not only affects the individuals and their families but also has broader economic implications, as entire communities may suffer from reduced workforce participation and increased healthcare costs. Moreover, the burden of caring for those with drug-resistant infections often falls on women, who are typically the primary caregivers in African households. This responsibility can limit their ability to engage in income-generating activities, further perpetuating the cycle of poverty and reinforcing gender inequalities. The social and economic costs of AMR thus ripple through communities, widening the gap between the wealthy and the poor.

The entrenchment of poverty and poor health

The interplay between AMR and health inequalities creates a feedback loop that is difficult to break. As the prevalence of AMR increases, so too does the burden of disease, particularly among those who are already disadvantaged. This, in turn, leads to higher healthcare costs, which many cannot afford, resulting in inadequate or delayed treatment. The consequences are severe: increased morbidity and mortality, further economic hardship, and a deepening of poverty. For example, when individuals in low-income communities' contract drug-resistant tuberculosis (TB), they face a significantly higher risk of death compared to those with drug-sensitive TB. The treatment for drug-resistant TB is more complex, costly, and prolonged, often requiring hospitalisation and multiple drugs that may not be readily available in low-resource settings. The financial strain of such treatment, combined with the loss of income during illness, can devastate families, leading to a cycle of poverty that is difficult to escape.

Call to action

The intersection of health inequalities and AMR in Africa is a crisis that demands immediate and sustained action. The time to act is now before the cycle of poverty, poor health, and rising resistance becomes even more entrenched. To break this cycle, a coordinated effort is required from governments, international organisations, healthcare providers, researchers, communities, and individuals. Here are key actions that must be taken:

1. African governments and international partners must invest in strengthening healthcare infrastructure, particularly in rural and underserved areas. This includes building and equipping healthcare facilities, training healthcare workers, and improving access to diagnostic tools. Strengthening healthcare systems will ensure that infections are properly diagnosed and treated, reducing the misuse of antibiotics and the spread of AMR.
2. Investment in research and development is pertinent to combating AMR. African governments, international donors, and private sector partners must allocate resources to support research on new antibiotics, vaccines, and alternative therapies. Additionally, research should focus on understanding the unique

patterns of AMR across different regions in Africa, as well as developing context-specific solutions. Building local research capacity is essential to ensure that Africa can contribute to the global fight against AMR and develop strategies tailored to its specific challenges.

3. It is key to develop and enforce antibiotic stewardship programs that promote the appropriate use of antibiotics. This includes regulating the sale of antibiotics, ensuring that they are only available with a prescription, and educating all healthcare providers, including patent medicine vendors, on the importance of prescribing antibiotics only when necessary. In many parts of Africa, patent medicine vendors serve as primary healthcare providers, especially in rural and underserved areas. Therefore, it is essential to engage and train these vendors in proper antibiotic use and resistance awareness. Additionally, these programs should include public awareness campaigns to educate communities about the dangers of antibiotic misuse, ensuring that everyone, from healthcare providers to patients, understands the critical role they play in combating AMR.
4. Effective action against AMR requires robust surveillance systems to monitor resistance patterns and track the spread of resistant infections. Governments, in partnership with international organisations, should invest in data collection and analysis to better understand the scope of the problem and to inform policy decisions. This data is essential for tailoring interventions to the specific needs of different regions and populations.
5. Tackling the root causes of health inequalities is essential to reducing the impact of AMR. Governments and NGOs should work together to improve living conditions, provide access to clean water and sanitation, and promote education, particularly in marginalised communities. Economic empowerment programs, especially those targeting women, can help lift families out of poverty, making them less vulnerable to the impacts of AMR.
6. AMR is a global problem that requires global solutions. The international community must prioritise funding and resources to combat AMR, particularly in regions like Africa where the burden is greatest. Governments, international organisations, and private sector partners must collaborate to ensure that the necessary resources are available to support sustainable healthcare improvements and AMR interventions. This includes financing for research initiatives that seek to understand and address AMR in the African context.
7. Community engagement is critical in the fight against AMR. Grassroots education campaigns can empower individuals to make informed decisions about their health, understand the importance of completing antibiotic courses, and avoid self-medication. Community leaders, healthcare workers, and educators must be mobilised to spread awareness and drive behaviour change at the local level.
8. Policymakers must be urged to take AMR seriously as a public health threat. Advocacy efforts should focus on the creation, evaluation and implementation of national action plans to combat AMR, incorporating strategies for reducing health inequalities. Civil society organisations, healthcare professionals, and the general public should hold governments accountable for their commitments to address this crisis.

Conclusion

The growing threat of AMR, compounded by the persistent health inequalities in Africa, requires immediate and coordinated action. Governments, non-governmental organisations, and international organisations must prioritise the fight against AMR as an integral part of their public health agendas. Without equitable access to quality healthcare, education, and resources, efforts to control AMR will remain inadequate and unsustainable. There is an urgent need for governments to invest in expanding access to healthcare, particularly in rural and underserved areas, and to strengthen healthcare infrastructure across the continent. NGOs and international organisations should support these efforts by providing funding, and technical expertise, and facilitating knowledge exchange. Moreover, public awareness campaigns and health literacy programs must be scaled up to educate communities about the dangers of antibiotic misuse and the importance of responsible antibiotic use.

Looking ahead, several areas require further research and policy development to effectively address the dual challenges of health inequalities and AMR in Africa. First, there is a need for more comprehensive and context-specific data on AMR prevalence and antibiotic use patterns across the continent. This data is important for informing targeted interventions and for monitoring the effectiveness of strategies aimed at reducing AMR. Research should also focus on developing new antibiotics and alternative therapies that are affordable and accessible to African populations. This includes exploring traditional medicine and its potential role in combating AMR, as well as investing in innovations in healthcare delivery, such as telemedicine and mobile health technologies, that can bridge the gap between urban and rural healthcare services. Policy development should prioritise the integration of AMR surveillance into existing health systems, with a focus on improving diagnostic capabilities and regulating antibiotic use in both human medicine and agriculture. Furthermore, strengthening international cooperation is essential for sharing best practices, securing funding, and addressing the global dimensions of AMR.

In conclusion, addressing health inequalities is a critical component of any effective strategy to combat AMR in Africa.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 23

The burden of antimicrobial resistance in Uzbekistan

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Introduction

Antimicrobial resistance (AMR) has emerged as a global public health challenge, threatening the efficacy of modern medicine and increasing the burden of infectious diseases, with the most severe impacts in low-income settings. A 2022 study on the global burden of AMR identified it as a major cause of mortality worldwide. In 2019, AMR contributed to nearly 5 million deaths, with 1.3 million directly attributed to bacterial AMR across 88 pathogen-drug combinations in 204 countries and territories. Among these deaths, one in five occurred in children under the age of five, highlighting the significant impact on vulnerable populations. When compared to all underlying causes of death in the 2019 Global Burden of Disease report, AMR would have ranked as the third leading cause of death, following ischemic heart disease and stroke. If not addressed optimally, then by 2035, AMR is projected to cost the global economy US$ 412 billion annually due to additional healthcare costs and $ 443 billion annually due to lost workforce productivity.

AMR plays a pivotal role in achieving several of the 17 Sustainable Development Goals (SDGs) that all 191 UN Member States have committed to attain by 2030. AMR is explicitly referenced under SDG 3, and progress towards many other SDGs is contingent upon effectively addressing AMR. First, access to effective antibiotics is essential for preventing maternal, neonatal, and childhood deaths, as well as managing epidemics of communicable diseases such as HIV, gonorrhea, and tuberculosis (SDG 3). Second, antibiotics are critical not only for human health but also for food and animal production, and by extension, livelihoods (SDGs 1, 2, and 8). Third, inadequately managed healthcare waste and wastewater can contaminate groundwater, drinking water, and soil with antibiotics or resistant bacteria, posing risks to water quality and environmental health (SDGs 6 and 12). Finally, partnerships are essential to combat AMR. The Tripartite—comprising the World Health Organization (WHO), the Food and Agriculture Organization (FAO), and the World Organisation for Animal Health —has adopted the One Health approach to address AMR (SDG 17). Since 2020, AMR has been included as an indicator within SDG 3, which focuses on "Good Health and Well-Being". As a member of the UN family, Uzbekistan is committed to achieving SDG 2030. This review will focus on the burden of AMR in Uzbekistan, exploring key statistics, pathogen profiles, and the challenges the country faces in addressing this issue.

Uzbekistan, a doubly landlocked country located in Central Asia, is the region's most populous nation. With a population of 36.8 million, it accounts for nearly half of Central Asia's total population. The country's demographic profile is notably youthful, with 30.1% of its citizens under the age of 14.

Uzbekistan bore the highest AMR burden in the region. In 2019, there were 4,500 deaths directly attributable to AMR, while 17,200 deaths were associated with AMR. Among 204 countries, Uzbekistan ranks 73rd in age-standardized mortality rates associated with AMR, and within the Global Burden of Disease (GBD) region of Central Asia, it has the third-highest rate across nine countries. Alarmingly, the number of AMR-related deaths in Uzbekistan surpasses those caused by other major health concerns such as digestive diseases, respiratory infections, tuberculosis, diabetes, kidney diseases, maternal and neonatal disorders, and unintentional injuries.

According to GBD data from the Institute for Health Metrics and Evaluation (IHME) in 2019, the following five primary pathogens contribute significantly to AMR-related deaths in Uzbekistan: *Escherichia coli* (3,000 deaths), *Klebsiella pneumoniae* (2,600 deaths), *Staphylococcus aureus* (2,500 deaths), *Streptococcus pneumoniae* (2,200 deaths), *Mycobacterium tuberculosis* (1,500 deaths) These pathogens are responsible for a range of infections, including peritoneal and intra-abdominal infections, tuberculosis, bloodstream infections, lower respiratory tract infections, and urinary tract infections. These infections significantly contribute to the growing AMR crisis, complicating treatment and increasing mortality rates.

AMR and tuberculosis in Uzbekistan

Uzbekistan is listed by the World Health Organization (WHO) as a high-burden country for multidrug-resistant tuberculosis (MDR-TB). According to the latest WHO Global TB Report, the 2022 TB incidence in Uzbekistan was 29,000 cases (83 per 100,000 population). Of these, 16% of new cases and 31% of previously treated cases were estimated to have MDR-TB. The case detection rate for TB remains low at 49%, with the MDR-TB/rifampicin-resistant (RR-TB) detection rate even lower at 29%. Despite improvements in TB treatment and monitoring, with success rates increasing from 84% in 2012 to 89% in 2021, MDR-TB remains a significant challenge. The Government of Uzbekistan has also initiated extensive health reforms, including the adoption of the National Strategy Concept for Healthcare Improvement (2019–2025). This strategy specifically targets tuberculosis (TB) reduction, setting ambitious goals outlined in the TB National Strategic Plan (NSP). The NSP aims to reduce the TB incidence rate by 50% and TB-related deaths by 75% by 2025, relative to 2015 figures. The National Tuberculosis Program (NTP), being implemented in cooperation with USAID, aligns with the targets of the United Nations High-Level Meeting (UNHLM), focusing on enhancing TB diagnosis and treatment, particularly for drug-resistant TB (DR-TB), childhood TB, and preventive treatment.

Health systems challenges

Misuse of antibiotics, lack of awareness among healthcare workers, and inadequate training in the rational use of antibiotics have contributed significantly to the escalating AMR crisis in Uzbekistan. During the first two years of the pandemic, numerous reports indicated widespread inappropriate use of antibiotics in several countries, including Uzbekistan, Russia, and Kazakhstan, where antibiotics were used to treat non-severe COVID-19 cases. This practice persisted despite WHO guidelines that do not recommend antibiotic therapy or prophylaxis for patients with mild to moderate COVID-19. Over-the-counter sales of antibiotics and other prescription drugs without a prescription are widespread in Uzbekistan.

In healthcare settings, frequent and inappropriate use of antibiotics fosters the development of resistant bacterial strains. This, coupled with insufficient infection control measures, inadequate preventive strategies, and under-resourced microbiological laboratories, further exacerbates the AMR crisis. Moreover, Uzbekistan's regulatory framework for combating AMR is not fully harmonized with international standards, limiting its effectiveness.

In order to reduce the inappropriate use of AB and to prevent the rapid increase of AMR rates, a clear understanding of key antimicrobial prescribers and the consumers' motivation to use ABs is needed, with an emphasis on their knowledge, attitudes, and behaviors regarding AB use and AMR. Surveys on public perception and antimicrobial consumption have been conducted to inform policymakers. A recent survey among citizens from 14 WHO member states across the Balkans, Caucasus, and Central Asia (Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Georgia, Kazakhstan, Kyrgyzstan, Montenegro, North Macedonia, the Republic of Moldova, Tajikistan, Türkiye, and Uzbekistan) revealed that only one-third of respondents reported obtaining their most recent course of antibiotics with a medical prescription. These findings were part of a broader survey on knowledge, attitudes, and behaviors related to AMR, conducted for the first time in the eastern WHO European Region, including the Caucasus and Central Asia.

In 2020, a survey was conducted among key antimicrobial prescribers and consumers—general practitioners, patients, and farmers—in Uzbekistan to identify gaps in knowledge, attitudes, and practices related to antimicrobial resistance. The survey revealed that irrational antibiotic use is widespread in the country. Many patients, unaware of the risks associated with antibiotic misuse, use antibiotics for viral infections such as influenza, where antibiotics are ineffective. The survey indicated that 30-43% of respondents expect physicians to prescribe antibiotics for viral symptoms, and 40% anticipate receiving antibiotics regardless of the diagnosis. Moreover, 37% of individuals purchase antibiotics without a prescription. While 50% believe antibiotics should be prescribed by a doctor, 62% still make independent decisions regarding their use. This widespread misuse is exacerbated by poor adherence to treatment regimens, with one-quarter of respondents discontinuing antibiotics as soon as their symptoms subside. The majority of patients believed that antibiotics could cure influenza and colds. Every third farmer thought that antibiotics were an antiviral and every fifth farmer a tool to increase productivity. Almost two-thirds of them used antibiotics to protect livestock/poultry/fish from disease. For all three groups, the strongest predictor for the right attitude was the knowledge level. All three groups had knowledge gaps in the form of misconception and problem underestimation which manifests itself as a wrong practice. Interventions are needed at the national, institutional and individual levels, in particular in the training of general practitioners and farmers.

The national response to AMR

The National Antimicrobial Resistance (AMR) Programme of the Republic of Uzbekistan is focused on human health and currently has only limited activities in the animal health sector. A draft interinstitutional national action plan does exist (the National AMR Control Programme 2022-2026) and reflects all elements of the WHO Global Action Plan on AMR. Although relevant stakeholders have been identified and the importance of cross-sectoral work is understood, multisectoral coordination and collaboration do not occur.

In collaboration with the U.S. Centers for Disease Control and Prevention (CDC), Uzbekistan founded the National Center for AMR in 2017. Moreover, since 2017, the Ministry of Health, in partnership with the World Health Organization's Country Office in Uzbekistan, has been actively working on the "Control of AMR" project.

The 2020 Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR) report reveals that Uzbekistan has seven laboratories testing for AMR pathogens. Nine pathogens tested for in the country, including four of the WHO priority pathogens (*Escherichia coli*, *Klebsiella pneumoniae*, *Salmonella* species, and *Streptococcus pneumoniae*), as well as *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Staphylococcus aureus*, *Enterococcus faecalis*, and *Enterococcus faecium*. There is a plan to submit data to GLASS in the future, along with the expansion of AMR surveillance across all provinces. Community surveillance protocols are being developed for clinically significant microorganisms.

While some progress has been made in AMR containment in the Republic of Uzbekistan, several systemic challenges remain unresolved. Specifically:

1. A comprehensive and effective program has yet to be developed across various sectors, such as healthcare, veterinary medicine, agriculture, education, and environmental protection, to coordinate efforts against antibacterial drug resistance
2. There is no national system in place to monitor the prevalence of antibacterial drug resistance, raise awareness about its detrimental consequences, or collect and control related data. Public awareness of the dangers of improper antibacterial drug use remains low.
3. The irrational and uncontrolled use of antibacterial drugs in the livestock sector persists, coupled with inadequate infection prevention measures.
4. Preventive healthcare, veterinary services, and plant protection are underutilized. Moreover, microbiological laboratories, as well as systems for training and professional development on antibacterial drug resistance, are not meeting current demands.
5. Regulatory measures to combat the spread of antibacterial drug resistance are insufficient, lacking alignment with international standards and regulations.

To effectively address AMR in Uzbekistan, the following critical steps must be taken:

1. Intersectoral coordination. Promote collaboration between the health, agriculture, veterinary, and education sectors through a "One Health" approach.
2. Strengthening surveillance systems. Develop and strengthen a national surveillance system for AMR, including robust data collection and reporting mechanisms.
3. Public awareness campaigns. Implement public education programs on the dangers of antibiotic misuse.
4. Improve training. Improve training programs for health care providers and veterinarians on antimicrobial stewardship and AMR.
5. Regulatory enforcement. Strengthen enforcement of prescription-only antibiotic sales and ensure compliance with international standards to control AMR.
6. Infection control. Improve infection prevention practices in healthcare and veterinary settings to reduce the need for antibiotics.
7. Antibiotic stewardship. Establish comprehensive antibiotic stewardship programs to guide the responsible use of antibiotics.

Conclusion

Uzbekistan faces considerable challenges in managing AMR, including widespread misuse of antibiotics, high MDR-TB rates, and a lack of robust AMR surveillance. However, through coordinated strategies, strengthened regulations, and public education, the country has the potential to reduce the burden of AMR and improve overall health outcomes. Continued support from international organizations and strong political will are essential for the successful implementation of these strategies.

Competing interests

The author has no financial and non-financial competing interests to declare.

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Chapter 24

Engaging the youth in mitigating antimicrobial resistance

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Introduction

For many generations, the youth have been at the frontline of solving many world challenges such as universal suffrage, the civil rights movement, multi-party democracy, and climate change among many others. This is driven by many different factors that are to be addressed in this chapter but among them is the fact that young people have a unique viewpoint, an innovative mindset, and a proactive spirit in making the world a better place for themselves and their future generations. One of the reasons is that they are not entrenched in existing systems, their behaviours are not construed in a particular way, and thus they do not harbour the fatigue of advocating for change. Not being construed into existing systems also expands their mindset and allows them to be innovative in the approaches they curate in addressing social challenges.

Given the existing evidence in the engagement of the youth in different social challenges, it makes a case that there is immense potential that can be tapped in terms of engaging the youth in solving some of the pressing challenges such as antimicrobial resistance (AMR). Results from global consultations held by the Quadripartite (Food and Agriculture Organization, United Nations Environmental Program, World Health Organization, and World Organization for Animal Health) aimed at developing a common approach to raising awareness on AMR showcased a consensus that children, students, and youth were a top priority audience for joint AMR awareness efforts. This led to several structural efforts such as the formation of the Quadripartite Working Group on Youth Engagement for AMR. This group guides the engagement of the Quadripartite with the youth to harness the population's global response to AMR. It is tasked with exploring innovative and untapped methods of engaging with the youth, mobilizing young people across the continent to advocate for various improvements across the different spheres of youth engagement, facilitating the development of youth-friendly AMR mitigation tools among other efforts. There have also been efforts by different civil society organizations to advocate for regional collaborations in youth engagement. An example is the launch of the African Youth AMR Alliance Task Force, a consortium of youth-led organizations working to mitigate the threat of AMR in the African continent.

The current landscape of youth engagement in AMR Initiatives

Over the last four years, there has been a significant growth in terms of the youth engaged in AMR interventions. This has led to the development of various structures such as the Quadripartite Working Group of Youth Engagement on AMR, and the African Youth AMR Alliance Task Force. Several international organizations such as the International Pharmaceutical Students Association, International Federation of Medical Students Association, International Veterinary Students Association, and International Association of Students in Agricultural and Related Sciences in collaboration with other youth-led organizations and other stakeholders have previously organized the Global AMR Youth Summit that happens during the World AMR Awareness Week since 2020. The summit is usually a virtual 3-day event featuring workshops, panel discussions, competitions, presentations, activities fair, and training among other activities.

The summit serves to empower and showcase the diverse roles that focus on the role youth can play in mitigating AMR. There are also myriads of efforts and interventions led by several funding agencies and civil society groups aimed at supporting youth interventions. Organizations such as the Foundation to Prevent Antibiotic Resistance (PAR Foundation), and the Trinity Challenge offer grants targeting youth-led initiatives in Antimicrobial Resistance.

In the African region, youth engagement in AMR is quite unique with many youth-led organizations focusing on AMR being established. A key contributor to this is the youth engagement efforts that have been spearheaded by Zihi Institute (formerly Students Against Superbugs Africa) and ReAct Africa in the continent for the last five years. These efforts have catalysed a proactive youth movement, and strengthened partnerships with different stakeholders working with the youth in the African continent. This engagement has also led to enhanced engagement of the youth in the policy landscape at the national and sub-national level in multiple countries with young people being involved in the formulation and development of National Action Plans.11

A lot of the efforts undertaken. The investment made has nurtured passionate leaders in the AMR space who have founded their organizations and initiated efforts in the AMR space. Key among them include: the AMR intervarsity Program, Working Against Virulent Epidemics (WAVE), Uganda Youth Consortium for Antimicrobial Stewards, Alliance Against Antimicrobial Resistance, Snowman Artland, Actions des Jeunes contre la Resistance aux Antimicrobiens, Solving Resistance, Consummate Health and Sanitation, Africa Public Health Students Network, Students One Health Innovation Club, and AMR Now.

Some of the key outcomes realized in the African continent include; a generally increased understanding and interest in AMR among tertiary-level students in the continent, improved leadership, and increased implementation of AMR mitigation projects. There has also been an increase in the number of tertiary-level students pursuing AMR-related careers after completion of their undergraduate courses as well as an increase in the number of young people engaging in AMR-related research.

Challenges experienced by youth working in the AMR space

There are a lot of challenges and barriers that hinder active youth engagement in the AMR landscape. One of the major challenges is poor integration into governments' AMR implementation strategies such as AMR National Action Plans. The youth are often underrepresented and at times not represented at all in AMR policy initiatives, governance, and technical structures. The youth are left out in many of the critical discussions and thus most of their innovative and unconventional strategies and ideas are not taken into account. Young people are also faced with diverse socio-cultural barriers due to existing cultural norms. These barriers

vary with different communities and are at times influenced by gender beliefs. For example, young women may have limited access to decision-making platforms.
In some accounts, youth-led interventions are perceived to be sub-standard and poorly organized due to stereotypes that they have limited experience and technical capacity. However, this is not usually the case since some youth-led interventions have emerged to be more impactful in terms of their reach and ability to influence behavior change. The negative perceptions make it difficult for youth-led organizations to forge sustainable collaborations and partnerships. Many funders also shy away from funding youth-led organizations due to limited confidence in their ability to deliver effective interventions. Youth-led organizations and proactive youth champions are thus disadvantaged in terms of access to financial and technical resources to implement AMR interventions. Additionally, like most of the general public, most young people are unaware of the magnitude of the threat that AMR poses. With this limited understanding, it becomes difficult for them to engage proactively.

The case of meaningful youth engagement

To effectively define the role of youth in tackling Antimicrobial Resistance, it is important to first understand the different ways through which the youth can be engaged. It is only right that as we explore tapping the potential of the youth and exploring the role that they can play in AMR mitigation, that we engage them meaningfully. Meaningful youth engagement has different definitions as per different institutions and contexts. In this context, after reviewing several definitions it can be described as "a participatory process where the ideas, expertise perspectives, and experiences of the youth are integrated throughout policy, programmatic and institutional decision-making structures to best inform outcomes. Meaningful youth engagement requires that the youth are involved at all stages and levels of program, campaign, and initiative development for programs that affect their lives which is inclusive of almost all AMR spheres. To engage the youth meaningfully, power has to be shared, engagement has to be respectful, and all inputs have to be appropriately valued.
According to the Women Deliver review of meaningful youth engagement, engagement, and participation of the youth in alleviating the social challenges (in this case AMR) has to be supported by access to accurate and youth-friendly information, integrated accountability mechanisms, and well-structured decision-making mechanisms. Some of the mechanisms that need to be taken into account to engage the youth in a meaningful approach include:

1. Diverse representation that extends beyond tokenism and that equitably incorporates youth from underrepresented populations.
2. Effective power-sharing is important so that young people are not only beneficiaries of interventions but are also partners and leaders.
3. Effective inclusion in the different stages including the development, implementation, monitoring and evaluation of programs, policies, and investment of resources.

In roles where the youth are to be engaged, participation in the early stages of programming ensures that planning and design are relevant to the needs and rights of young people. This participation allows for more effective and accountable programs. Youth participation can be broken down to five levels: informing, consulting, involving, collaborating, and empowering.
While engaging the youth, there are different ways to structure programs that align with different levels of their participation. Engaging the youth as beneficiaries infers that they have not been involved in designing

the program but are invited to participate after being informed of the program, its purposes, and the opportunities it offers for them. When young people are engaged as "collaborators", they are engaged as the target group for an intervention but they are also engaged as collaborators in co-designing the program and makes them assume ownership which encourage them to take advantage of the opportunities offered. The youth can also be engaged as stakeholders in the development of interventions. Engagement of the "youth" as leaders is quite different since they are engaged right from the time the intervention is designed.

Understanding diversity in youth engagement

When engaging the youth, it is important to recognize that they are not a homogenous group. Acknowledging the socioeconomic, cultural, religious, historical differences, and experiences ensures that interventions are contextualized for specific target audiences, and designed respectfully. Not doing so can lead to diminished trust from the perception that their values and beliefs are being imposed. Some of the ways to ensure that diversity is maintained include:

1. Clear mapping of the youth target group.
2. Embracing intersectionality

Recognizing that the youth are diverse enables one to benefit from a broad breadth of insights from young people of different backgrounds. One can categorize the youth as:

1. Those making the transition from education to work.
2. Those still in their formal education phase
3. Those still in the early phases of work or self-employment.

Each phase requires a different level of engagement and they all have their opportunities, perspectives, and challenges. This serves to guide when deciding strategies, policies, and programs to be employed

Driving gender equity in youth engagement

It is important to ensure gender-inclusivity and equity in terms of opportunities offered to the different genders throughout the project. It is also important to ensure gender equity when onboarding facilitators and role models while enhancing capacity building for appropriate knowledge, attitudes, and behavior in terms of promoting gender equality.

Promoting youth-led gender transformative interventions that explicitly address social norms, power hierarchies, attitudes, and values around gender framing and roles is paramount. This approach ensures that there is an integrated and multifaceted engagement Lastly, one should provide safe spaces for the youth to gather and share experiences and avail opportunities that strengthen interventions.

The importance of self-determination

As addressed in a section before, the youth are a diverse group from different backgrounds, with different expertise and interest. There are no predefined roles for the youth in AMR engagement and as such, prescribing roles for the youth without their adequate participation in the process should be discouraged. When engaging the youth, it is crucial they are offered a right to self-determination, and the autonomy to explore AMR interventions and initiatives aligned to their interests and the gaps they have identified in their communities. Scientifically, it has been expressed by the self-determination theory that outlines that human beings have three psychological needs; autonomy, competence, and relatedness which when adequately fulfilled trigger motivation.

Relatedness, in this case, involves the need to feel connected and belongingness with others working in the same AMR landscape. This can be promoted by creating platforms for cross-learning, where like-minded young people have the opportunity to collaborate and synergize efforts. Autonomy, in this case, refers to the freedom one has to implement or pursue the innovative idea of their choice in the AMR landscape. Competence in this case is the ability to be effective in the interventions that one decides to explore. It can be acquired through capacity-building programs and self-training. Motivation is key in driving sustainable youth engagement that has a catalytic ability to grow and expand even after initiation intervention ceases or a project lifecycle is completed.

Strengthening leadership among the youth

Leadership is key in ensuring sustainable interventions. It is important to channel the youth's passion, commitment, and energy and amalgamate these strengths into leadership. Youth leadership opportunities allow the youth to grow in a positive environment that promotes growth and avails opportunities which in turn increases opportunities among the youth allows them to become more active in community and extracurricular activities. It also informs effective program development and management. For example, a leadership capacity-building program implemented by Zihi Institute (formerly Students Against Superbugs Africa), and ReAct Africa empowered many tertiary-level students to initiate their AMR interventions.

It is also important to recognize leadership as an outcome of experiential learning. Experiential learning allows the involvement of lessons learned by offering a platform for one to look critically, determine what is useful or important to remember and utilize this information to perform another activity. It provides one with a platform of iteratively reacting to situations, and analyzing scenarios happening in practice. It involves being exposed to initiating difficult decisions and handling tough conversations. Currently, AMR interventions are complicated and dynamic which exposes the youth to diverse skills. In summary, experiential learning immerses the youth in real-world challenges allowing one to analyze the situation, generate solutions, and evaluate outcomes. To effectively develop the leadership skills of young people, it is thus imperative to engage them in the designing and implementation of Interventions.

Developing youth-friendly structures at the national, and sub-national Levels

For sustainable youth engagement, in the AMR landscape, the youth must be involved in the AMR policy landscape within their countries at both national and sub-national levels. A priority intervention is incorporating the importance of youth engagement efforts in the AMR National Action Plans (NAPs) and the implementation strategies that are developed from the NAPs. Another area that could be considered is having NAPs to reflect youth's perspectives. Governments should avail platforms needed to initiate intergenerational dialogue and showcase commitment to supporting youth movements at the grassroots level. Government agencies should also design programs and policies that build the capacity of the youth. Depending on a country's governance structure and health landscape, this can be implemented at the national and subnational levels.

Areas the youth can consider exploring in AMR mitigation interventions

As highlighted above, self-determination is critical for sustainable and meaningful youth engagement. Capacity building and guidance on potential areas one can venture into are key in empowering the youth as they walk their AMR journey. Below is an overview of areas in AMR that the youth could consider engaging in:

Research
There is a dearth of research within the African continent on AMR and other global health challenges. This is an area that the youth could consider exploring either as researchers, supporting ongoing research, or being willing to participate in AMR studies. A low-hanging fruit is research undertaken at tertiary-level institutions as one completes their undergraduate or postgraduate research. The youth can also undertake research training, and apply for fellowships, scholarships, and grants to pursue AMR-affiliated research. Collaboration and multidisciplinary engagement can also expand the research breadth of the tertiary level students.

Governance, policy and advocacy
The youth are strategically positioned to engage in policy efforts at both regional and local levels. These efforts can help make a case for the prioritization of AMR by governments and the formulation and implementation of AMR-friendly policies. Young people have been at the frontline of various policy processes such as climate change. Opportunities for cross-learning can help promote this capacity in the AMR landscape. Youth-led advocacy efforts can also help promote domestic investment into AMR efforts, a key gap since many AMR National Action Plans are not funded.

Community engagement
The youth could explore taking leadership in AMR interventions within their communities. Interventions initiated in the community can be diverse depending on the needs of particular communities. Youth have extra skills and expertise such as the ability to mobilize, pooling of resources, and innovative ways of engagement which can improve the uptake of interventions in their respective communities.

Engaging fellow youth, and children at the secondary and primary school level
Given the lesser age difference, the youth are better positioned to engage children in AMR than other older colleagues. They can design interventions in ways relatable to the younger ones, improving uptake and catalyzing positive behavior change. The innovative nature of the youth allows them to design programs that can promote sustainable engagement of younger ones on AMR. They also can engage with the government and key stakeholders to advocate for the inclusion of AMR into the curriculum.

Peer mentorship

To widen the pool of youth investing in AMR priorities, youths already working in the AMR landscape could mentor others and help them improve their capacity in this field. Young people can also develop platforms where they can obtain mentorship from older colleagues in their respective fields.

Antimicrobial stewardship from a One Health perspective

The youth can also explore AMR interventions in Antimicrobial Stewardship. This could be from human health, animal health, or environmental health scopes. The field of antimicrobial stewardship is very vast and is not defined for particular professions as may be the conventional thought process. There is a need to encourage multidisciplinary engagement in antimicrobial stewardship, and also explore different areas that are yet to be addressed. For example, expertise in Informational technology is key to developing effective surveillance strategies.

Drug discovery and development of alternative therapeutic interventions

Youth can play a critical role in the development of alternative therapeutic interventions for example phage therapy, herbal medicine, and exploration of other novel drug discovery strategies and therapeutic interventions. These efforts also require multi-sectoral expertise and thus the youth can take part in different roles. Capacity-building interventions are also required in this area to support in building the expertise required.

Health Systems Strengthening

A key driver of AMR especially in low- and middle-income countries are poor health systems. Young people can invest their expertise in bolstering the health systems. This is quite a wide landscape that requires diverse experience and expertise. Young people can bring on board innovative approaches and promote transdisciplinary engagement.

Awareness and education

A key intervention that the youth can take up in promoting awareness and education on AMR is ideating on relatable ways to frame AMR to promote uptake and improved understanding of AMR among the general public. The youth can also take the lead in the translation of key messages, and creating tailored toolkits for key target audiences. The youth can also build capacity among fellow young people to improve expertise in the AMR which provides a larger pool that can create awareness among the public.

All the above are just examples of areas that the youth can explore. The areas covered are very high level and there are multiple focus areas and interventions that fall under or out of the areas highlighted. It is important to recognize that multi-disciplinary engagement beyond the conventional disciplines engaged in AMR and to also create thriving platforms that provide opportunities for self-determination among the youth.

Conclusion

For AMR to be addressed sustainably, the youth must be meaningfully engaged. It is important when empowering the youth to grant them the opportunity to build their leadership skills through capacity building and experiential learning. To engage the youth effectively, we must recognize that they are a large heterogeneous group from diverse backgrounds with varying expertise and experiences. Gender equity should also be considered in any engagement among other pressing issues as per context. Lastly, there are no predefined roles that the youth have to take up when engaging in AMR interventions. Guidance can be provided on potential areas to explore but self-determination is key as per a young person's interest and gaps identified, to ensure that the career paths they follow or initiatives and interventions they create have a sustainable lifeline.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 25

Antimicrobial resistance and patient safety

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Introduction

Antibiotics have been one of the most significant medical innovations of the 20th century, playing a crucial role in public health worldwide. Penicillin, discovered by Alexander Fleming, was massively produced and hailed as a miraculous drug. However, while antibiotics have successfully curbed infectious diseases, their widespread use and misuse have led to the emergence of antibiotic-resistant bacteria. In some cases, resistance affects all available treatments, creating "superbugs" that pose a severe challenge to modern medicine, potentially turning back the clock to the pre-antibiotic era. This is especially concerning given the lack of new drugs to combat multidrug-resistant bacteria.
Fleming foresaw the issue of antimicrobial resistance (AMR) in 1945, warning against the dangers of self-medication and under-dosing, which could educate microbes to resist treatment. He cautioned that the careless use of penicillin could lead to resistant infections, for which the individual would bear moral responsibility and concluded with his own words “I hope this evil can be averted”.
Despite these early warnings, AMR has escalated dramatically over the last 40 years, reaching an incongruous level worldwide and becoming a serious challenge to patient safety. Globally, AMR causes over 1.2 million deaths annually and is projected to become the leading cause of death by 2050, with over 10 million deaths each year.

AMR poses a multifaceted threat, impacting patient safety, healthcare systems, and the economy. It increases the risk of treatment failure, complications, and adverse outcomes, undermining the quality of healthcare. Quantifying the full extent of morbidity and mortality due to AMR is challenging, as it often affects the most vulnerable patients. However, the significant clinical and public health burden of AMR is undeniable. This paper explores the profound impact of antimicrobial resistance on patient safety.

Patient safety definition

According to the World Health Organization (WHO), the definition of "Patient safety" is "the absence of preventable harm to a patient and reduction of risk of unnecessary harm associated with health care to an acceptable minimum". Within the broader health system context, it is "a framework of organized activities that creates cultures, processes, procedures, behaviors, technologies and environments in health care that consistently and sustainably lower risks, reduce the occurrence of avoidable harm, make the error less likely and reduce the impact of harm when it does occur."

The WHO dressed a list of the 11 most common sources of patient harm. Healthcare-associated infections (HCAI) and Sepsis are part of this list and are closely related to the burden of AMR. The worldwide rate of healthcare-associated infections (HCAIs) is 0.14%, rising by 0.06% annually. Furthermore, Sepsis is a harmful illness that develops when the body's immune system overreacts to an infection, damaging its own tissues and organs in the process. A systematic review and meta-analysis of the frequency and mortality of septic shock in European and North American intensive care units (ICUs) revealed that c.a. 10.4% of patients were diagnosed with sepsis at admission, and 8.3% during their ICU stay, and estimated a high mortality of around 38%. This study revealed a high degree of heterogeneity likely driven by variability in defining and applying the diagnostic criteria, as well as differences in treatment and care across settings and countries. According to a systematic review and meta-analysis dealing with HA sepsis worldwide (high-, middle- and low-income countries), of all sepsis cases managed in hospitals, 23.6% were found to be healthcare-associated, and approximately 24.4% of affected patients lost their lives as a result.

AMR & the patient safety alert

The impact of AMR, therefore, extends into all aspects of medicine and threatens the significant progress that has been made in managing patients with complex conditions including transplantation, anti-cancer chemotherapy, and surgery. There is a wealth of literature that estimates the incidence, mortality, length of stay in the hospital, and health care costs related to AMR. However, many publications pointed to the heterogeneity across the studies and explored a few confounding variables and biases of mortality, such as characteristics relating to patients, infections, organisms, and therapies.

In a global context, bacterial resistance has direct implications for patient safety by multiplying the risks of complications, extending their Length of Stay (LOS) in hospitals and consequently fatal outcomes due to the absence of effective therapeutic options. AMR also imposes mandatory prolonged treatment, increased dosing and requires expensive, novel last resort molecules (when available), thus resulting in increased costs for health systems. AMR has also implications for the patient's quality of life, longer recovery leading to

Prolonged absenteeism from work and loss of earnings during recovery. Surgical site infection (SSI) often requires hospital readmission, as treatment often necessitates novel surgery and long antibiotic treatments.

Patients with SSI are predicted to have a two to eleven times higher risk of morbidity and death than patients without the infection. With AMR, the situation is even more complex, as these infections represent a great therapeutic challenge complicating further the clinical outcomes of the disease.

Impact of AMR on length of stay (LOS)

Extended LOS in ICUs has been clearly demonstrated for patients infected or colonized with carbapenem-producing *Enterobacterales* (CPE), with an average hospital stay ranging between 21 to 87 for CPE cases *versus* 15 to 43 days for control patients. A recent retrospective matched case-control study in a low-endemic setting using conditional logistic regression to look at significant risk factors revealed that carbapenem resistance was the main risk factor for LOS. Indeed, they found that when admitted to the ICU, patients with carbapenem-resistant bacteria often stay 1.59 times (CI, 0.81-3.14) longer in the ICU. In addition, prior carbapenem treatment seems to be associated with the development of carbapenem resistance. Finally, the authors determined that the most significant factor linked to hospital death was related with an odds ratio of 1.10 (CI, 0.05-1.17) to the LOS in the ICU. The substantial threat posed by carbapenem-resistant *Enterobacterales* (CRE) and especially CPE to both public health and infected patients is further highlighted by the pervasiveness of *Enterobacterales*-related infections, the limited options for antimicrobial therapy, and the potential for the dispersion of the carbapenemase encoding gene to other bacterial species.

Impact of AMR on mortality rate

Several meta-analyses evaluated the relationship between CRE infections and mortality by contrasting the mortality result with that of patients infected with carbapenem-susceptible *Enterobacteriaceae* (CSE). They reported that the risk of in-hospital mortality due to CRE bloodstream infection is considerably greater than carbapenem-susceptible bloodstream infection (ARD, 0.25; 95% CI, 0.17–0.32). A systemic review by Zhou and collaborators, revealed a high level of heterogeneity among the different studies, but using meta-regression analysis showed that, for any type of mortality outcome, carbapenem resistance was associated with a greater probability of death for patients infected with CRE than those infected with CSE.
Deaths attributable to bacterial antimicrobial resistance in 2019 according to the Antimicrobial Resistance Collaborator's paper in the Lancet by Global Burden of Diseases per 100,000 ranged between 45.4 and 124.2 depending on the countries.
The estimated burden of infections with antibiotic-resistant bacteria in the high-outcome countries is substantial compared with that of other Middle and Low outcome countries. Deaths attributable to the AMR per 100,000 were 67.7 in Central Europe, Eastern Europe, and Central Asia, 55.7, in high-income countries, 57.9 in Latin America and the Caribbean, 42 in North Africa and the Middle East, 76.8 in South Asia, 47.1 in Southeast Asia, east Asia, and Oceania. The highest death rate per 100,000 was noted in Sub-Saharan Africa (98.9 (78.6–124.2)). Although the exact cause of the higher mortality rates among LOC remains undefined, it is likely driven by inequitable access to new molecules.
These results are in line with earlier studies on the association between carbapenem resistance and mortality among patients infected with *Enterobacterales*.
Similarly, Pranita D. Tamma and collaborators showed that after adjusting for severity of illness on day 1 of bacteremia, underlying medical conditions, and differences in antibiotic treatment administered, the odds

of dying within 14 days were more than 4 times greater for Carbapenemase-producing CREs (CP-CRE) as compared with non-CP-CRE bacteriemic patients (adjusted odds ratio, 4.92; 95% CI, 1.01-24.81).

AMR as a global burden

Despite extensive literature estimating the effects of AMR on morbidity, mortality, hospital length of stay, and healthcare costs for specific pathogen–drug combinations in mostly high-income countries there's a lack of data covering global issues and dealing with a wide range of pathogens and pathogen–drug combinations in LMIC. The study by the Antimicrobial Resistance Collaborators (is the first study assessing the burden of AMR at a global level. These authors investigated 204 countries and territories, 23 bacterial pathogens, and 88 pathogen-drug combinations in 2019. They calculated/estimated the number of deaths and disability-adjusted life years (DALYs) linked to and caused by bacterial AMR based on the counterfactual scenario for the 23 pathogens and 88 major infectious syndromes. They estimated that 4.95 million (3.62–6.57) deaths were associated with bacterial AMR in 2019, including 1.27 million (95% UI 0.911–1.71) deaths directly attributable to bacterial AMR. Three infectious syndromes: bloodstream infections, intra-abdominal infections, and lower respiratory infections, dominated the worldwide burden associated with AMR, accounting for 78.8% (95% UI 70.8–85.2) of AMR-related deaths in 2019; lower respiratory infections alone were responsible for about 400,000 deaths that were attributed to AMR and accounted for more than 1.5 million deaths associated with resistance in 2019, making it the most burdensome infectious syndrome.

Six pathogens: *Escherichia coli*, *Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, Acinetobacter baumannii*, and *Pseudomonas aeruginosa*, were responsible for 73% [929,000 (95% UI 660,000–1,270,000)] and 72% of deaths attributable and associated with AMR globally, respectively. Most of these pathogens belong to the critical priority list of pathogens by WHO for which urgent novel therapies are needed.

Methicillin-resistant *S. aureus*, caused more than 100,000 deaths attributable to AMR, while six other pathogen–drug combinations, were responsible for 50,000 to 100,000 deaths, namely MDR excluding XDR *M. tuberculosis*, third-generation cephalosporin-resistant *E. coli*, carbapenem-resistant *A. baumannii*, fluoroquinolone-resistant *E. coli*, carbapenem-resistant *K. pneumoniae*, and third-generation cephalosporin-resistant *K. pneumoniae.*

Health outcome studies associated with CPE infections are focused on short-term issues (e.g., in-hospital); long-term sequelae and loss of good quality of life are not well studied. In addition, once the patients are released from hospitals, the potential consequences of intra-familial dissemination of these bacteria is not studied. A few studies have addressed the role of international travel in the dissemination of antimicrobial resistance, mainly ESBLS, and the potential dissemination of these resistant bacteria to non-travelling household members. Intrafamilial spread occurred in 12.8% of the cases. Whether these bacteria were subsequently responsible for infections is not known.

Conclusion

Modern medicine heavily depends on antibiotics, particularly ß-lactams like penicillins, cephalosporins, monobactams, and carbapenems, known for their safety, effectiveness, and reliable bacterial killing properties. These antibiotics are frequently prescribed to treat bacterial infections. However, the emergence of resistance is a natural evolutionary process in bacteria, and while we cannot completely prevent it, we can slow it down through proper antibiotic stewardship and by preventing the spread of resistant bacteria in hospitals.

Understanding the link between antimicrobial resistance (AMR) and patient safety is crucial. It should drive the implementation of measures to prevent healthcare-associated infections with multidrug-resistant organisms, thereby ensuring that hospitals remain safe spaces where patients are treated for their underlying conditions, not for infections acquired in the hospital. The WHO has recognized the control of bacterial resistance as a global priority due to its significant impact on public health. To combat AMR, five key actions have been identified: (i) enhancing knowledge through training, education and communication; (ii) regulating and prudent antibiotic use; (iii) promoting research for new antimicrobials; (iv) improving surveillance systems for infections caused by resistant pathogens; and (v) advocating for effective infection control measures in healthcare settings.

In May 2019, the World Health Assembly adopted a resolution recognizing patient safety as a global health priority, leading to the creation of World Patient Safety Day on September 17th each year. The resolution also called for the development of a Global Patient Safety Action Plan for 2021–2030, to reduce avoidable harm in healthcare and ensure that every patient receives safe and respectful care worldwide.

As AMR is a global issue, it demands global solutions. Action is urgently needed from everyone—patients, healthcare providers, hospitals, and national organizations—to manage antimicrobial stewardship effectively. Failing to do so could lead to disastrous consequences for the future of healthcare.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 26

Building robust and resilient health systems to control antimicrobial resistance

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Introduction

Antimicrobial resistance (AMR) in a wide range of infectious agents continues to be a serious threat to human, animal and environmental health, as well as the well-being of the global economy and development. AMR is a growing global health threat with far-reaching consequences hence necessitating urgent action. The global burden of AMR is significant, particularly in low- and middle-income countries where access to healthcare is limited and the prevalence of infectious diseases is high. AMR poses a significant threat to human health, food security and economic development thus strategies to build robust and resilient health systems capable of effectively controlling AMR are much needed. The overuse and misuse of antimicrobials have contributed to the emergence and spread of AMR, rendering infections increasingly difficult to treat. This has led to increased mortality rates, prolonged hospital stays, and higher healthcare costs.
Addressing the AMR crisis requires a multifaceted approach that involves strengthening surveillance and reporting systems by implementing comprehensive surveillance systems to monitor antimicrobial resistance patterns, identify emerging threats and track the effectiveness of interventions and facilitating the sharing of AMR data among healthcare providers, public health agencies and researchers to enable timely detection and response; promoting the appropriate use of antimicrobials by providing healthcare professionals with continuous education and training on the appropriate use of antimicrobials, including when to prescribe, dose and duration, implementing antimicrobial stewardship programs to promote the appropriate use of antimicrobials within healthcare settings and strengthening infection prevention and control measures to reduce the need for antimicrobials; investing in research and development of new antimicrobials to address emerging AMR threats, exploring alternative therapies and preventive measures to reduce the reliance on antimicrobials and investing in rapid diagnostics tests to enable early diagnosis and appropriate treatment and strengthening international collaboration through development and implementation of global action plans to address AMR by coordinating efforts among countries, facilitating the exchange of knowledge and best practices among countries to accelerate progress in AMR control and mobilizing resources to support AMR control in low and middle income countries.

Strengthening surveillance and reporting systems

Effective surveillance and reporting systems are essential for understanding the burden of AMR, detecting emerging threats and guiding appropriate interventions. Strengthening these systems will assure countries of robust and resilient health systems capable of effectively controlling AMR. One critical component of effective AMR surveillance is comprehensive data collection. This involves gathering information on antimicrobial use, infections and antimicrobial resistance patterns. Collecting data from a wide range of healthcare settings will be useful for countries gaining a better understanding of the prevalence and trends of AMR. It is important to use standardized data collection tools and definitions to ensure consistency and comparability across different settings.

In addition to data collection, analyzing and reporting AMR data is crucial. By analyzing collected data, countries can identify trends, patterns and emerging threats (**Figure 1**).

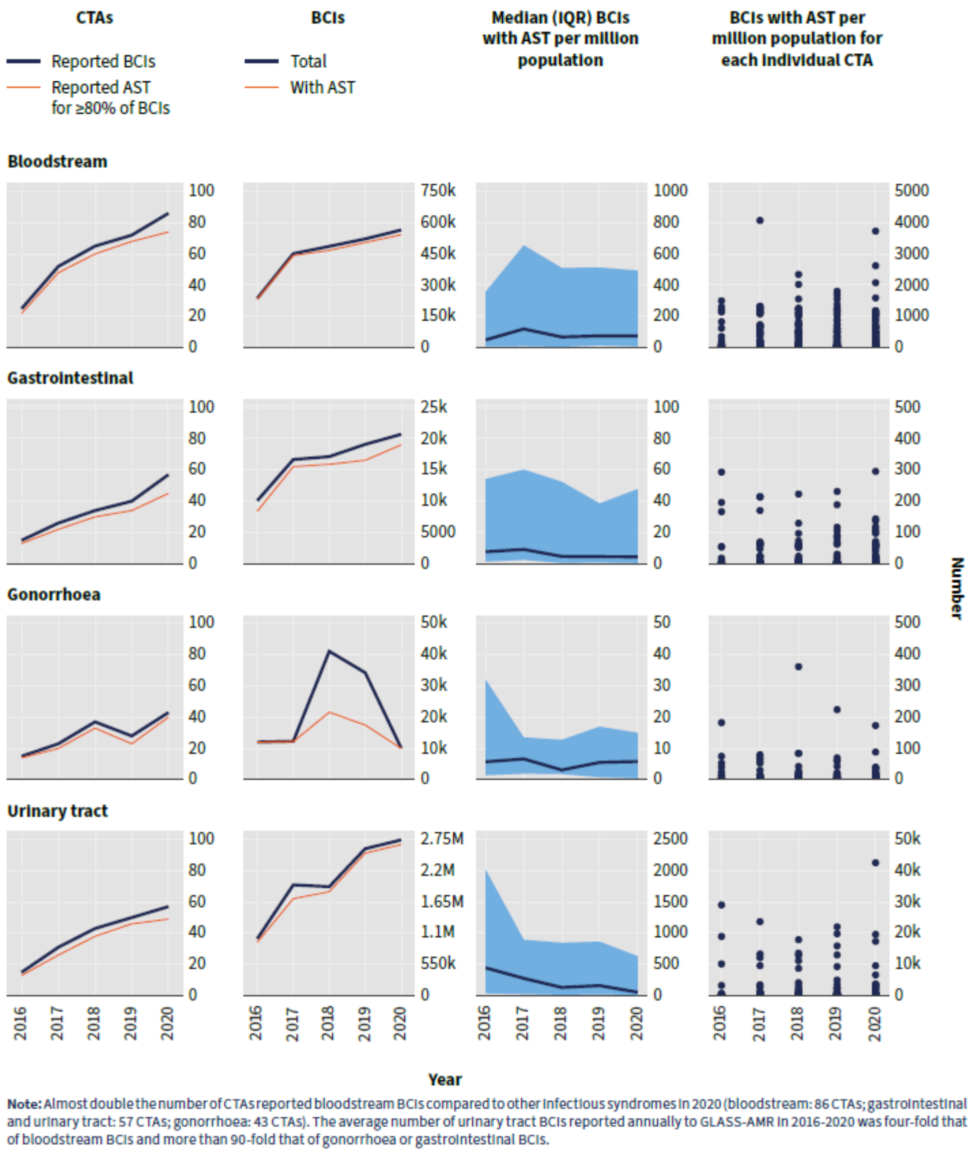

Figure 1. Progress in reporting BCI's and AST test results to GLASS-AMR for infectious syndromes under surveillance (2016 -2020) (Adapted from: Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report 2022).

This information can be used to inform public health policies and interventions. Developing clear and concise reports can help to disseminate AMR data to relevant stakeholders, including healthcare providers, policymakers and the public. Sharing AMR data among healthcare providers, public health agencies and researchers is another important aspect of effective surveillance and reporting (**Figure 2**).

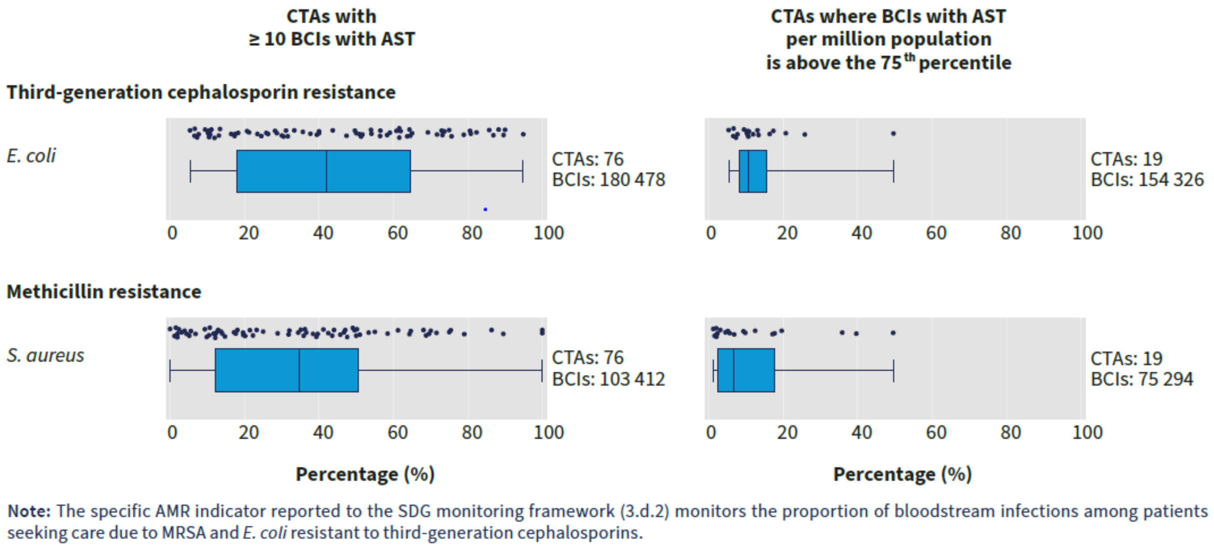

Figure 2. Percentage resistance to third-generation cephalosporin in *E. coli* and methicillin resistance in *S. aureus* in CTAs reporting ≥ 10 bloodstream BCIs with AST results compared to CTAs where the reported numbers per million populations were above the 75th percentile in 2020 (Adapted from: Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report 2022).

Countries can leverage the expertise of a wider range of stakeholders to address AMR through data sharing. Developing secure data-sharing platforms and promoting international collaboration can help to facilitate the exchange of AMR data.

Finally, establishing comprehensive surveillance networks is essential for effective AMR surveillance. These networks should cover a wide range of healthcare settings, including hospitals, clinics and community-based facilities. Integrating AMR surveillance into existing public health surveillance systems can improve efficiency and data quality. Investing in laboratory capacity and training can ensure accurate and timely detection of AMR.

Promoting the appropriate use of antimicrobials

The overuse and misuse of antimicrobials have contributed significantly to the emergence and spread of antimicrobial resistance (AMR). Promoting the appropriate use of antimicrobials is essential for combating AMR and building resilient health systems. One key strategy for promoting appropriate antimicrobial use is to provide healthcare professionals with continuous education and training on the appropriate use of antimicrobials. This includes when to prescribe, dose and duration of treatment. Healthcare providers equipped with the necessary knowledge and skills can make informed decisions about antimicrobial use and reduce the risk of contributing to AMR.

Another important strategy is to implement antimicrobial stewardship programs in healthcare settings. These programs aim to promote the appropriate use of antimicrobials through a variety of interventions, such as developing guidelines for antimicrobial use, monitoring antimicrobial consumption and providing feedback to healthcare providers. Building a culture of antimicrobial stewardship in healthcare organizations can reduce the unnecessary use of antimicrobials and minimize the risk of AMR. In addition to education and

stewardship programs, it is essential to promote infection prevention and control measures. By preventing the spread of infections, the need for antimicrobials can be reduced. This includes implementing effective hygiene practices, ensuring proper sanitation and promoting vaccination programs.
Finally, investing in research and development is crucial for addressing the AMR crisis. This includes developing new antibiotics and alternative therapies, as well as improving diagnostic testing to enable early identification and appropriate treatment of infections. By supporting research and development, countries can enhance their capacity to combat AMR and build resilient health systems.

Investing in research and development

Investing in research and development (R&D) is crucial for addressing the growing threat of antimicrobial resistance (AMR). By supporting innovative research, countries can develop new strategies to prevent, detect and treat AMR infections. This includes investing in the discovery and development of new antibiotics, antivirals and antifungals that are effective against drug-resistant pathogens. Additionally, research can focus on developing rapid diagnostic tests to enable early detection and appropriate treatment of AMR infections, as well as exploring alternative therapies and preventive measures to reduce the reliance on antimicrobials. Investing in R&D for AMR can have significant benefits for public health and economic development. New therapies and diagnostic tools can improve patient outcomes, reduce healthcare costs associated with prolonged hospital stays and complications and prevent the spread of AMR infections. Furthermore, R&D can stimulate economic growth by creating jobs in the healthcare and biotechnology sectors and fostering innovation. By supporting R&D initiatives, countries can contribute to the global effort to combat AMR and build resilient health systems.

Fostering international collaboration

Through international collaboration, countries can share knowledge, resources and best practices to build robust and resilient health systems capable of controlling Antimicrobial Resistance (AMR). Collaborative efforts can involve sharing data on AMR patterns, developing and implementing joint research projects, harmonizing regulatory frameworks and mobilizing resources to support AMR control initiatives. International partnerships can help to overcome the challenges posed by AMR, such as limited resources, lack of technical capacity and differing cultural and social contexts. By working together, countries can leverage their strengths and expertise to develop innovative solutions and accelerate progress in AMR control. Additionally, collaboration can help to build trust and solidarity among nations, promoting global health security and fostering a collective response to the AMR crisis.
Examples of successful international collaboration in AMR control include the Global Antimicrobial Resistance Surveillance System (GLASS) established by the World Health Organization (WHO), which facilitates the sharing of AMR data among countries. The G-20 has recognized AMR as a global health threat and has taken steps to promote international cooperation in addressing this issue. By strengthening international collaboration, countries can enhance their capacity to control AMR and protect public health.

Conclusion

Antimicrobial resistance (AMR) is a pressing global health threat that requires urgent and coordinated action. Building robust and resilient health systems will enable countries to effectively control AMR and protect public health. This manuscript has highlighted the importance of strengthening surveillance and reporting systems, promoting the appropriate use of antimicrobials, investing in research and development and fostering international collaboration. By implementing these strategies, countries can enhance their capacity to prevent, detect and treat AMR infections, reduce the spread of drug-resistant bacteria and improve patient outcomes. Addressing AMR requires a multifaceted approach that involves all stakeholders, including governments, healthcare providers, researchers and the public. Through collective action and sustained commitment, we can build a healthier world for all.

Competing interests

The author has no financial and non-financial competing interests to declare.

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Chapter 27

Surveillance of antimicrobial resistance: why and how?

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Introduction

Antimicrobial resistance (AMR) is a global calamity with adverse clinical and socio-economic impacts and is currently regarded as one of the most pressing threats worldwide. The burden of AMR is further challenged by the occurrence and dissemination of the multi-drug resistant (MDR) bacteria within and across human, animal, and environmental sectors calling for concerted One-Health interventions to curb the situation. The World Health Assembly deliberations in 2015 capitalized on the Global Action Plan on AMR and urged all member state countries to develop their context-specific National Action Plans on AMR, with overarching five strategic objectives (one of which being AMR surveillance). AMR surveillance is pivotal because all responsive actions can only be practical, effective, and efficient if driven by robust data systematically collected by standardized tools.
The AMR surveillance implementation requires three pre-requisites (human, material and financial resources), and strategic investment into these resources requires mapping, priority setting, implementation activities roll-out taking into account the local context within and across countries, and finally, systematic monitoring, evaluation, adaptation and learning to ensure sustainability. Even though countries are striving to implement their NAP-AMR, the implementation paths are variable within and across countries; underscoring a critical need to strengthen, standardize and translate existing initiatives into tangible actions holistically and inclusively.
This review focuses on why AMR surveillance is more pertinent now than ever before, and how reliably AMR surveillance can be conducted to delineate robust data which can inform AMR mitigation strategies, and ultimately avert adverse AMR-attributable impacts. It highlights the pressing need to generate robust One-Health AMR surveillance data, and articulate level/tier-specific AMR surveillance data utilization for specific responsive actions. Furthermore, this chapter addresses public-private engagement, and leverages local-

global funding mechanisms for sustainability. The review is primarily focused on the human sector but makes inferences on animal and environmental sectors to ensure comprehensiveness.

Significance of antimicrobial surveillance (Why AMR surveillance?)

The escalating burden of AMR is worrisome and is disproportionate to the rate at which antimicrobials are discovered. Systematic monitoring of AMR through standardised surveillance systems is pertinent across human, animal and environmental sectors as AMR has no boundaries, and therefore, addressing it should not be in silos (**Figure 1**).

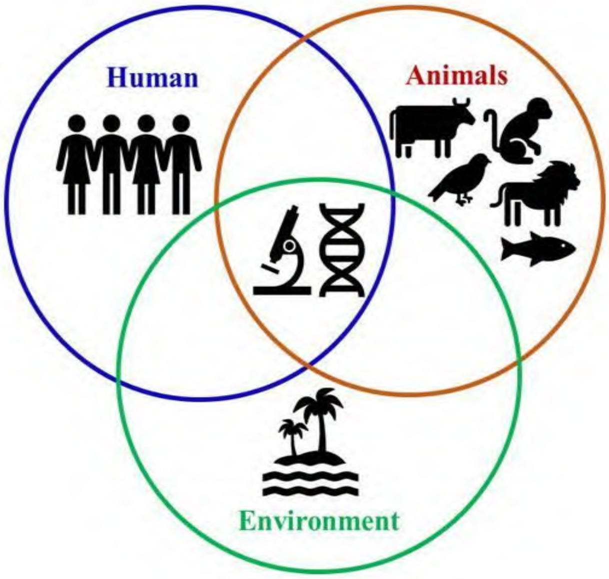

Figure 1. Intra- and inter-sectoral One-Health in AMR surveillance.

This section articulates ten thematic areas which highlight the significance of AMR surveillance.
One, the AMR-attributable infections notably by the World Health Organisation's priority list of pathogens are significantly increasing, causing adverse patient outcomes in terms of progression from mild to severe diseases, prolonged patients' hospital stays, and increase in deaths associated or attributable to AMR. For example, in 2014, there were approximately 700,000 deaths worldwide associated with AMR, which increased within five years to 1.27 million deaths in 2019 worldwide (surpassing 860,000 deaths from HIV/AIDS and 640,000 deaths from malaria), and if no concerted responsive efforts are done to mitigate this burden, it is estimated that AMR attributable deaths will increase to approximately 10 million per annum by 2050 surpassing all communicable and non-communicable diseases' attributable deaths worldwide. The AMR surveillance systems can be used to associate patients' morbidity and mortality with particular AMR phenotypes. For example, neonatal sepsis mortality in Tanzania was reported to be significantly higher in neonates infected with ESBL-producing Gram-negative bacteria than in their counterparts, reiterating priority setting to this vulnerable population.
Two, patients' adverse impacts are directly or indirectly associated with huge costs to individual patients, their families, their surrounding communities, and governments; and further compromise pre-constrained health systems especially in LMICs. Indeed, if AMR is not properly addressed, it will drain limited resources

designated for other health care services such as vaccination/immunization to children, maternal and child health, safe surgeries, and other curative, preventive and promotive health programs.
Three, because of its multi-sectoral nature, AMR will also affect animal production systems compromising food safety and biosecurity. Studies have shown how *Streptococcus agalactiae* bovine mastitis affects milk production systems, and hence, a critical need to have surveillance systems to monitor and promptly respond. Similarly, outbreaks of Gram-negative bacteria affecting fish have been reported to significantly affect aquaculture systems. Improper sewage disposal into water bodies resulting in environmental premises' contamination with MDR bacteria cannot be underestimated, as it creates antimicrobial selective pressure which favors the proliferation of MDR bacterial pathogens affecting aquatic lives, and which in turn directly or indirectly affect human health.
Four, AMR surveillance is important to compare trends within and across countries, thereby, guiding focused interventions. For example, most countries have pyramidal referral health care systems from primary, secondary and tertiary levels/tiers. Rolling comprehensive AMR surveillance to represent all levels is of paramount importance so that generated antimicrobial therapeutic guidelines are level-specific (**Figure 2**).

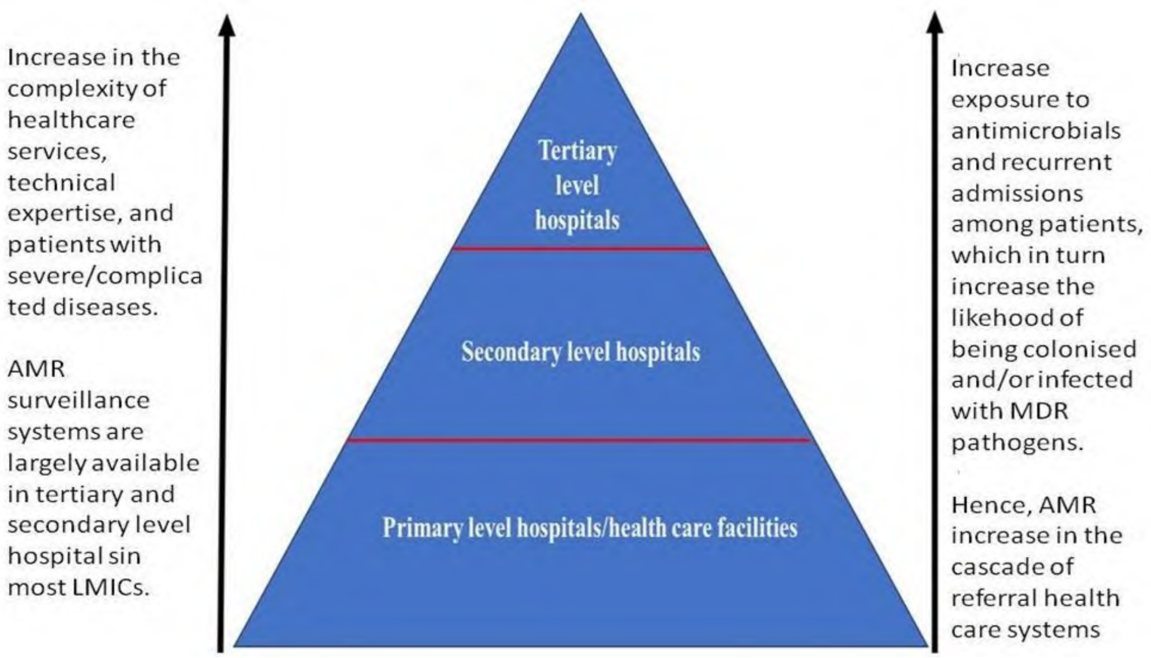

Figure 2. Pyramidal structure of health care systems in most countries.

One implementation project in Tanzania called Supporting the National Action Plan on AMR (SNAP-AMR) enrolled over 2,300 patients with three infectious diseases for AMR surveillance (namely bloodstream infections, urinary tract infections, and skin and soft tissue infections) between June 2019 to June 2020. The project used the 3rd generation cephalosporin resistance in Gram-negative bacteria (notably *Escherichia coli* and *Klebsiella pneumoniae*) as an AMR prototype owing to the frequent use of this agent. The findings from the SNAP-AMR project showed that there was a progressive increase in the 3rd generation cephalosporin resistance (irrespective of the type of infectious diseases) from the primary level where resistance was less than 15.0% through the secondary level (up to 50% resistance) to the tertiary level (45.0% to 60.0%). The findings reiterate a critical need to generate level-specific antimicrobial guidelines.

These findings are also reflected in the existing WHO Global Antimicrobial Resistance and Use Surveillance Systems (GLASS) whereby most of the data are generated from tertiary and a few secondary level hospitals, and therefore, translation of generated data to inform evidence-based responsive actions should not be generalized but rather extrapolated to reflect specific levels in the respective countries. In addition, most of the AMR surveillance data generated are from public sectors, calling for more private sector engagement to foster comprehensiveness and holistic interventions.

Five, sub-analysis of AMR surveillance data should also take into account disparities related to other parameters such as rural *versus* urban settings, public *versus* private sectors, varying socioeconomic status, and varying patient populations. Intricacies in the pediatric, medical and surgical patients; as well as non-critical *versus* critical patients in the intensive care units and high-dependent units should be clearly articulated in the existing AMR surveillance datasets. For example, multicenter surveys, systematic reviews and meta-analyses are showing a preponderance of MDR-attributable infections in neonates, surgical patients and patients in critical care units. These infections are most often driven by to increased use of antimicrobial agents in these vulnerable patient populations, hence, culminating in adverse outcomes.

Six, AMR surveillance is not only for guiding the appropriate selection of antimicrobial therapeutic options, but also can guide infection prevention and control (IPC) measures, and antimicrobial stewardship (AMS) programs. One of the critical values of a systematic surveillance system is to identify the sources of MDR pathogens in the hospital settings, delineating whether they are endogenous from patients or exogenous from external sources like environmental premises, and thereby, guide prompt responsive measures. Laboratory-based AMR surveillance systems have widely been used to provide timely alerts for prediction of occurrence of WHO priority pathogens like vancomycin-resistant *Staphylococcus aureus* (VRSA), vancomycin-resistant Enterococci (VRE), and Carbepenem-resistance Gram-negative bacteria in the hospital ICUs and other critical units, by specifically pinpointing the sources of these pathogens and therefore, guiding mitigations.

Seven, AMR surveillance data can retrospectively guide AMS programs to track conformity on the prudent use of antimicrobial agents, especially reserve antimicrobial agents in the Access Watch and Reserve (AWaRe) groups of antibiotics, bridging AMS and diagnostic stewardship programs. Indeed, AMR surveillance and AMS programs are bidirectional in nature and can complement one another, i.e. AMR surveillance data can show irrational use of an agent and therefore, prompt close follow-up on the prudent use of that agent in the hospital and community settings, on the other hand, alarmingly high use of reserve antibiotic can prompt evaluation of resistance trends of pathogens toward that agent through AMR surveillance. Capitalizing on IPC and AMS programs, especially in LMICs should be an enduring cost-effective direction for all countries while implementing their respective NAP-AMR and GAP-AMR.

Eight, robust data generated through AMR surveillance can be aggregated, analyzed and sub-analyzed to fit various settings and patients' populations. This allows the generation of specific antibiograms which in turn through the Delphi technique/approach can be used to develop antimicrobial treatment guidelines. Generated antimicrobial treatment guidelines can be used to guide empirical antimicrobial therapies in hospitals that lack laboratory diagnostic infrastructures for culture and antimicrobial susceptibility testing (AST), and can also guide empirical antimicrobial therapies in critically ill patients (after clinical sample collection) while waiting for culture and AST results which most often takes three to five days.

Nine, AMR surveillance is critical for monitoring, evaluation, learning and adaptation (MELA) to assess the performance of AMR interventions in all five strategic objectives. Ideally, if AMR interventions in awareness, education and communication; or IPC or AMS are effectively and efficiently working out, they should translate into a reduction of AMR burden in a respective setting, and the reverse is also true if the AMR interventions are not working. Last but not least, AMR surveillance generates robust data and pathogens which can be archived and subsequently used for technological advances and innovations spanning from the development of novel diagnostics, antimicrobial therapeutic targets, and novel targets for vaccines. AMR surveillance data when aggregated over time can show the predominant pathogens at species and sub-species levels (like genotypes) using high-resolution molecular assays like multilocus sequence typing (MLST) or whole genome sequencing (WGS). However, these typing methods are costly, and need state of art laboratory infrastructures and extensive human resource technical expertise. Knowing the dominant genotypes can allow designing PCR-based cost-effective typing methods useful in LMICs and allow deployment of MLST and WGS only for a few non-typeable strains. Recent studies have shown that conventional PCR- and real-time PCR can reliably type the *Escherichia coli* ST131 global clone, and link its clades C1 and C2 with fluoroquinolone and 3rd generation cephalosporin resistance, respectively in Nigeria and Tanzania. Therefore, pharmaceutical and diagnostic companies should be part and parcel of the ongoing AMR surveillance to leverage this platform for innovations and scientific breakthroughs.

AMR surveillance methodological underpinnings (How AMR surveillance is done?)

The prerequisites of AMR surveillance methodological underpinnings entail the deployment of laboratory methods using standard guidelines and tools to ensure that reliable results are generated to guide rational antimicrobial therapies for clinical and veterinary practices. They also aim to foster comparability of generated results within and across countries. The principles rely on two major criteria. Firstly, convenience (efficiency) criteria involve the deployment of laboratory methods that are accessible, easy to use, rapid, and flexible. Secondly, performance (efficacy) criteria involve the deployment of methods that are reproducible, stable, and with high typeability, high discriminatory power, and appealing epidemiologic and typing scheme concordance.

Diagnostic stewardship and clinical samples' anatomical sites as core elements for AMR surveillance
The AMR surveillance is built from cumulative culture and AST results generated carefully while taking into account the patient population involved intricacies. Diagnostic stewardship is pertinent in this approach as it promotes the rational use of laboratory diagnostic services to guide the right test, for the right patient which culminates in the right action on a specific selection of antimicrobial therapy. A thorough technical guidance by experienced laboratory scientists/technologists/technicians or medical/clinical microbiologists is required when interpreting culture results from non-sterile sites like sputum, stool, or pus from diabetic foot ulcers to take into account the role of normal microbiota as opposed to clinical samples from sterile sites. Critical attributes to connote infections, as opposed to normal microbiota colonisation, would be the presence of distinct bacterial morphology and the predominance of inflammatory cells in contrast to epithelial cells in the primary Gram-staining reaction. On the other hand, clinical samples from non-sterile sites like blood, cerebral spinal fluid or other body fluids when collected appropriately following standard operating procedures would most often have mono-microbial growth, and therefore, will not pose any diagnostic uncertainties.

The power of numbers in AMR surveillance
The AMR surveillance is recommended to be done over a prolonged period of time to allow the collection of enough data for not only credible translation of generated findings but also to allow sub-analysis of generated data to cater to varying populations or settings. A minimum period for AMR surveillance is usually recommended to be one year, and in order to generate appealing antibiograms, it is recommended that the

number of bacterial isolates per one species per sample type (or one disease) should be at least 30. For example, when generating antibiograms for bacterial pathogens implicated in causing urinary tract infections, a number of *Escherichia coli* isolates from patients' urine samples should be at least 30 to be tested against a panel of relevant antibiotics. Testing a small number of bacterial isolates would result in over-exaggeration of AMR profiles. For example, if only 6 *Escherichia coli* urinary isolates are tested against nitrofurantoin, and 4 are resistant, then, the percentage of resistant may be erroneously concluded as 66.7%.

A critical appraisal of methods used in AMR surveillance

Selection of laboratory methods for analysis is of paramount importance, whether conventional phenotypic methods, automated methods like matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) VITEK MS and VITEK 2 technologies, or molecular methods. While the conventional phenotypic and automated methods are pivotal in guiding routine clinical and veterinary practices, molecular methods are largely designated for AMR surveillance to guide IPC responsive measures or outbreak investigations by delineating the source of pathogens at sub-species levels. For phenotypic AMR surveillance, standardised interpretation is usually based on either the Clinical Laboratory Standard Institute (CLSI) or The European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints for semi-quantitatively interpretation of isolates' sensitivity, intermediate or resistance; or for minimum inhibitory concentration (MIC) for quantitative interpretation. It should be reiterated that although there are subtle variations between CLSI and EUCAST schemes, they should not be used interchangeably for one AMR surveillance.

The second key area in the AMR surveillance methods is the clinical sample-bacteria-antibiotic(s) matching. This is indeed critical as any mismatch would adversely impact patients' management, and also would generate unreliable AMR surveillance data. For example, nitrofurantoin or nalidixic acids are exclusively designated for urinary pathogens, and as such should not be tested against pathogens from other body systems. Similarly, while vancomycin, erythromycin and clindamycin are exclusively used for Gram-positive bacteria; piperacillin-tazobactam and meropenem are exclusively used for Gram-negative bacteria; and gentamicin, and ciprofloxacin are used for both Gram-positive and Gram-negative bacteria. In addition, various categories of penicillin are used for various bacterial species. For example, cloxacillin (or its surrogate marker cefoxitin) are used exclusively for screening of methicillin-resistant *Staphylococcus aureus* (MRSA) or Coagulase-negative Staphylococci (MR-CoNS); the non-fermentative bacteria like *Pseudomonas aeruginosa* and *Acinetobacter baumannii* should are tested against piperacillin and a combination of piperacillin-tazobactam (not penicillin/ampicillin or amoxycillin-clavulanate); and *Klebsiella pneumoniae* should not be tested against ampicillin as it is inherently resistant to this antimicrobial agent.

Thirdly, there are isolates whose resistance cannot be entirely confirmed by only the semi-quantitative disk diffusion AST method, and require confirmation with the MIC-based quantitative AST method. Examples of these include vancomycin testing against *Staphylococcus aureus* and colistin testing against Gram-negative bacteria.

Lastly, quality control and quality assurance programs (internal and external platforms) are prerequisites to AMR surveillance programs.

Confirming AMR phenotypes, and their laboratory and clinical inferences

The WHO has recently provided a priority list of pathogens requiring research and development, and key AMR phenotypes are clearly stipulated to be embraced in the ongoing AMR surveillance within and across countries. Two AMR phenotypes (ESBL and MRSA) require special emphasis in terms of interpretations. The ESBL is the main AMR mechanism for Gram-negative bacteria, and owing to the extended nature of the beta-lactamase enzyme in degrading the beta-lactam rings of the 3rd generation cephalosporins, this resistance is also inferred to 1st and 2nd generation cephalosporins, monobactams and penicillins by default, and therefore these agents should also be reported as resistant even if not tested. Similarly, the mec-A genes encoding for altered penicillin-binding proteins in strains showing MRSA phenotype (i.e. *Staphylococcus aureus* resistant to oxacillin or cefoxitin in-vitro) should be reported as resistant also to all other beta-lactam antibiotics like penicillins, cephalosporins, monobactams and carbapenems. Lastly, the inducible clindamycin resistance in *Staphylococcus* spp. or *Streptococcus* spp. should also should also be reported as resistant to erythromycin. Laboratory scientists/technologists/technicians and medical/clinical microbiologists should include comments/recommendations on their laboratory reports highlighting these key AMR phenotypes, and their respective laboratory and clinical implications. Similarly, clinicians should also understand the basis of these AMR phenotypes and their implications to translate them in context while selecting rational antimicrobial therapies in patients.

Data storage, management and interpretations for AMR surveillance systems

The AMR surveillance data generation is an ongoing process, and as such, electronic systems for data storing, management and interpretation are pivotal to allow real-time data visualisation, prompt responsive actions and comparison of trends within and across countries. The two AMR surveillance systems for human and veterinary sectors are WHONET and In-FARM, respectively. Capacity building for key technical personnel handling AMR surveillance data is crucial so that they are not only generating, storing and wiring AMR surveillance data to the national and global platforms, but they are also utilizing them at the generation points to inform evidence-based clinical and veterinary practices.

AMR surveillance data sharing mechanisms and ethical considerations

The AMR surveillance data generation is progressively increasing within and across countries, and these appealing strides come with a responsibility of ensuring data protection and data sharing mechanisms in a harmonised and respectful ways. Safeguarding the interests of patients and countries where these data are generated is of paramount importance, and especially when generated data are digitalised. Local, regional and global authorities should ensure the implementation of robust data governance frameworks to manage data access, usage, and sharing, abiding by professional code of conduct, and complying with local, regional, and international laws governing data protection, copyright, and more importantly safeguarding participants' values.

Overarching challenges facing AMR surveillance systems and mitigation strategies

Challenges in the AMR surveillance implementation within and across countries need to be continuously addressed at institutional, country, regional and global levels. Firstly, disproportional resources within and across countries like limited human resources capacities; secondly unharmonized material resources like guidelines, protocols and policies; thirdly limited laboratory diagnostic infrastructures. In a recently published Mapping Antimicrobial Resistance and Antimicrobial Use Partnership (MAAP) report, it was reported that only 1.3% of existing laboratories in 14 countries in Africa have microbiological testing capacity required for AMR surveillance, and only a quarter of these use electronic laboratory information systems. Capitalising on human resources capacity building through structured training and supportive supervision mentorship programs at country, regional and global levels are urgently needed to be strengthened. Programs like the Qualifying the Workforce for AMR Surveillance in Africa and Asia (QWArS), Fleming Fund Fellowship and many other similar program systems have already shown the way and should be maintained and rolled out to many counties at national and sub-national levels.

Secondly, the disproportional gaps in the AMR surveillance implementation within and across countries are largely caused by a lack of sustainable funding mechanisms at institutional, country and regional levels. Fostering local funding mechanisms is reiterated to ensure that these gains are maintained and sustained. The National Multisectoral Coordinating Committee on AMR should envision leveraging existing funds based on mapped priorities to address the local context. In addition, this committee should also guide the allocation of implementing and development partners based on mapped needs to avoid duplication of efforts and foster synergy. The public-private partnership should also be fostered to sustain gains, foster local ownership and ultimately ensure sustainability.

Thirdly, there is still limited community and civil society engagement, private sector engagement and political commitment in different countries to ensure that AMR surveillance implementation activities are holistically fostered. A recent case study from Tanzania is capitalising on this by forming The Tanzania Parliamentarian Alliance for AMR to mobilize policymakers to combat the growing threat of AMR through collaboration between the One Health Society and the Tanzania National Multisectoral Coordinating Committee on AMR (https://www.ohs-health.org/projects/tanzania-parliamentarian-alliance-for-amr/). In addition, a recently launched community awareness and advocacy campaign in the Kiswahili language called "Holela Holela Itakucost" which translates into "Recklessness in antibiotic misuse is costly" under the auspicious Break Through Action project funded by the USAID using contextualised visual aids and social media takeovers using a campaign ambassador called "KIDO" or "Tablet" whose character evolves to align with the user-generated content, and is envisaging to reach millions (https://www.usaid.gov/tanzania/press-release/jun-03-2024-us-and-tanzania-unite-combat-antimicrobial-resistance-and-animal-transmitted-diseases).

Holistic involvement of all key actors and stakeholders in the AMR surveillance would translate into responsive actions, local ownership and ultimately, sustainability of AMR mitigation.

Conclusion

AMR surveillance implementation is progressing across countries at different paths reflecting existing human resource and diagnostic infrastructural capacities, and financial resources. Standardised robust AMR surveillance data are pertinent to guide the development of antibiograms which are the pre-requisites in the development of antimicrobial treatment guidelines for various infectious diseases. While AMR surveillance data can be routinely used to guide clinical and veterinary practices, they are also pertinent in MDR pathogens sources' attribution specifically to IPC responsive measures in the community- and hospital settings, and to guide concerted efforts during outbreak investigations. Circumventing these hurdles is required to eliminate every adverse patient outcome and associated cost. The AMR surveillance provides avenues for data and pathogens to be used for technological innovations to develop new diagnostic tests, antimicrobial therapeutics and vaccinations. It is important that the "whole system' is engaged in the AMR surveillance from patients, health care facilities, communities, governments, the private sector, civil societies, other key sectors (in both animals and environmental sectors), and local and global implementing partners to ensure ownership and sustainability. While AMR surveillance is largely based on phenotypic methods, a paradigm shift is slowly moving towards genomic AMR surveillance which also comes with cost implications and therefore, calls for multi-sectoral and multi-disciplinary policy dialogues to ensure deployment that addresses local context issues.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 28

Control measures to tackle antimicrobial resistance in low-resource settings

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Introduction

Antimicrobial resistance (AMR) is a significant threat to global health, especially in low-resource settings. Limited access to medications and healthcare infrastructure exacerbates the issue, leading to increased healthcare expenses and economic burdens. Combating AMR in these settings requires a comprehensive, sustainable, and community-centered approach that addresses environmental, animal, and human health. This includes strengthening surveillance, promoting rational antibiotic use, implementing infection prevention and control measures, addressing environmental factors, and adopting a One Health approach.

Drivers of AMR in low-resource settings

AMR is a growing global health threat, particularly in low-resource countries. Several factors drive AMR in these settings, including:

1. *Unregulated antibiotic use*. The widespread availability of antibiotics without prescription, coupled with their misuse in treating viral infections, accelerates AMR. In many low-resource settings particularly LMICs, lax regulation of antibiotic sales enables unchecked self-medication and inappropriate use. Research published in The Lancet reveals that LMICs have significantly higher antibiotic consumption rates than high-income countries, fuelling the rise of resistant pathogens
2. *Healthcare access barriers*. In LMICs, restricted access to quality healthcare services, including essential diagnostic tools and effective treatments, results in delayed or incorrect treatment of infections. This heightens the risk of severe complications and necessitates the use of broad-spectrum antibiotics, thereby exacerbating AMR. A study published in BMJ Global Health underscores the critical role of inadequate healthcare access in fuelling AMR in LMICs, emphasizing the need for improved healthcare infrastructure and services.
3. *Inadequate infection control*. Insufficient sanitation, hygiene practices, and Infection Prevention and Control (IPC) measures in healthcare facilities and communities facilitate the spread of infections, creating an

environment conducive to AMR. As bacteria are exposed to antibiotics in these settings, they develop resistance, further fuelling the AMR crisis. The WHO stresses the critical importance of robust IPC practices in mitigating AMR, particularly in resource-constrained countries.

4. *Health system vulnerabilities*. Fragile health systems, characterized by inadequate infrastructure and resources, hinder the implementation of robust AMR surveillance and response programs. This limitation impedes the accurate tracking of resistance spread, effective intervention deployment, and timely outbreak containment. Research published in the Antimicrobial Resistance and Infection Control journal underscores the significant challenges of establishing reliable AMR surveillance in LMICs.
5. *Antibiotic use in agriculture and veterinary practices*. The application of antibiotics in agriculture and veterinary medicine to enhance growth and prevent diseases in animals plays a significant role in the emergence of AMR. Residual antibiotics can enter the human food chain, exposing bacteria to sub-therapeutic levels and driving resistance development. The One Health approach acknowledges the intricate relationships between human, animal, and environmental health, emphasizing the need for a holistic strategy to combat AMR.
6. *Socioeconomic determinants*. Socioeconomic factors, including poverty, limited education, and cultural beliefs, significantly influence healthcare-seeking behavior and treatment adherence, thereby contributing to the development of AMR. Research published in PLOS ONE reveals that low-income communities in LMICs exhibit higher rates of antibiotic misuse and AMR compared to more affluent populations, underscoring the need to address these socioeconomic disparities.
7. *Environmental influences*. Environmental factors, including inadequate sanitation, poor waste management, and contaminated water sources, play a crucial role in the spread of AMR. These factors can expose bacteria to antibiotics, facilitating the emergence and dissemination of antibiotic-resistant bacteria. Research published in Environmental Health Perspectives emphasizes the significant contribution of environmental contamination to the AMR crisis.

Control measures to tackle AMR in low-resource settings

Strengthening AMR surveillance

Effective AMR surveillance is crucial for understanding the extent of resistance, identifying emerging trends, and guiding interventions. However, low-resource settings face several challenges that hinder effective AMR surveillance as follows:

- *Infrastructure and resource gaps*. Inadequate laboratory infrastructure, equipment, and trained personnel limit the accurate identification and testing of antibiotic-resistant bacteria
- *Fragmented surveillance systems*. Uncoordinated data collection without standardized protocols leads to incomplete and inconsistent data.
- *Limited geographic coverage*. Urban-focused surveillance neglects rural and remote areas, skewing data and underestimating AMR burden.
- *Data management and analysis challenges*. Inadequate data management systems and analysis capacity hinder the timely interpretation and utilization of surveillance data.
- *Inadequate funding and prioritization*. Underfunding and lack of prioritization limit resource allocation for surveillance activities.
- *Lack of standardized protocols and quality assurance*. Inconsistent data quality and comparability across settings hinder aggregation and analysis.

- *Limited genomic surveillance capacity*. Lack of expertise and capacity for genomic surveillance limits the tracking of resistant strains and identification of emerging threats.
- *Weak linkages between surveillance and response*. Surveillance data fails to inform policy and practice due to weak linkages between surveillance and response mechanisms.

Addressing these gaps and problems requires a multi-faceted approach, including strengthening laboratory capacity, developing standardized protocols, improving data management and analysis, increasing funding and prioritization, establishing coordinated surveillance networks, expanding geographic coverage, building capacity for genomic surveillance, and strengthening linkages between surveillance and response. An example to this is the Mini-Lab, a turnkey solution developed by Médecins Sans Frontières (MSF) to address the gaps in AMR surveillance in LMICs. It offers a simplified, standardized, and affordable approach to AMR surveillance in resource-limited settings. The key features and benefits include a simplified and standardized approach to bacterial culture and antibiotic susceptibility testing, affordable and accessible technology, a turnkey solution with comprehensive training, data collection and analysis capabilities, and scalability and adaptability. The impact and potential of the Mini-Lab include improved AMR surveillance, enhanced capacity building, data-driven decision-making, and global collaboration.

Diagnostic stewardship: a critical tool in the fight against antimicrobial resistance

Diagnostic stewardship is a vital component in the battle against AMR in low-resource settings. It involves coordinated guidance and interventions to optimize the use of microbiological diagnostics, ensuring timely and accurate testing, proper specimen collection, and prompt reporting of results to inform treatment decisions.

In low-resource settings, diagnostic stewardship plays an even more crucial role due to challenges such as choice of empirical treatment leading to overuse and misuse of antibiotics, Limited access to quality diagnostics resulting in delayed or inaccurate diagnosis and inappropriate treatment and weak health systems, struggling to implement and maintain effective diagnostic stewardship programs.

Strategies for implementing diagnostic stewardship

To overcome these challenges, the following strategies can be employed:

1. *Prioritize essential diagnostics*. Focus on providing access to essential diagnostic tests for common infections.
2. *Strengthen laboratory capacity*. Invest in laboratory infrastructure, equipment, and training for laboratory personnel.
3. *Develop Point-of-Care testing*. Introduce point-of-care testing to facilitate rapid and accurate diagnosis.
4. *Implement antimicrobial stewardship programs*. Integrate diagnostic stewardship with antimicrobial stewardship programs.
5. *Engage community health workers*. Train and empower community health workers to collect specimens, perform basic diagnostic tests, and educate the community.
6. *Utilize digital health technologies*. Leverage digital health technologies to facilitate remote consultation, test result reporting, and provider education.
7. *Advocate for policy changes*. Advocate for policy changes that promote the availability, affordability, and quality of diagnostic tests.

Implementing diagnostic stewardship in low-resource settings can yield numerous benefits, including, Improved patient outcomes as timely and accurate diagnosis leads to appropriate treatment, reducing morbidity and mortality associated with infectious diseases. Also, diagnostic stewardship guides the appropriate use of antibiotics by identifying causative pathogens and their antibiotic susceptibility, reducing the risk of AMR. Avoiding unnecessary antibiotic use and hospitalizations reduces healthcare costs for individuals and health systems. Implementing diagnostic stewardship strengthens laboratory capacity, improves healthcare provider knowledge, and enhances overall health system performance. Diagnostic stewardship is a vital component of the global effort to combat AMR, especially in low-resource settings. By improving access to accurate and timely diagnosis, we can optimize antibiotic use, improve patient outcomes, and preserve the effectiveness of these life-saving drugs for future generations.

Vaccination as a combatting tool for preventing AMR

Vaccination plays a crucial role in combating AMR in low-resource settings. By preventing infections, vaccines reduce the need for antibiotics and thereby limit the opportunities for bacteria to develop resistance. The following points elaborate on this mechanism:

1. *Direct impact*. Vaccines directly target specific pathogens, preventing infections they cause. This reduces the number of individuals requiring antibiotic treatment, thus limiting antibiotic exposure and selective pressure on bacteria to develop resistance. For example, pneumococcal conjugate vaccines (PCVs) have been shown to significantly reduce pneumococcal infections and the subsequent use of antibiotics in children, leading to a decline in antibiotic-resistant pneumococcal strains.
2. *Indirect impact*. Vaccines can indirectly prevent AMR by reducing the incidence of viral infections that often lead to secondary bacterial infections. These secondary infections are frequently treated with antibiotics, increasing the risk of AMR. For instance, influenza vaccination not only prevents influenza but also reduces the incidence of secondary bacterial pneumonia, thereby limiting antibiotic use and the emergence of resistant bacteria.
3. *Herd immunity*. Vaccines contribute to herd immunity, whereby high vaccination coverage in a population protects even unvaccinated individuals by reducing the overall circulation of pathogens. This indirect protection further limits the spread of infections and the need for antibiotics, ultimately reducing the risk of AMR.
4. *Impact on antibiotic consumption*. Several studies have demonstrated a significant reduction in antibiotic consumption following the introduction of vaccines. For example, the introduction of *Haemophilus influenzae* type b (Hib) vaccine has dramatically reduced Hib infections and the associated antibiotic use, leading to a decline in antibiotic-resistant Hib strains.
5. *Cost-effectiveness*. Vaccines are often cost-effective interventions compared to the treatment of infections and the management of AMR. By preventing infections and reducing the burden of disease, vaccines save healthcare costs and resources, which can be invested in other essential health interventions. However, there are challenges to implementing vaccination programs in low-resource settings, including limited access to vaccines as vaccine availability and affordability can be barriers, especially for newer vaccines. weak health systems with Inadequate infrastructure, limited healthcare workforce, and logistical challenges can hinder vaccine delivery and uptake. Also, the vaccine hesitancy among the people in LMIC is high due to misinformation and mistrust in vaccines affecting vaccination coverage. Despite these challenges, vaccination remains a powerful tool in combating AMR in low-resource settings. Strengthening health systems, improving vaccine access, addressing vaccine hesitancy, and investing in research and development of new vaccines are essential steps in maximizing the potential of vaccines to prevent AMR.

One Health approach

The One Health approach is a powerful tool to combat AMR in low-resource settings. It recognizes the interconnectedness of human, animal, and environmental health and emphasizes the need for collaboration across sectors to address complex health challenges like AMR.

Key aspects of the One Health approach in addressing AMR in low-resource settings.

1. *Integrated surveillance*. Implementing integrated surveillance systems that monitor AMR in humans, animals, and the environment. This allows for early detection of resistance patterns, identification of hotspots, and targeted interventions. In low-resource settings, where surveillance is often fragmented, the one health approach can streamline data collection and analysis, providing a more comprehensive picture of AMR.
2. *Joint action and collaboration*. Fostering collaboration between human health, veterinary, and environmental sectors to develop and implement joint action plans. This can include harmonizing policies and regulations on antibiotic use, promoting responsible antibiotic stewardship, and sharing information and expertise across sectors. In resource-constrained settings, collaboration can leverage limited resources and expertise to achieve greater impact.
3. *Capacity building*. Strengthening the capacity of health systems, laboratories, and personnel to effectively diagnose, treat, and prevent AMR infections. This includes training healthcare workers on appropriate antibiotic use, improving laboratory infrastructure for AMR testing, and raising awareness among communities about AMR risks and prevention. In low-resource settings, where capacity is often limited, the One Health approach can facilitate the sharing of resources and knowledge to enhance capacity building.
4. *Community engagement*. Engaging communities in AMR prevention and control efforts through education and awareness programs. This can include promoting good hygiene practices, proper waste management, and responsible antibiotic use. In low-resource settings, where community engagement is crucial for behavior change, the One Health approach can leverage existing community networks and communication channels to reach a wider audience.
5. *Research and innovation*. Investing in research to better understand the transmission dynamics of AMR, develop new diagnostic tools, and discover alternative therapies to antibiotics. This can include exploring traditional medicines, developing vaccines, and promoting the use of phage therapy. In low-resource settings, where innovation is often constrained by limited resources, the One Health approach can facilitate partnerships between researchers from different sectors to explore novel solutions to AMR. The successful One Health interventions in low-resource settings include integrated AMR surveillance in Tanzania, joint action on antibiotic use in India, and community-based AMR awareness programs in Nepal. These interventions led to improved detection of AMR, reduction in overuse and misuse of antibiotics, improved hygiene practices, and increased demand for appropriate medical care, contributing to the prevention of AMR. The One Health approach provides a holistic framework for addressing AMR in low-resource settings. By integrating surveillance, promoting collaboration, strengthening capacity, engaging communities, and investing in research, the One Health approach can significantly contribute to combating AMR and safeguarding human, animal, and environmental health.

Role of eco-pharmacovigilance in tackling AMR

Eco-Pharmacovigilance (EPV) refers to the monitoring and assessment of the environmental impacts of pharmaceuticals, including antibiotics, to mitigate their unintended ecological consequences and reduce the development of AMR.

1. *Reducing environmental contamination*. Pharmaceuticals, particularly antibiotics, can enter the environment through various routes such as wastewater from pharmaceutical manufacturing, improper disposal of medications, agricultural runoff, and effluents from healthcare facilities. EPV aims to monitor and manage these environmental releases to prevent the proliferation of antibiotic-resistant bacteria in the environment. Implementing proper waste management protocols and wastewater treatment systems can significantly reduce contamination levels and the subsequent risk of resistance development.
2. *Monitoring and surveillance*. EPV provides a framework for the systematic monitoring of pharmaceutical residues in the environment. This includes tracking the presence of antibiotics in water bodies, soil, and wildlife. Regular surveillance helps in identifying hotspots of contamination and facilitates the timely implementation of mitigation measures. In low-resource settings, where such monitoring may be lacking, establishing EPV systems can enhance the understanding of environmental AMR patterns and inform targeted interventions.
3. *Promoting rational use of antibiotics*. One of the primary strategies of EPV is to promote the rational use of antibiotics to minimize their environmental impact. This includes educating healthcare providers and the public about the responsible use and disposal of antibiotics, thereby reducing unnecessary consumption and preventing excess antibiotics from entering the environment. In low-resource settings, awareness campaigns and educational programs can be crucial in promoting better practices.
4. *Improving regulatory frameworks*. EPV can support the development and enforcement of regulatory frameworks that govern the production, use, and disposal of antibiotics. Strong regulations can ensure that pharmaceutical manufacturers adhere to environmental standards, reducing the risk of antibiotic pollution. In low-resource settings, building capacity for regulatory oversight and providing technical assistance can help establish and maintain effective EPV systems.
5. *Encouraging research and innovation*. EPV drives research into the environmental impact of antibiotics and the development of sustainable alternatives. This includes investigating biodegradable antibiotics, improved formulations that minimize environmental release, and advanced treatment technologies for contaminated water and soil. Collaborative efforts between governments, research institutions, and the pharmaceutical industry can foster innovations that are particularly beneficial in low-resource settings.

<u>Implementation strategies for low-resource settings</u>

1. *Capacity building*. Training and capacity building are essential for implementing EPV in low-resource settings. This includes training healthcare workers, environmental scientists, and regulatory officials on EPV practices and the importance of environmental monitoring in combating AMR.
2. *Community engagement*. Engaging local communities in EPV efforts can enhance the effectiveness of AMR interventions. Community-led initiatives for proper disposal of antibiotics, environmental monitoring, and awareness campaigns can create a grassroots movement towards reducing antibiotic pollution.
3. *Partnerships and collaboration*. Partnerships between local governments, international organizations, non-governmental organizations (NGOs), and the private sector can provide the necessary resources and expertise for implementing EPV. Collaborative projects can leverage funding, technology, and knowledge transfer to build robust EPV systems.
4. *Integration with One Health approach*. EPV should be integrated into the broader One Health approach, which recognizes the interconnectedness of human, animal, and environmental health. This holistic approach ensures that AMR interventions address all potential sources of antibiotic resistance and promote a coordinated response across sectors. Eco-pharmacovigilance: eco-pharmacovigilance is a vital component in the fight against antimicrobial resistance, particularly in low-resource settings where the environmental impact of antibiotics can be more pronounced due to inadequate infrastructure and regulatory

oversight. By reducing environmental contamination, enhancing monitoring and surveillance, promoting the rational use of antibiotics, and fostering research and innovation, EPV can significantly contribute to mitigating AMR. Implementing EPV in low-resource settings requires concerted efforts in capacity building, community engagement, partnerships, and integration with broader health strategies. Through these measures, we can create a sustainable and effective response to the global challenge of AMR.

Artificial intelligence to combat AMR

Artificial Intelligence (AI) has emerged as a promising tool to combat AMR in low-resource settings, where the burden of AMR is particularly high. AI can address several challenges in AMR management, including:

1. *Early and accurate diagnosis*. AI-powered diagnostic tools can rapidly and accurately identify pathogens and determine their antibiotic susceptibility. This enables timely and targeted treatment, reducing the unnecessary use of broad-spectrum antibiotics that drive AMR. For example, AI-based algorithms can analyze microscopy images or genetic data to identify bacterial strains and predict their resistance profiles.
2. *Personalized treatment recommendations*. AI can leverage patient data, including clinical history, laboratory results, and local resistance patterns, to provide personalized treatment recommendations. This optimizes antibiotic selection, ensuring effective treatment while minimizing the risk of resistance development. AI-powered clinical decision support systems can assist healthcare providers in choosing the most appropriate antibiotics for individual patients.
3. *Surveillance and outbreak detection*. AI algorithms can analyze large datasets from various sources, including electronic health records, laboratory reports, and social media, to identify emerging resistance trends and detect outbreaks early. This enables the timely implementation of control measures, preventing the spread of resistant pathogens. AI-powered surveillance systems can also monitor antibiotic consumption patterns, identifying areas with overuse or misuse.
4. *Drug discovery and development*. AI can accelerate the discovery and development of new antibiotics by analysing large chemical libraries, predicting the activity of potential drugs, and optimizing their design. This can address the shortage of effective antibiotics and provide new treatment options for resistant infections. AI-powered platforms can also repurpose existing drugs for new indications, potentially offering faster solutions to AMR.
5. *Public health interventions*. AI can support public health interventions by identifying high-risk populations, predicting the spread of AMR, and evaluating the effectiveness of interventions. This can guide targeted interventions, such as vaccination campaigns or educational programs, to prevent the spread of resistant infections. AI-powered models can also simulate different scenarios to assess the impact of various interventions.

Challenges and considerations

While AI holds great promise for combating AMR in low-resource settings, several challenges need to be addressed:

- *Data availability and quality*. Access to high-quality and representative data is essential for training and validating AI algorithms. In low-resource settings, data collection and infrastructure may be limited, hindering the development and deployment of AI-powered tools.
- *Technical expertise and infrastructure*. Implementing AI-powered solutions requires technical expertise and infrastructure, which may be lacking in resource-constrained settings. Building local capacity and establishing partnerships with external organizations can help overcome these barriers.

- *Ethical and regulatory issues*. The use of AI in healthcare raises ethical and regulatory considerations such as data privacy, algorithm bias, and liability. Addressing these issues is crucial to ensure the responsible and equitable use of AI in AMR management.
- *Cost and sustainability*. The cost of developing and deploying AI-powered tools may be prohibitive for low-resource settings. Ensuring the affordability and sustainability of these solutions is essential for their widespread adoption.

AI has the potential to revolutionize the fight against AMR in low-resource settings. By improving diagnosis, treatment, surveillance, drug discovery, and public health interventions, AI can contribute to reducing the burden of AMR and saving lives. However, addressing the challenges and ensuring equitable access to these technologies is crucial for realizing the full potential of AI in combating AMR.

Conclusion

Antimicrobial resistance poses a major global health challenge, especially for low-resource settings. However, there are practical and innovative approaches to combat AMR, such as improved surveillance, infection prevention, optimized antimicrobial use, and education efforts. Integration of diagnostic stewardship, vaccination strategies, AI, One Health approaches, and eco-pharmacovigilance can further enhance the arsenal of tools. The global community must prioritize research and development tailored to low-resource settings, invest in capacity building, and strengthen international cooperation to address AMR effectively. Resistant pathogens know no borders, and combating AMR in resource-limited environments is crucial for global health security. By supporting these settings, we contribute to a safer and healthier world for all.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 29

Educational strategies for appropriate antimicrobial prescribing among healthcare providers in low- and middle-income countries

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Introduction

Strengthening competencies for appropriate antimicrobial prescribing in low- and middle-income countries (LMICs) is a major challenge. The burden of antimicrobial resistance (AMR) is greatest in LMICs. The comprehensive approach to the growing global problem of AMR has been through the development and implementation of national action plans (NAPs) to combat AMR. In 2019, the region of sub-Saharan Africa had the highest all-age mortality rates associated with bacterial AMR at 98.9 deaths per 100,000, followed by South Asia at 76.8.

A systematic review of awareness and education on AMR in 47 African countries found generally good knowledge among healthcare and veterinary care workers on AMR, but a lower appreciation of the drivers of AMR in day-to-day patient interactions and health systems management. One of the strategic gaps identified in a review of over 120 national action plans (NAPs) on AMR, including two-thirds from less developed countries, was the lack of context-appropriate and locally-driven strategies for appropriate health-providing behavior.

Thus, educational strategies that target the appropriate use of antimicrobial strategies in LMICs must be contextualized and recognize issues in LMICs such as limited human resources for healthcare, dearth of competency-based educational programs on AMR and antimicrobial stewardship (AMS), limited access to diagnostics and quality-assured antibiotics, weak regulatory policies and monitoring of over-the-counter purchase of antibiotics and self-medication, as well as heavy behavioral nudges and detailing from pharmaceutical companies, among others.

This chapter aims to review the range of practical educational approaches that may be applied in LMIC settings across various levels of health care. In keeping with the theme of this ebook, we focus on educational strategies for healthcare workers who have direct patient contact in hospital settings, specifically early and mid-career development and continuing professional education on strategies that build and shape their knowledge, attitudes, and practices related to antimicrobial prescribing. More importantly, we discuss these using contextual and cultural drivers in LMICs that can reinforce and sustain positive prescribing behavior and reduce inappropriate prescriptions.

Readers are referred to other chapters of this ebook for details on competency frameworks for AMR and other core elements of AMS programs such as infection prevention and control, surveillance, antibiotic access, and AMS governance.

Practical educational approaches to appropriate antimicrobial prescribing

Educational approaches for healthcare professionals in clinical practice cut across a range of complementary strategies, from traditional lectures and formative knowledge building to active behavioral feedback (**Figure 1**). These strategies can reinforce competencies needed for appropriate antimicrobial prescribing while mitigating potential negative influencers such as pressure from patients, peers, or pharmaceutical promotions. We describe below the most common practical approaches that have been used in various LMIC settings or have the potential to be applied based on a few studies. It should be noted that the context in which LMICs operate can range from basic primary healthcare facilities to advanced tertiary care hospitals, hence the context and health system backbone should always be considered in the choice of strategies.

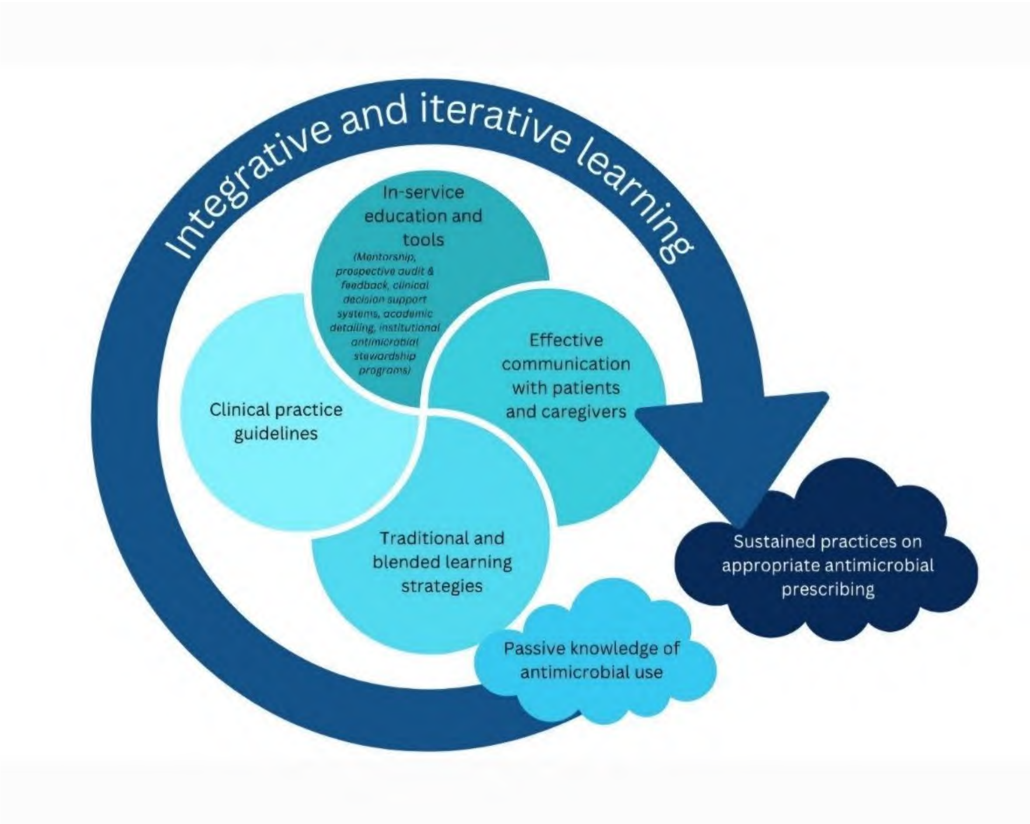

Figure 1. Practical learning approaches to improve antimicrobial prescribing.

Traditional and blended learning

AMS education should build a solid foundation of knowledge needed to support optimized antimicrobial prescribing, beginning with pre-service training of health providers and continuing professional education for practicing and prescribing physicians. AMS education includes information on the full spectrum of antimicrobials, mechanisms of action, development of AMR, core principles of diagnosis and management of infections, and most importantly, principles of appropriate antimicrobial prescribing.

Passive education techniques are modestly effective for increasing prescriber knowledge. These techniques include didactic large group activities, such as lectures, symposia, and webinars, as well as small group didactic workshops that are problem-based. In LMICs, these can be hosted by a variety of groups such as educational institutions, ministries of health, professional healthcare societies, multilateral international agencies such as the World Health Organization, and pharmaceutical companies. In resource-constrained settings, pharmaceutical companies may be frequently tapped for continuing education activities. In such cases, it is good practice for the resource persons and the hosting organization to disclose potential conflicts of interest and avoid inducements.

Online courses have become more available and accessible. In the Philippines, following the Department of Health (DOH) tagline "Education for Healthcare Workers Anytime, Anywhere," free AMS courses, which were conducted as in-person workshops pre-COVID, were shifted to an online platform called the DOH Academy. At a global scale, Massive Open Online Courses (MOOCs) have become more widely available and play a pivotal role in providing high-quality learning resources to a vast number of students, while recognizing different paces and styles of learning. For example, the first MOOC on AMR focuses on the role of diagnostics in the response to AMR, which responds to the need for diagnostic stewardship. First offered by the London School of Hygiene and Tropical Medicine in 2019, it was designed as a free, six-week course, requiring only up to four hours of learning per week, allowing learners to stop and start at their own pace. This MOOC attracted more than 10,000 learners and continues to be offered online.

Developing and localizing clinical practice guidelines

Evidence-based clinical practice guidelines (CPGs) have become important educational resources for healthcare providers who prescribe antibiotics. A review of AMS programs (ASPs) in LMICs found that the creation and availability of hospital guidelines and national guidelines have been identified as enablers in implementing ASPs. For the guidelines to be applicable in LMICs, the recommendations should take into account the local epidemiology and microbiology of the most common infections as well as the antimicrobial susceptibility patterns of etiologic agents. Local hospital antibiograms and national antimicrobial resistance surveillance programs, such as the annual reports of the Philippines DOH – Research Institute for Tropical Medicine Antimicrobial Resistance Surveillance Program of the Philippines, are important resources for guideline developers and AMS committees in determining local susceptibility rates, monitoring, and comparing antimicrobial resistance trends over time within institutions and across hospitals. Point prevalence surveys (PPS) on antimicrobial use can likewise inform the degree of appropriate uptake of prescribing guidelines.

In the Philippines, the DOH has authorized the creation of evidence-based CPGs on common infections such as community-acquired pneumonia, urinary tract infections, tuberculosis, HIV, and sepsis. Smartphone applications, such as the DOH – Philippine Society for Microbiology & Infectious Diseases National Antibiotic Guidelines app, a web-based mobile application, can be used at the point of care (POC).

Having a national quality policy that requires health facilities and health service organizations to provide ready access to updated evidence-based guidelines is a best practice that can be adapted in LMICs. Converting key recommendations into quality policy statements with key performance indicators will aid the governance and monitoring process on adherence to CPGs.

Guideline development needs to be accompanied by a carefully planned dissemination and implementation process. To inform implementation planning and promote uptake, it is essential to understand the existing culture and prescribing practices, the drivers affecting them, and any barriers to change. Guideline implementation and adherence can be facilitated through education, coupled with audit and feedback. Examples of support tools that can facilitate the update of CPGs are clinical pathways and AMS care bundles that document the indication for the prescribing decision and the rationale for deviating from the guideline.

In-service education and tools

Although traditional educational strategies as well as CPGs provide fundamental knowledge on appropriate antibiotic prescribing, behavior change interventions are more likely to bridge passive knowledge to real action. A systematic review of interventions to improve antibiotic use in LMICs demonstrated that behavioral change interventions incorporating education-based strategies had a positive impact on antibiotic use compared to structured training, enablement, or persuasion tactics. The educational approaches included face-to-face interactions and small group discussions involving interactive and learner-centered teaching, role play, and didactic and field-based training.

Mentorship also offers a more personalized approach to influencing behavioral change. It involves experienced and trusted practitioners serving as role models, teaching and counseling less experienced staff. While one-on-one mentorship is widely used in corporate settings and the field of education, its application in AMS, particularly in resource-limited settings, has not been well studied. Nevertheless, positive mentorship experiences in upper-middle- and high-income countries suggest that this approach may be applicable in LMIC settings where there is a complement of AMS-trained physicians and pharmacists who can set up the mentorship program.

One such example is the Mentored Quality Improvement Impact Program® of the American Society of Health-System Pharmacists. This seven-step mentoring process centered on self-assessments by mentees, continuing education activities, telephone calls, site visits, and, most importantly, mentoring sessions that included hospital administrators, pharmacy directors, and identified leaders, resulting in an action plan for the hospital. The post-mentoring survey demonstrated the significant role of experienced mentor teams–consisting of infectious diseases physicians and pharmacists–in providing valuable insights and guidance in establishing successful AMS programs. In South Africa, train-the-trainer mentorship programs for AMS have been key to expanding ASPs to resource-constrained areas in the country. These approaches to mentorship may be applicable in LMICs where NAPs for AMR have triggered and built the capacities for AMS, allowing integration of the mentorship program into the roles of specific AMS committee members.

Prospective audit and feedback (PAF), a core ASP strategy, generally requires a multidisciplinary team often comprised of a physician, a clinical pharmacist, and a microbiologist, or either of the latter two professionals. However, various healthcare professionals with adequate expertise and motivation can be trained optimally to perform AMS activities. In the one-step model, an AMS team member provides direct feedback during clinical rounds. In the more intensive two-step method, an AMS team member first reviews the cases from a specific ward or hospital unit. Subsequently, cases meeting the criteria for intervention are presented to a senior team member, who then communicates recommendations for treatment modification or discontinuation of antibiotics to the treating physician through written or direct verbal advice.

Although labor-intensive and time-consuming, PAF has been successful even in resource-limited countries. In a tertiary-level institution in India, multiple stakeholders spent a year developing their data record form, electronic system, and key intervention points before implementing a 6-month intervention phase. The key component of the intervention was rooted in PAF and various methods of stewardship were used, including on-site rounds, training of residents, policy for surgical prophylaxis, and referrals for tailoring of doses according to the patient's profile, among others. This interventional study showed a significant decline in double anaerobic coverage and a decrease in antibiotic consumption, measured through a defined daily dose. In another study in a private tertiary hospital in India, a two-year PAF program was implemented, and the AMS team reviewed 1,801 prescriptions. Of these, 12.5 percent were deemed unjustified and recommendations for antimicrobial de-escalation were accepted by 89 percent. A pharmacy-driven weekly PAF initiative in Ethiopia was also successful, and resulted in the discontinuation of 54 percent of antibiotics, with 96 percent compliance to the recommendations of the AMS team. However, the success of PAF interventions can be temporary. Cessation of audit-feedback activities in this same study was associated with immediate and sustained increases in antibiotic consumption, reflecting a rapid return to pre-intervention prescribing practice. As such, long-term commitment by multiple stakeholders and organization leadership is often needed for sustainable outcomes.

Clinical decision support systems (CDSS). To ensure the sustainability of AMS programs, it is critical that the younger generation of health professionals receive comprehensive training and develop a profound understanding of its significance. Consequently, ASPs must incorporate advanced technology-driven tools that align with contemporary learning styles. Leveraging technology can also address the shortage of infectious diseases specialists.

Electronic CDSS, including electronic health records and mobile apps, provide rapid access to information to help clinicians make appropriate therapeutic decisions. Data from resource-rich settings indicate that CDSS significantly impacts multiple AMS outcomes, including reducing antibiotic consumption, enhancing guideline adherence, and promoting de-escalation. However, the use of CDSS in LMICs remains limited due to factors such as a lack of structural frameworks and financial constraints.

A cluster randomized trial in a pediatric clinic in Tanzania demonstrated a significant reduction in antibiotic prescriptions when CDSS was combined with POC tests like C-reactive protein and pulse oximetry. Additionally, a pharmacist-led intervention in four African Commonwealth countries (Ghana, Tanzania, Uganda, and Zambia) included developing a mobile application to improve access to antimicrobial prescribing guidelines. A cross-sectional study evaluating healthcare providers' perspectives on this app found it useful for increasing AMS awareness, documenting antimicrobial indications and durations, and encouraging pharmacists and nurses to challenge inappropriate antimicrobial prescribing. However, the study did not assess whether these positive attitudes led to actual reductions in antimicrobial prescriptions.

Systematic reviews on CDSS highlight the diversity of these systems, each with a narrow scope of intervention, making impact evaluation challenging. Given the varying algorithms and diverse patient-physician contexts in LMICs, it is essential to have a better understanding of end-users' workflows and decision-making pathways, while considering cultural and socio-behavioral factors.

Academic detailing is defined as “a structured educational outreach program in which a trained health professional visits practicing health professionals in their practice settings to deliver tailored evidence-based information”. Despite its potential, there is little experience in academic detailing for improving antimicrobial prescribing behavior in LMICs. However, given the pervasiveness of pharmaceutical company detailing and other promotional activities for their products, the application of academic detailing in LMICs could be considered.

A study in Sudan of 20 health centers showed that PAF together with academic detailing significantly reduced the number of patient encounters with inappropriate antibiotics. On the other hand, a pilot randomized controlled trial of academic detailing for childhood management of diarrhea in Nepal showed a significant decrease in prescriptions for metronidazole and metronidazole-diloxanide furoate combination, but no effects on ciprofloxacin, norfloxacin, or nalidixic acid prescriptions.

Institutional AMS programs. Health facilities that have established ASPs can adopt one or more of the above educational strategies and tools into a bundle of educational interventions. These ASPs are transforming in-service training and continuing professional development through the adoption of more interactive small-group educational techniques, such as inter-professional team discussions, role-playing, case studies, audit and risk management meetings, and journal clubs.

The involvement of multidisciplinary teams in the ASP's educational activities is key to the success of an institution's ASP. For example, as part of its multi-pronged ASP, a tertiary-care hospital in the Philippines engaged ID specialists for its roadshows and lectures; ID fellows in training for PAF; and nurses and pharmacists as part of the persuasive interventions in the hospital wards. Overall, the combination of persuasive, restrictive, and structural components of the ASP resulted in significant improvements in indicators of antibiotic prescribing, based on data from PPS conducted every six months as part of the Global PPS.

Effective communication with patients and caregivers on appropriate antimicrobial use

For appropriate antimicrobial prescribing to be fully effective, healthcare providers also need training in communicating with patients to improve understanding and expectations regarding appropriate antimicrobial use. To effectively raise awareness and change behavior, information must be tailored to specific patient needs and communicated clearly in a manner that the patient can act on. The degree to which this patient-provider interaction promotes better understanding and informed decisions regarding antimicrobial use defines AMS health literacy. This concept also aligns with the WHO's people-centered approach to AMR, which aims to shift the focus from a purely biological issue to a more holistic, people-centered perspective.

However, reviews on AMS education for prescribers and non-prescribers lack sufficient details regarding the inclusion and implementation of communication training. Studies that cite such skills training have been patient-centered educational interventions performed in outpatient settings in high-income countries, underscoring the use of shared decision-making tools for enhancing provider-patient interaction. In LMIC settings, shared decision-making tools are lacking and require thoughtful integration of sociocultural, and economic considerations, and values of the patient and relatives. It should be noted that the passive distribution of educational leaflets without supportive face-to-face guidance by the trained provider has little impact on antimicrobial use.

Training on a combination of communication approaches may be more effective. In a cluster randomized controlled trial among outpatient departments of primary care hospitals in rural China, educational interventions included the following: interactive training sessions for doctors covering the use of evidence-based CPGs; communication skills and case study-based role plays; monthly peer review meetings; and provision of leaflets to parents or caregivers during consultations and an educational video in the waiting room. The intervention package reduced antibiotic prescriptions for childhood upper respiratory infections by 29 percent and decreased antibiotic costs. This supports a multifaceted approach that addresses communication between trained providers and patients (and caregivers) and promotes shared decision-making.

Challenges and research gaps

Despite the array of possible interventions that can be applied to improve antimicrobial prescribing in LMICs, there are many challenges that must be addressed to achieve significant and sustainable change. As **Figure 1** illustrates, there should be a systematically planned program of action where cumulative gains are achieved from multiple and complementary interventions. However, there are many constraints to implementation in LMICs, among them: lack of AMS champions within institutions; inadequate human resources and rapid turnover of trained staff; inadequate funding for the different interventions, including information and reminder systems; weak regulatory systems and access to quality antibiotics; and pervasive economic, social and cultural factors that reinforce antibiotic misuse.

Moreover, it should be noted that the evidence from LMIC settings on the effectiveness of the interventions reviewed in this chapter is lean, and many research gaps remain. **Table 1** outlines some of the issues and research gaps related to specific interventions.

Table 1. Selected issues and research gaps on specific interventions for improving antimicrobial use in LMICs.

Interventions	Challenges	Research gaps/needs
Knowledge building and strengthening strategies	• Generally passive learning; not automatically translated to appropriate antimicrobial prescribing	• Difficulty evaluating the effectiveness of individual interventions
Dissemination and use of CPGs, clinical pathways, and algorithms	• Infrequent updating of national CPGs • Inadequate dissemination and access to evidence-based localized updated guidelines	• Effectiveness of localized CPGs in reducing inappropriate antibiotic use • Monitoring adherence to CPGs in LMICs
Mentoring	• Lack of trained and skilled mentors	• Effectiveness of mentorship in various LMIC settings on appropriate antimicrobial use
Audit and feedback	• Requires specific training, dedicated time and resources • Voluntary nature of physician's acceptance of AMS team's recommendations may limit effectiveness	• More robust studies on effectiveness of PAF in LMICs
Clinical decision-support tools	• Requires funding for infrastructure and information systems • Needs customization to patient preferences and availability of diagnostic tests and antimicrobials	• Trials of affordable and improved CDSS in LMIC settings
Academic detailing	• Requires considerable human and financial resources and time • Needs adequate information systems	• Effectiveness in various LMIC settings

(cont.)

Table 1. Selected issues and research gaps on specific interventions for improving antimicrobial use in LMICs *(cont.)*

Interventions	Challenges	Research gaps/needs
Communication skills with patients and relatives	• Limited health literacy and prevailing misconceptions regarding antimicrobial use • Influence of cultural beliefs and practices on healthcare decisions • Widespread misinformation (through social media) and distrust of medical advice	• Assessment of effectiveness of current health literacy and communication interventions • Development and evaluation of communication strategies culturally tailored to diverse populations • Application of behavioral science to understand patients' decision-making

Abbreviations. AMS: antimicrobial stewardship, CDSS: clinical decision support systems, CPGs: clinical practice guidelines, LMICs: low- and middle-income countries, PAF: prospective audit and feedback.

A discussion on challenges and research gaps is not complete without considering the role of diagnostic stewardship in appropriate antimicrobial prescribing behavior. In LMICs, gaps in diagnostic stewardship education at pre-service and in-service levels are significant. In particular, few training programs integrate AMS principles with practical diagnostic skills, which are essential for accurately interpreting complex test results. Another critical gap is the development and validation of cost-effective POC tests tailored to the resource constraints of LMICs, as current technologies are often too expensive or complex.

Finally, research should examine the role of international partnerships in providing the necessary resources, expertise, and regulatory support to implement effective ASPs, including diagnostic stewardship programs. Addressing these gaps is crucial for developing comprehensive educational strategies to improve antimicrobial prescribing and combat AMR in LMICs.

Conclusion

Health professionals in LMICs play a significant role in combating AMR by implementing a program of multiple, often and multidisciplinary interventions to improve antimicrobial use. The evidence of the effectiveness of these interventions is still limited to mostly observational studies in a few LMICs and high-middle-income countries. In designing educational programs in LMICs, implementation research and evaluation should also be integrated so that local and tailor-fit solutions to the global problem of AMR can be built and sustained.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 30

Promoting cross-regional collaboration in antimicrobial stewardship

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Introduction

Antimicrobial resistance (AMR) is an unavoidable evolutionary step in the life cycle of all living pathogens, that tends to be amplified by increasing exposure to these agents in health care, agriculture, and the environment. The spread of resistant bacteria is exacerbated by globalization and travel, easy access to poor quality over-the-counter antibiotics in many countries, increasing numbers of private healthcare facilities that operate without clinical governance, limited access to new safe and effective antibiotics, lack of structured undergraduate and post-graduate education curricula on AMR and antimicrobial stewardship (AMS) and ineffective or even non-existing AMS programs in many healthcare systems. Other contributors to AMR spread are poor infection control measures, lack of clean water and sanitation and poor laboratory diagnostics.

AMR is a global problem that needs global solutions. With this alarming increase in AMR rates and the development of very few antimicrobials, it is essential to prescribe antimicrobials only when truly necessary. AMS is important in this effort as it focuses on optimizing the use of antimicrobials, reducing unnecessary prescriptions, and preventing the further spread of resistance without compromising clinical outcomes. These principles are not only limited to human health but are also important in the animal and agriculture sectors. While many countries have incorporated AMS as a key pillar in their national action plans to combat AMR, achieving measurable impacts requires more than just national initiatives. Effective AMS demands a coordinated and collaborative approach not only at the national level but extends at regional and global levels.

There are both similarities and differences in how the regions tackle AMR, which significantly tend to impact the effective control and the speed of the spread of resistance. In fact, current challenges faced by countries within a region reflect those related to cross-sector collaborations, particularly between the animal and health sectors. Population migration, globalization, and trade may create unique challenges in some regions that require the development of specific interventions and guidelines based on global standards and practices.

This chapter explores existing global and national AMS activities, highlighting the best interventions that can be implemented across different regions and opportunities for cross-regional collaboration.

AMS in global action plan on antimicrobial resistance

In 2015 World Health Assembly (WHA) adopted a global action plan on antimicrobial resistance (**Figure 1**), which focuses on five key actions: 1) To improve awareness of AMR through education and training, 2)To strengthen knowledge of AMR through research and surveillance, 3)To reduce the incidence of infection through effective infection control measures and sanitation, 4) To ensure sustainable investment in fighting against AMR that addresses the need of all countries and 5) To optimize the use of antimicrobial agents in human and animal health.

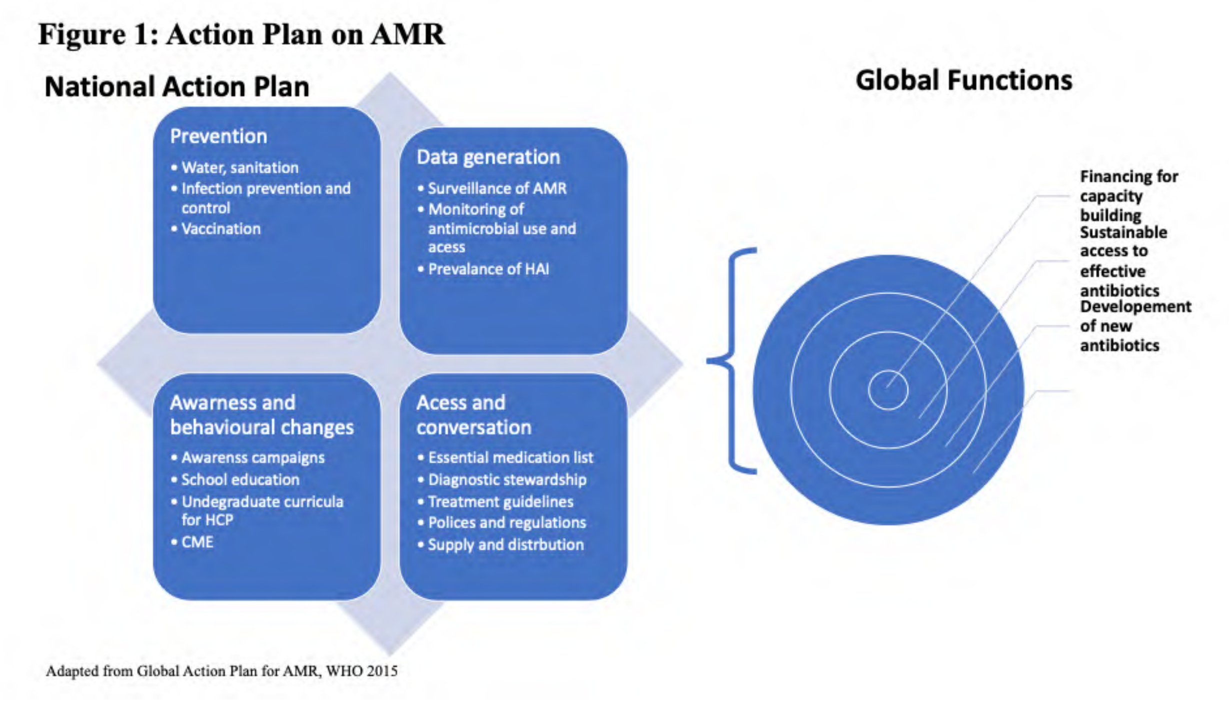

Figure 1. Action plan on AMR (Adapted from World Health Organization. 2015).
Abbreviations. AMR: antimicrobial resistance, HAI: healthcare-associated infection. HCP: healthcare professionals, CME: continuing medical education.

The last key action emphasizes the implementation of AMS programs are designed to promote the optimization of antimicrobial use by international standards. The goals include ensuring the “correct choice of medicine at the right dose based on evidence", and fostering effective collaboration with regional and international partners across multiple sectors including animal and human health. Additionally, the plan focuses on actions to guarantee affordable and equitable access to antimicrobials for those in need.

The 2015 WHA was followed by the commitment of member states in the 2016 political declaration of the high-level meeting of the United Nations General Assembly on AMR requesting the Quadripartite (World Health Organization (WHO), Food and Agriculture Organization of the United Nations (FAO), World Organization for Animal Health (WOAH)) and United Nations Environment Programme (UNEP), to scale up activities through a 'One Health' approach and to engage all relevant stakeholders, while strengthening sector-specific responses. 'One Health' issue that cannot be addressed within one sector but requires an 'all-out effort' and 'whole-of-society engagement'. The "One Health" integrates data collection, analysis, and information sharing among human health, animal and marine health, food safety, agriculture, and environmental sectors. This is supported by the establishment of laboratories with diagnostic ability to detect antimicrobial resistance to mitigate the spread of AMR. Members of the assembly emphasized the need for countries to create a national action plan that prioritizes these key actions while adapting to local circumstances and resources.

A significant milestone in the global collaborative effort to combat AMR was the release of the "Muscat Manifesto" during the Third Global Ministerial Conference on Antimicrobial Resistance in November 2022, held in Oman. This manifesto aims to accelerate "One Health" actions on antimicrobial resistance. Representatives from over 40 countries around the world who are experts in the field of human, animal, and environmental health are committed to several critical goals which include reviewing and updating AMR National Action Plans (NAPs) with the involvement of all relevant stakeholders through 'One Health' framework; thus, strengthening national, regional, and global surveillance systems by improving data management; and reducing overall antimicrobial consumption in different sectors. To support these efforts, three global targets are set to be achieved by 2030: a 30-50% reduction in total antimicrobial use within the agri-food sector, the elimination of medically important antimicrobials for human medicine in animals for non-veterinary medical purposes and in crop production and agri-food systems for non-phytosanitary purposes and ensuring that ACCESS group antibiotics account for at least 60% of overall antibiotic consumption in human.

ACCESS antibiotics are selected based on the WHO Model list of essential medicines and the AWaRe classification of antibiotics. ACCESS antibiotics have a narrow spectrum of activity. They typically have fewer side effects, lower risk of promoting antimicrobial resistance and lower cost. These antibiotics are recommended for the empiric treatment of common infections and should be widely accessible to ensure effective management of infections in the general population.

Other global initiatives on AMS outlined in **Table 1** are available and considered useful tools for international and cross-regional collaboration.

Table 1. Global initiatives on AMS (Modified from: Wernli D, et al. 2022)

Initiatives for AMS	Year	Activities
Alliance for the Prudent Use of Antibiotics (APUA)	1981	A major platform exchange, and facilitator of multi-sectorial actions, from education to advocacy, targeting the lay population as well as health care workers and politicians
ReAct	2005	A global catalyst, advocating and stimulating for global engagement on AMR by collaborating with a broad range of organizations, individuals and stakeholder
The Global Antibiotic Resistance Partnership (GARP)	2009	Collaborative platform for developing actionable policy proposals on AMR
United Nation declaration of the high-level meeting of the General Assembly on AMR	2016	Nation leaders from all over the world committed to fighting AMR together
Conscience of Antimicrobial Resistance Accountability (CARA)	2016	To monitor what is done to preserve the effectiveness of antibiotics in every country on Earth
Third High-Level Ministerial Conference on AMR	2022	Muscat Manifesto that showcased international commitments to accelerate One Health Actions on AMR in 47 countries

AMS in AMR National Action Plan

Many countries worldwide have developed an Antimicrobial Resistance National Action Plan (NAP) to combat the growing threat of AMR (**Figure 1**). These NAPs serve as a comprehensive, cross-sectoral policy framework designed to curb the spread of antimicrobial resistance (AMR) within each country. They emphasize a coordinated national response engaging various sectors and stakeholders by following five key objectives rooted in the 'One Health' approach:

1) Reduce the spread of antimicrobial resistance, 2) Minimize the negative impact on patient outcomes, 3) Establish a robust surveillance system to monitor AMR trends, 4) Promote rational use of antimicrobial agents across healthcare and veterinary settings and, 5) Promote research on the detection of AMR and the optimal use of antimicrobials

On a national level, enabling AMS requires robust governance and coordination for AMS activities, along with the establishment of national guidelines and standards across both animal and human health sectors. Access to high-quality assured antimicrobials, diagnostics, and vaccines is essential as well as, strict regulation of non-prescription antimicrobials use in private sectors. Additionally, the implementation of an effective local system for surveillance and monitoring is important. The stakeholders are responsible for promoting awareness, education, and training to support AMS activities. Concurrently, other efforts include water and sanitation hygiene (WASH) initiatives, proper infection control and prevention measures, and wide-scale vaccination programs (**Figure 1**).

A prime example of a national-level initiative in combating AMR is Qatar's implementation of AMS programs which was mandated across governmental hospitals in 2017 as part of national medication management policy, aligned with the Joint Commission Accreditation Standards. This initiative was led by Hamad Medical Corporation which oversees all government hospitals in Qatar and is aligned with the Qatar National Health Strategy 2018-2022. All facilities across HMC report at a national level certain key performance indicators such as antibiotics consumption which is measured using a daily defined dose per 1000 patients' day measured every month. Studies conducted in Qatar demonstrated that AMS programs have achieved significant milestones including reducing antimicrobial utilization, lowering associated costs with antimicrobial use, and improving timely administration and appropriate discontinuation of antibiotics especially for surgical prophylaxis. One of the main pillars of the AMS program in Qatar is formulary restriction where all prescribed restricted antimicrobials need infectious disease team approval within 48 hours of prescribing. Other interventions include the hard stop of restricted antimicrobials after 48 hours by the pharmacy, prospective data collecting, the analysis of clinical interventions and feedback to prescribers, and the conversion of IV to oral antimicrobials. The studies also highlighted areas for improvement including enhanced IT support and dedicated financial resources to support AMS activities.

Qatar has also demonstrated the capacity to support the global action plan on AMR by improving awareness and understanding of AMR. This includes the observance of World Antimicrobial Awareness Week, held annually from November 18th to 24th. Additionally, Qatar has also taken further steps to raise awareness about AMR, including educating healthcare professionals, strengthening antimicrobial stewardship programs in healthcare facilities, promoting vigilant antimicrobial use, engaging patients on the importance of medication adherence, and enhancing surveillance systems to monitor resistance patterns.

To further strengthen the AMS efforts, the Ministry of Public Health in Qatar in collaboration with the WHO regional office for the eastern Mediterranean has initiated additional measures. These include developing and utilizing antimicrobial consumption data to inform policymaking and improving regional collaborations to ensure effective implementation of AMS across the healthcare sector. This example from Qatar illustrates the importance of coordinated national efforts and the critical role of regional and global partnerships in addressing the challenge of AMR.

To establish successful cross-regional collaboration in AMS activities, it is important to recognize the differences in the AMS program implementation between low- and income middle-income countries (LMIC) compared to high-income countries (HIC). In many LMICs, there is often a lack of strong governmental and political commitment to prioritize AMS initiatives and provide adequate funding. Formal AMS, infection prevention and control (IPC) programs and microbiological services are significantly less prevalent in LMIC and face challenges like high patient loads and inadequate human resources. Additionally, access to antimicrobials including WHO Access, Watch and Reserve antibiotics is limited in LMIC. This underscores the critical need to balance enhancing access to antimicrobials and preventing their overuse, especially because recent data have shown a 77% increase in antibiotic use in LMIC. Procurement of antibiotics is highly heterogeneous in many LMIC, and they are often available without a prescription. In addition, LMIC lacks national electronic surveillance systems for tracking AMR and antimicrobial consumption (AC), both of which are key elements of AMS. The most common IPC intervention in both LMIC and HIC settings is hand hygiene promotion, however, hospitals in LMIC often face limitations in access to clean water for handwashing or alcohol-based hand sanitizers. Similarly, regular training on IPC practices and antimicrobial prescribing is limited in LMIC facilities. These differences highlight the need for a multi-faceted approach to strengthening healthcare systems in LMIC, to improving access to diagnostics, enhancing education and training, and establishing robust regulatory frameworks to support sustainable AMS implementation. The diversity of healthcare systems in LMICs necessitates that AMS programs be carefully tailored to address local needs and challenges. Despite the need for such tailored programs, international collaborations remain crucial. This collaboration can take various forms, such as adapting successful AMS models from HIC to LMIC or sharing high-quality policies and educational resources that can be implemented in various contexts worldwide.

To bridge the gap between AMS programs across the regions it is pivotal to foster collaborations, learn from successful interventions, and share best practices in the approach towards proper use of antimicrobials. Some of these interventions that can be standardized and widely implemented across the regions are discussed below.

Legislation for antibiotics consumption

The existence of legislation prohibiting the sale of antibiotics without prescriptions is an important step toward promoting responsible antimicrobial use that should be standardized to be adopted by all countries across the regions. The role of the MOH in monitoring and enforcing these regulations is crucial for ensuring compliance and safeguarding the public. Furthermore, countries should work on increasing awareness among healthcare providers and the general public of these regulations through conducting targeted educational campaigns and training programs.

Surveillance data for reporting antibiotic use

Establishing a standardized system for collecting and reporting antimicrobial consumption data would provide valuable insights into the patterns and trends of antimicrobial use, enabling more targeted interventions to avoid the overuse of antibiotics. Similarly, the establishment of a national cumulative antibiogram of the susceptibility patterns of common pathogens to various antibiotics nationally and regionally would be beneficial.

Regional policies and treatment guidelines

The publication of regional treatment guidelines for empiric treatment of common bacterial and fungal infections and common infections such as community-acquired pneumonia is an important opportunity for collaboration across the regions. These guidelines provide healthcare professionals with evidence-based recommendations for appropriate antimicrobial therapy, promoting optimal treatment outcomes and reducing the misuse of antibiotics.

Awareness campaigns for healthcare professionals and the public

Regional collaboration to develop targeted educational initiatives and AMS messages directed to healthcare professionals and the general public is important. Countries within the regions with similar health systems can collaborate to develop AMS campaign messages, formal educational programs and online courses that will promote awareness throughout the region. Examples of cross-regional online training programs on AMS are the Clinical Antibiotic Stewardship for South Africa and the Clinical Antibiotic Stewardship for Middle East in collaboration with The British Society for Antimicrobial Chemotherapy.

Effective establishment of cross-regional collaboration necessitates a deep understanding of similarities and disparities among countries within and across the regions. This can be achieved through collaborative research initiatives. By gathering data and insights, stakeholders can identify common challenges and opportunities, thus facilitating effective partnerships and knowledge sharing across the regions.

An example of regional collaboration in AMS research from the Arab world

Experts in microbiology, infectious disease, and ICU intensive care units from Arab countries of the Middle East developed an online survey. The survey was completed by around 122 physicians and included 39 multiple-choice questions covering topics such as understanding of the epidemiology, preferred treatment options for common infections, choice of antimicrobial agents for combination therapy, length of treatment, selection of empiric therapy, common factors contributing to AMR, and availability and structure of AMS programs.

The identified key AMS initiatives (**Figure 2**) that can be implemented across the region and provide recommendations for potential collaborative activities in the Middle East are mentioned below. These initiatives aim to strengthen the collective response to AMR in the Arab World by improving data collection, fostering collaboration, and ensuring research efforts are aligned with global standards.

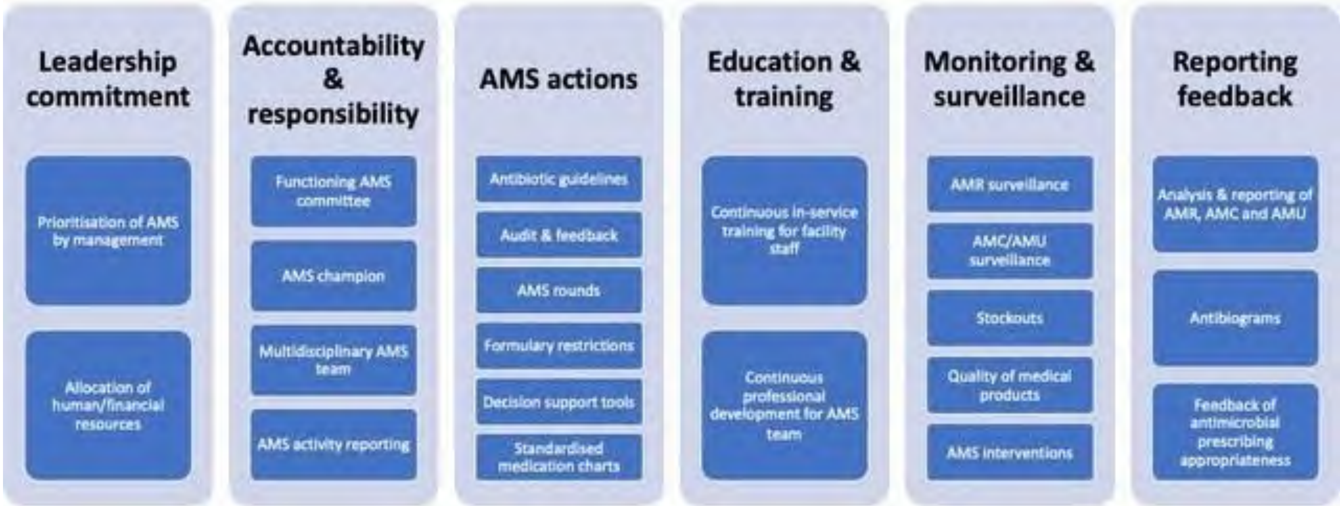

Figure 2. Key health-care facility antimicrobial stewardship (AMS) interventions
(Adapted with permission Al Salman J, et al. 2021).

1. *Training and education*

- To develop targeted training in AMR and AMS that focuses on training IT support staff, laboratory personnel, and healthcare workers.
- Involve media to promote the responsible use of antimicrobials.
- Utilizes global educational resources such as
  - e-Bug. Offer free online educational materials for teachers, and students, including interactive lesson plans, complimentary games, and quizzes. https://e-bug.eu/.
  - MUFASA. A multidisciplinary French course on AMS in Africa by Foundation Mérieux, and the French Society of Infectious Diseases, SPILF). http://www.diu- antibio.org.
  - BSAC resources. The British Society for Antimicrobial Chemotherapy provides various educational materials related to AMS. http://bsac- jac- amr.com/jac- amr- resources/.

2. *Capacity building*

- Continuous medical education. Implement Continuing Professional Development (CPD) focused on AMR and ASP for healthcare professionals (HCP).
- Undergraduate training for HCP. Incorporate AMR and ASP into undergraduate medical education.
- Online learning. Develop online courses to broaden access to training and share educational resources with minimal cost.
- WHO collaboration. Partner with the WHO and other international organization to promote AMR awareness and education.

3. *Infrastructure strengthening and support*

- Enhanced data system. Investments in technology, such as electronic health records (EHR), can lead to long-term savings and improved patient management and data accuracy.

- Consistent monitoring. Ensure uniformity in data collection and analysis across the region.
- Budget efficiency. Optimize budget allocation for AMS initiatives. Encourage efficient use of budgets to ensure that healthcare services are effective and sustainable.
- Governance adaptability. Develop flexible governance structures to support ASP implementation. This should align with available resources to ensure that the infrastructure can evolve with changing healthcare needs.
- Drug registration. Streamline the acquisition and rapid registration in the region for new drugs that are developed for multidrug-resistant organisms (MDROs).
- Molecular testing. Introduce rapid molecular tests for detecting MDROs. These tests can facilitate timely diagnosis and treatment, ultimately improving patient outcomes.

4. *Improving regional surveillance*

- National surveillance system. Establish and maintain robust national surveillance systems to monitor AMR rates and antimicrobial use across different countries in the region. This data is essential for informed decision-making and policy development.
- Standardized categorization. Ensure consistency in the categorization of resistance and surveillance techniques to enable comparability of data across the regions. This will enhance the reliability of findings and facilitate regional cooperation.
- Regional database. Create a central database that consolidates AMR data from various countries. This database will support regional data analysis and strategic development, allowing for a comprehensive understanding of AMR trends.
- GLASS reporting. Encourage enrollment in the Global Antimicrobial Resistance Surveillance System (GLASS) and improve adherence to its principles. Enhanced reporting will provide valuable insights into AMR patterns and facilitate international comparisons. It is important to ensure the regular and timely publication of AMR reports. This transparency and accessibility of data are vital for monitoring the AMR situation.

5. *Enhancing regional and international collaborative research*

- Focused research. Conduct comprehensive research to provide insights into AMR rates across the region. This involves gathering data from various healthcare settings to understand the prevalence and patterns of resistance.
- Point prevalence studies. Utilize cross-sectional and longitudinal studies to collect point prevalence data on resistance and antibiotic use. This will help in monitoring trends over time and identifying critical areas needing intervention
- Professional collaboration. Foster collaboration between healthcare professionals, researchers, and government bodies to facilitate regional and international research efforts. This can include joint studies, shared resources, and coordinated responses to AMR challenges.

Cross-regional collaboration for AMS may face some challenges. Differences in healthcare systems, policies, and practices across regions can limit the consistent implementation of AMS guidelines and pose barriers to cooperation. Some of the key challenges identified are:

1. *Inter-sector collaboration*

Effective AMS requires collaboration with the health agriculture and environmental sectors. However, establishing these collaborative frameworks can be difficult due to differing priorities and operational practices among different sectors.

2. *Developing universal guidance for countries*
   There is a need for guidance tailored to the specific contexts of the region, based on international practices and standards. This requires a comprehensive understanding of local healthcare systems, practices, and challenges. The capacity of individual nations to address these challenges may differ considerably. Solutions and actions need to appreciate intra-regional variation in MDRO management.
3. *Population dynamics within the regions*
   The movement of populations, including migrants and travelers, can complicate the spread of antimicrobial resistance (AMR). Diverse health needs and varying levels of access to healthcare among these populations necessitate adaptable AMS strategies.
4. *Resources and funding*
   Countries in the region may face challenges related to insufficient funding for AMS initiatives. Competing health priorities often divert resources away from AMS, making it difficult to implement effective programs
5. *Cultural and social factors*
   Cultural attitudes towards diseases and treatment can influence adherence to therapy and the effectiveness of AMS initiatives. Understanding and addressing these cultural factors is crucial for promoting responsible antimicrobial use.
6. *Political instability*
   Ongoing conflicts and civil unrest in some regions destabilize healthcare systems, leading to the displacement of populations and creating vulnerable groups with unique healthcare needs. This complicates the implementation of AMS programs and requires tailored approaches to address the specific challenges faced in conflict-affected regions.
7. *Antibiotic consumption in the animal sector and environment*
   The use of antibiotics in the animal sector and environmental contamination can contribute to the spread of AMR., It is essential to adopt integrated approaches that link agricultural practices, environmental health, and human health initiatives to effectively tackle these challenges.

Addressing these challenges necessitates a coordinated effort among governments, healthcare providers, and international organizations to develop context-specific AMS strategies that are considerate to the unique social, economic, and political landscapes of different regions.

Conclusion

Despite the need to individually tailor AMS programs, cross-regional collaborations remain highly valuable. Cross-regional collaboration can save time and resources by avoiding duplication of efforts across different settings. Collaboration facilitates the exchange of knowledge, best practices, skills and initiatives among colleagues which can enhance the effectiveness of AMS programs. By addressing the strengths and resources of HIC and LMIC we can create the most adaptable AMS programs that will address the unique challenges faced by different regions. Thus, regions can benefit from each other’s successes and failures, fostering a culture of continuous improvement. Collaborative efforts can also enforce existing policies and systems related to AMS. Cross-regional surveillance data can be shared to improve understanding and management of

AMR. Standardization of laboratory services enhances the laboratory's capacity for monitoring antibiotic resistance and can lead to better data and informed decision-making. Global implementation of AMS interventions helps to reduce the spread of MDROs. One Health Approach which integrates the role of prescribers, patients, animals, and the environment, is crucial for comprehensive AMS strategies. Collaboration can promote the development and use of tools such as vaccines, strengthen infection control measures and improve sanitation to reduce the burden of AMR. Ultimately these efforts can aid in improving healthcare systems and enhancing patient care, thus contributing to a successful global response to AMR. Implementing these interventions is a key component towards an effective "One Health" approach regionally and globally.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 31

Artificial intelligence in controlling antimicrobial resistance

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Introduction

The realisation that computers can perform certain cognitive activities better than humans is not new (the Sumerian abacus arrived circa 2500 BCE). However, all past technologies were essentially "tools," utilised by humans to make our work and lives easier, or as a type of cognitive prosthetic that enabled us to complete otherwise impossible or inefficient activities. Newer artificial intelligence (AI) technologies now have the potential to go beyond the concept of a "tool" by enabling not only the execution of human-led or human-defined tasks but also the generation of new knowledge and new methods of making sense of the world. Antimicrobial resistance (AMR) has emerged as one of the most pressing global health challenges of the 21st century.

As pathogens evolve to resist existing antibiotics, the efficacy of our medical arsenal diminishes, threatening to return us to a pre-antibiotic era. One key area where AI has shown promise is in the analysis of large, complex datasets related to antibiotic resistance, enabling the identification of patterns, trends and risk factors that can inform public health strategies. By leveraging advanced data analytics and machine learning-techniques, AI-powered systems can uncover insights that may have been previously obscured, providing a more comprehensive understanding of the drivers and dynamics of antimicrobial resistance. This article explores the various applications of AI in combating AMR, from drug discovery to antimicrobial stewardship, and examines the challenges and future prospects of this technological integration in healthcare.

How do we start understanding artificial intelligence? We are already aware that artificial intelligence (AI) holds significant promise in combating antimicrobial resistance (AMR), a critical global health challenge. Here are some key areas where AI is making an impact:

Drug Discovery. AI accelerates the identification of new antimicrobial compounds by analysing vast datasets to predict potential candidates.

Antimicrobial Stewardship. AI helps optimize antibiotic use by providing clinical decision support, ensuring the right drug is used at the right time and dose.

Surveillance. AI enhances AMR surveillance by analysing trends and patterns in resistance data, enabling timely interventions
Diagnostics. AI-powered tools can rapidly detect antibiotic resistance, significantly reducing the time needed for susceptibility testing
Predictive Modelling. AI models predict the spread of resistance, helping in planning and implementing effective control measures.

Background on AMR

Antimicrobial resistance occurs when microorganisms such as bacteria, viruses, fungi, and parasites evolve to become less susceptible to antimicrobial drugs. This natural process has been accelerated by the overuse and misuse of antibiotics in healthcare and agriculture. The World Health Organization (WHO) has declared AMR as one of the top ten global public health threats facing humanity.
The mechanisms of AMR are diverse, including genetic mutations, horizontal gene transfer, and the formation of biofilms. These processes allow pathogens to develop resistance through various means such as drug inactivation, target site modification, and efflux pumps that expel antibiotics from bacterial cells.
The global impact of AMR is staggering. It is estimated that by 2050, AMR could cause 10 million deaths annually and result in a cumulative cost of $100 trillion to the global economy. This crisis affects all countries, regardless of their level of economic development, making it a truly global challenge that requires innovative solutions.

Overview of AI technologies relevant to AMR control

Artificial intelligence, particularly machine learning and deep learning offers powerful tools for addressing the complexities of AMR. These technologies can process vast amounts of data, identify patterns, and make predictions that would be impossible for humans to achieve manually.

Machine Learning (ML). ML algorithms can analyze large datasets to identify patterns and make predictions. In the context of AMR, ML can be used to predict antibiotic resistance patterns, optimize treatment regimens, and identify potential new antibiotics.

Deep Learning (DL). A subset of ML, DL uses artificial neural networks to model complex relationships in data. DL has shown promise in areas such as image recognition for rapid diagnosis and in modelling the 3D structures of proteins for drug discovery.

Natural Language Processing (NLP). NLP techniques can extract relevant information from medical literature, electronic health records, and other textual sources to support clinical decision-making and research in AMR.
Other AI techniques, such as reinforcement learning and evolutionary algorithms, also have potential applications in optimizing antibiotic use and developing new antimicrobial strategies.

Applications of AI in controlling AMR

Artificial intelligence (AI) plays a transformative role in diagnosing antimicrobial resistance (AMR) by enhancing the speed and accuracy of microbial diagnostics. AI systems, such as those utilizing machine learning algorithms, can analyze complex datasets, improving the identification of AMR patterns and susceptibility assessments in clinical settings. Moreover, AI contributes to antimicrobial stewardship programs by predicting inappropriate prescribing practices and optimizing antibiotic therapy choices, with performance metrics indicating significant predictive capabilities (**Table 1A** and **Table 1B**). The integration of nature-inspired intelligence further enhances genomic diagnostics, allowing for the identification of resistance-conferring mechanisms through advanced bioinformatics techniques. Despite ethical concerns regarding data integrity and biases, the overall impact of AI in AMR diagnosis is promising, offering robust solutions to a critical public health challenge.

Table 1A. Examples of artificial intelligence applications to address antimicrobial resistance.

Domain	AI techniques used	Examples	Utility
Diagnostics	ML-based algorithms	ML-assisted AST (Flow-cytometry AST, IR Spectrometry) BiotyperCA for MALDI-TOF MS	Improved turnaround time with accuracy to facilitate appropriate antimicrobial use
Predictive modelling	ML algorithm (XGBoost)	AMR from the patient's blood and urine	Risk assessment
	ML	Carbapenem resistance from electronic health records	Negative predictive value 99% (AUROC 0.846)
	Random Forest Multilayer perceptron, J48 ML algorithms (LR, k-NN, DT, RF, MLP)	Multidrug-resistant infections in ICU	Variable accuracy with better infection control
	Recursive partitioning, DT	Predictive AST from blood cultures	PPV 0.908 NPV 0.919
	ML	Epistatic interaction over rpoB gene among mycobacteria, *Pseudomonassp* and *Staphylococcussp*.	Judicious use of rifampicin
	DT, Gradient Boosting Machine (GBM)	DeepARG	Prediction of antimicrobial resistance genes from metagenomic data
Real-time monitoring	Supervised ML e.g. Auto-WEKA, multilayer perceptron, decision tree, SimpleLogistic, Bagging, AdaBoost	Surgical antimicrobial prophylaxis monitoring	Better identification of surgical prophylaxis appropriateness

Abbreviations. AI: Artificial Intelligence, AMR: Antimicrobial Resistance, AST: Antimicrobial Susceptibility Testing, AUROC: Area Under the Receiver Operating Characteristics, DT: Decision Tree, ICU: Intensive Care Unit, k-NN: k-Nearest Neighbours, LR: Logistic Regression, ML: Machine Learning. MLP: Multi-Layer Perceptron, NPV: Negative Predictive Value, PPV: Positive Predictive Value, RF: Random Forest, WEKA: Waikato Environment for Knowledge Analysis.

Table 1B. Examples of artificial intelligence applications to address antimicrobial resistance.

Domain	AI techniques used	Examples	Utility
Decision support systems	Decision tree algorithm	Antibiotic prescription for rhinosinusitis through RHINA	Reduce over-prescription of antibiotics
	Adaptive boosting, gradient boosting, RF, SVM, K-NN	Antibiotic prescription for admitted patients based on AST	Judicious use of antibiotics
	ML-assisted CDSS	Antibiotic use for complicated upper urinary tract infections	Advocated for 3rd generation cephalosporins over fluoroquinolones
Drug discovery	Joker algorithm	Generation of novel antimicrobial peptides (AMPs) e.g. PaDBS1R6 and EcDBS1R6 against *Pseudomonas* sp. and *Klebsiella* sp.	Disrupts both Gram-positive and Gram-negative bacterial membranes with promiscuity (versatility and diversity)
	Blackbox algorithm	Testing AMPs from a robust database and refining the model	Prioritizes precision and rationality in optimizing antimicrobial activity and selectivity
Targeted antimicrobial stewardship	Extreme Gradient Boosting (XGB), Logistic regression (LR), k-NN, Support Vector Machine (SVM), Multilayer Perceptron	Prescription pattern analysis, targeted education, practice-improving interventions, Telemedicine-alignment	Reduction of antibiotic use, medication discontinuation aligning with clinical intuition
	Logistic regression	Antibiotic use for Gram-negative bloodstream infections in ICU	Antibiotic de-escalation (29 *vs.* 21%; OR = 1.77; 95% CI, 1.09–2.87; p=0.02)
	ML	Mathematical pharmacodynamic model for treating carbapenem-resistant *Acinetobacter baumannii* infections	Source control and optimization of antibiotic dosing strategy
One Health	ML-assisted geographic information system (GIS)	Exposome-related dataset analysis to address AMR	Insight into plasmid-mediated and other ways of AMR gene transmission through the food chain
	Named Entity Recognition (NER) model	NLP-based information extraction	Capacity development and science-informed policy solutions to AMR in low-income countries

Abbreviations. AI: Artificial Intelligence, AMP: Antimicrobial Peptide, AMR: Antimicrobial Resistance, AST: Antimicrobial Susceptibility Testing, AUROC: Area Under the Receiver Operating Characteristics, CDSS: Clinical Decision Support System, CI: Confidence Interval, DT: Decision Tree, GIS: Geographic Information System, ICU: Intensive Care Unit, k-NN: k-Nearest Neighbours, LR: Logistic Regression, ML: Machine Learning. MLP: Multi-Layer Perceptron, NER: Named Entity Recognition, NPV: Negative Predictive Value, OR: Odds Ratio, PPV: Positive Predictive Value, RF: Random Forest, SVM: Support Vector Machine.

Drug discovery and development

AI is revolutionizing the drug discovery process for new antibiotics. Traditional methods of antibiotic discovery are time-consuming and costly, with diminishing returns. AI can significantly accelerate this process by:

- Screening vast chemical libraries to identify potential antibiotic candidates.

- Predicting the efficacy and toxicity of compounds before laboratory testing.
- Designing novel molecules with specific properties to combat resistant pathogens.

For example, in 2020, researchers used a deep learning model to identify a novel antibiotic, halicin, which showed activity against a wide range of bacteria, including some antibiotic-resistant strains.

Furthermore, AI-driven approaches in antimicrobial peptide (AMP) discovery enable the identification of new candidates with desirable properties, providing alternatives to conventional antibiotics.

Antimicrobial stewardship

AI can enhance antimicrobial stewardship programs by:

- Analysing patient data to optimize antibiotic prescriptions.
- Predicting which patients are at higher risk of developing resistant infections.
- Analysing prescription patterns and anomaly identification.
- Monitoring antibiotic use patterns to identify areas for intervention.
- Targeted education.
- Aligning stewardship practices with telemedicine platforms.

These applications can help reduce unnecessary antibiotic use, a key factor in slowing the development of AMR. Also, the vulnerabilities during the transition of drug administration can be avoided. A systematic review explored various AI-driven antimicrobial stewardship initiatives exhibiting the easy and flexible alignment with clinical intuition and meaningful positive outcomes in terms of de-escalation of antimicrobials, reduction in antibiotic usage and acceleration of pharmacist-led antimicrobial stewardship programs. Artificial intelligence is increasingly recognized as a valuable tool in clinical decision-support systems aimed at controlling antimicrobial resistance. Research indicates that AI can enhance antimicrobial stewardship programs (ASPs) by optimizing antibiotic prescribing practices and improving patient outcomes. For instance, machine learning algorithms have demonstrated predictive capabilities in identifying inappropriate prescriptions and selecting suitable antibiotic therapies, with performance metrics such as AUC ranging from 0.64 to 0.992. Additionally, AI applications utilizing electronic health record data have shown promise in predicting pathogen carriage and optimizing empiric therapy. However, the successful implementation of AI-based decision support systems faces challenges, including user knowledge, trust, and system compatibility with existing workflows. Overall, while AI presents significant opportunities for improving antimicrobial prescribing, careful consideration of implementation factors is essential for its effective clinical deployment.

Surveillance and early warning systems

AI-powered surveillance systems can:

- Analyse global data on antibiotic resistance patterns
- Predict outbreaks of resistant infections.
- Identify emerging resistance mechanisms.

Such systems can provide early warnings to healthcare systems and policymakers, allowing for proactive measures to contain the spread of resistant pathogens. A study utilized a machine learning algorithm in association with GIS to track AMR gene dispersion through exposome-related dataset analysis. AI significantly enhances AMR surveillance through innovative testing and predictive analytics. For instance, a novel AI system utilizing nanotechnology enables rapid AMR testing without bulky hardware, achieving a sensitivity of 82.61% and specificity of 92.31% in detecting AMR enzymes from blood samples. Additionally, systematic reviews indicate that machine learning algorithms effectively assist antimicrobial stewardship programs by identifying inappropriate prescribing practices and predicting AMR, with performance metrics showing an area under the curve (AUC) ranging from 0.64 to 0.992. Furthermore, AI-enhanced surveillance systems are gaining public support, contingent on ethical data use and governance, highlighting their potential in monitoring AMR across human, animal, and environmental contexts. Lastly, integrating AI with surface-enhanced Raman spectroscopy (SERS) offers transformative capabilities for early detection of drug-resistant strains, underscoring the critical role of ongoing research in this area. Together, these advancements illustrate AI's multifaceted contributions to improving AMR surveillance.

Diagnostic tools and rapid testing

AI can improve the speed and accuracy of diagnosing infections, which is crucial for appropriate antibiotic use. Applications include:

- Analysing medical images to identify signs of infection.
- Interpreting genetic sequencing data for rapid pathogen identification.
- Predicting antibiotic susceptibility based on pathogen characteristics.

Faster, more accurate diagnostics can lead to more targeted antibiotic use, reducing the selective pressure that drives AMR.

Predictive modelling of AMR spread

AI models can simulate the spread of AMR in various settings, from hospitals to communities. These models can:

- Predict the impact of different interventions on AMR rates.
- Optimize infection control strategies.
- Guide resource allocation for AMR control efforts.

Case studies of AI implementation in AMR control

Note: the following case studies are hypothetical examples to illustrate potential AI applications in AMR control.

Case Study 1: AI in clinical decision support.

A hospital system implemented an AI-powered clinical decision support tool to guide antibiotic prescribing. The system analyzed patient data, local resistance patterns, and clinical guidelines to provide real-time recommendations for antibiotic selection and dosing. After implementation, the hospital saw a 20% reduction in broad-spectrum antibiotic use and a 15% decrease in hospital-acquired resistant infections.

Case Study 2: AI in global AMR surveillance.

An international consortium developed an AI-driven platform to analyze AMR data from multiple countries. The system used machine learning algorithms to identify trends and predict emerging resistance patterns. This allowed health authorities to implement targeted interventions, resulting in a more coordinated global response to AMR threats.

Challenges and limitations of using AI for AMR control

While AI holds great promise in controlling AMR, several challenges must be addressed:

Data quality and availability

AI models are only as good as the data they are trained on. In many areas, particularly in low- and middle-income countries, high-quality data on antibiotic use and resistance patterns may be limited. Standardizing data collection and sharing practices globally is crucial for effective AI implementation.

Ethical considerations

The use of AI in healthcare raises ethical concerns, including:

- Privacy and security of patient data.
- Potential biases in AI algorithms that could lead to health disparities.
- The need for transparency and explainability in AI decision-making processes.

Implementation barriers

Integrating AI systems into existing healthcare infrastructures can be challenging. Barriers include:

- Resistance to change among healthcare professionals.
- The need for substantial investment in technology and training.

Overall, the current limitations include issues related to data quality, model performance, and ethical considerations. Many AI models face challenges such as imbalanced datasets, limited data availability, and inconsistent performance across different datasets, which can hinder accurate antimicrobial prediction. Additionally, the accessibility and cost of high-throughput sequencing data pose significant barriers to the broader application of AI in AMR research. Ethical concerns, including biases in data and the need for patient privacy, further complicate AI integration into healthcare. To address these limitations, enhancing data quality through better data collection and augmentation techniques is essential. Integrating deep generative models with bioinformatics can improve model performance and facilitate the discovery of new antimicrobial agents. Moreover, establishing ethical guidelines and regulations will ensure responsible AI use in medicine, ultimately fostering innovation while safeguarding public health.

Future directions and potential developments

The future of AI in controlling AMR is promising, with several exciting developments on the horizon:

- *Integration of multi-omics data*. Combining genomics, proteomics, and metabolomics data with AI could lead to more precise predictions of AMR and personalized treatment strategies.
- *Advanced imaging technologies*. AI-powered analysis of advanced imaging techniques, such as cryo-electron microscopy, could reveal new targets for antibiotic development.
- *Quantum computing*. As quantum computing technology matures, it could dramatically enhance the power of AI in simulating complex biological systems and discovering new antimicrobial compounds.
- *Global AI-driven surveillance networks*. The development of interconnected, AI-powered surveillance systems could enable real-time, global monitoring of AMR trends and rapid response to emerging threats.

In summary, the major aspects where AI may help in curbing the problem of antimicrobial resistance are:

- Use of machine learning or deep learning to evaluate a large volume of retrospective data to aid in outbreak investigation and healthcare-associated infection surveillance.
- Applying generative learning to predict real-time risk e.g. personalised antibiotic treatment recommendation, sepsis risk prediction tools.
- Incorporating large language models to summarize the electronic health records and to collate antibiograms.
- Installing image recognition to convert images to data to identify patterns e.g. microbe identification and rapid antimicrobial susceptibility testing.
- Utilizing Clinical Decision Support Systems (CDSS) to facilitate antimicrobial stewardship efforts.
- Development of new antimicrobial e.g. antimicrobial Peptides (AMPs).
- Prediction of antimicrobial resistance genes from a metagenomic pool to aid in appropriate antibiotic use.
- Use of robotics to limit the spread of multi-drug-resistant infections by autonomous surface disinfection and barrier nursing assistance.

Conclusion

When a new technology emerges, it is easy to “grab at shiny things". Artificial intelligence represents a powerful tool in the fight against antimicrobial resistance. From accelerating drug discovery to enhancing antimicrobial stewardship and improving diagnostics, AI has the potential to transform our approach to controlling AMR. The implementation of AI requires a robust framework that addresses regulatory, organizational, and data processing challenges, ensuring that AI systems are effectively integrated into healthcare settings. Moreover, the development of explainable AI (XAI) is crucial for improving transparency, as it allows healthcare professionals to understand and interpret AI-driven decisions, thus fostering trust and accountability. As we move forward, the integration of AI into AMR control strategies must be accompanied by continued research, international collaboration, and a commitment to responsible innovation. By harnessing the power of AI alongside traditional public health measures, we are optimistic about turning the tide against the growing threat of antimicrobial resistance and safeguarding the efficacy of these life-saving drugs for future generations.

Despite these advancements, challenges such as data quality, ethical considerations, and implementation barriers remain. Future directions include integrating multi-omics data and advanced imaging technologies to further enhance AI’s role in AMR control.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 32

How antimicrobial resistance is linked to climate change

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Introduction

Antimicrobial resistance (AMR) stands as one of the most pressing global health emergencies. In 2019, over 47.9 million Disability-Adjusted Life Years (DALYs) were estimated to be attributable to AMR globally. The increased risk of resistance development due to global warming suggests that AMR and climate change (CC) should be considered interconnected public health priorities. However, the intricate links between AMR and CC require thorough exploration through a One Health perspective, highlighting the urgent need for a systemic approach to planetary health. CC is increasingly driving closer interactions between humans and animals, leading to the emergence of zoonotic and vector-borne diseases with pandemic potential. In this context, the COVID-19 pandemic has further complicated the landscape, influencing the use of antibiotics, personal protective equipment, and biocides, with higher concentrations of contaminants in natural water bodies. These contaminants, which cannot be fully eliminated by wastewater treatment plants, may facilitate the spread of AMR. Considering the significant gap in research on the interplay between CC and AMR, there is a critical need for further investigation, potentially leveraging artificial intelligence (AI), to explore the multifaceted relationship between these global challenges and their impact on the spread of common diseases. AI can help predict future scenarios, identify hidden correlations, and foresee the potential impacts of CC on the spread of AMR. This approach can provide a more comprehensive understanding of how global warming, changes in weather patterns, and other environmental changes may influence the emergence and spread of resistant infections.

Antimicrobial resistance and climate change: two global challenges

AMR and CC are two of the most pressing global challenges, each with profound implications for human health, ecosystems, and the global economy. AMR arises primarily from the overuse and misuse of antibiotics and other antimicrobials in human healthcare, agriculture, and animal husbandry. This excessive and often inappropriate use accelerates the evolution of drug-resistant bacteria, making it increasingly difficult to treat common infections and rendering some of the most vital medicines ineffective. The consequences of unchecked AMR are dire, potentially leading to a future where routine surgeries, minor injuries, and common infections carry significantly higher risks of complications and mortality.

On the other hand, CC is driven by the relentless accumulation of greenhouse gases in the atmosphere, primarily from human activities such as burning fossil fuels, deforestation, and industrial processes. This results in rising global temperatures, shifting weather patterns, more frequent and severe extreme weather events, sea-level rise, and widespread ecological disruptions. According to the World Health Organization (WHO), CC is the greatest threat to human health, with an estimated 250,000 additional deaths per year between 2030 and 2050. The impacts of CC are far-reaching, affecting from food and water security to human migration, and biodiversity. It exacerbates existing vulnerabilities, particularly in low-income and marginalized communities, and poses new challenges to public health by altering the distribution and intensity of infectious diseases and straining healthcare systems. While AMR and CC are distinct challenges, their impacts often intersect in ways that magnify the risks posed by each. Despite their different origins and mechanisms, both AMR and CC demand urgent, coordinated global action.

Indeed, many pathological conditions and diseases are sensitive to climate, and changes in environmental conditions and temperatures can increase the spread of bacterial, viral, parasitic, fungal, and vector-borne infections in humans, animals, and plants. This can lead to the improper use of antimicrobial drugs, worsening AMR. For example, the climate crisis is altering the distribution of helminths in livestock, with large-scale outbreaks becoming more frequent. Additionally, the migration of species, such as sandflies, due to CC could expand the spread of diseases like leishmaniasis to new areas in Europe. CC can also increase the spread of malaria, especially in regions already affected, and introduce it to new areas. As drug resistance for these diseases grows, containing and treating them will become increasingly difficult. For instance, malaria parasites have already developed resistance to most of the currently available drugs.

Addressing AMR requires the prudent use of antimicrobials, robust infection prevention measures, and investment in research for new treatments, while combating CC necessitates a transition to sustainable energy sources, reforestation, and adaptation strategies that protect vulnerable populations. These efforts must be guided by an awareness of the interdependence of these challenges, ensuring that the solutions are not only effective but also sustainable in the long term.

The One Health approach to addressing the intersection of antimicrobial resistance and climate change

The interdependence of human, animal, and environmental health has never been more evident than in the context of AMR and CC. To reduce the impact of infectious diseases and AMR, it is essential to adopt integrated protection for humans, animals, and the environment, following the One Health approach. Addressing this complex relationship requires a One Health approach, which recognizes the interdependence of all living beings and the ecosystems they inhabit. By integrating efforts across human medicine, veterinary science, and environmental management, the One Health approach offers a holistic strategy to mitigate the dual threats of AMR and CC.

Human health is at the core of the One Health approach, particularly when considering the impacts of AMR and CC. CC is altering disease patterns, leading to the emergence of new infections and the re-emergence of others, many of which require antimicrobial treatment. CC, and particularly rising temperatures, can promote the spread of vectors such as mosquitoes and ticks, which transmit infectious diseases, leading to an increase in the use of antibiotics and AMR rates. Moreover, climate-induced environmental changes, such as flooding and water contamination, can exacerbate the spread of resistant bacteria. In this context, CC is expected to drive extensive human migrations as extreme weather events, rising sea levels, and resource shortages make certain regions uninhabitable. In 2020, over 40.5 million people were displaced, with 30.7 million forced to relocate due to natural hazards. Rising temperatures and erratic weather will likely increase the frequency of droughts, floods, and storms, making some areas unliveable and disrupting agriculture. Resource scarcity can also lead to conflicts, further driving migration. This shifting mobility presents challenges for both displaced communities and host regions, potentially causing overcrowding and socio-economic tensions.

Animals also play a crucial role in the One Health paradigm, especially in relation to AMR and CC. Livestock farming, which is heavily impacted by CC, is a significant driver of antimicrobial use. As temperatures rise and weather patterns shift, animals are more susceptible to diseases, leading to an increased reliance on antibiotics to maintain health and productivity. This overuse of antimicrobials in animals contributes to the development of resistance, which can be transferred to humans through direct contact, the food chain, or environmental pathways. The One Health approach advocates for the responsible use of antibiotics in veterinary medicine, the implementation of better animal husbandry practices, and the promotion of alternative disease management strategies that reduce the need for antimicrobials.

In this context, the environment serves as a critical component of the One Health approach, acting as both a reservoir and a conduit for AMR. CC exacerbates environmental conditions that favour the persistence and spread of resistant bacteria. For example, rising temperatures and altered precipitation patterns can lead to the contamination of water bodies with antimicrobial residues and resistant genes, which can spread through ecosystems. Additionally, the disruption of ecosystems due to CC, such as deforestation and habitat loss, can lead to closer interactions between wildlife, livestock, and humans, increasing the potential for the transmission of resistant pathogens.

The patterns of infectious diseases are changing as microorganisms adapt to CC and evolving environmental factors. The ability to test and treat infectious diseases is being challenged by emerging diseases that amplify difficulties in antimicrobial management and infection prevention. The climate crisis can contribute to the emergence of new threats and the re-emergence of pre-existing pathogens. For instance, *Candida auris*, a deadly and often drug-resistant fungus, may have acquired its pathogenic status due to CC. Additionally, recent evidence suggests that the thawing of permafrost in the Arctic, caused by global warming, could release ancient pathogens previously trapped in the ice.

Alongside CC, increased longevity may contribute to the worsening of AMR. As life expectancy increases, so does the likelihood of undergoing medical interventions that heighten exposure to infections, thus necessitating antimicrobial therapies. The excessive and inappropriate use of antibiotics promotes the development of resistant strains and the spread of resistance genes. By 2050, over two billion people will be over the age of 60, and AMR could cause 10 million deaths annually. The rise in life expectancy is correlated with greater antimicrobial use and increasing selective pressure on microbes. Elderly individuals and immunocompromised patients with chronic illnesses and prolonged interventions are particularly vulnerable to infections and the need for antibiotics. Diseases like pneumonia and urinary tract infections, already linked to resistant strains, disproportionately affect the elderly. Therefore, it is crucial to explore how longevity and CC interact within the context of AMR to develop effective strategies that address both issues and protect the health of the aging population.

The One Health approach calls for the integration of surveillance systems across human, animal, and environmental health sectors. This integration is essential for detecting and responding to the spread of AMR in the context of CC. Data sharing and collaborative research are vital to understanding the complex interactions between these global challenges and to developing effective interventions. Additionally, the One Health framework supports the development of policies that address the root causes of both AMR and CC, such as reducing the overuse of antibiotics, improving waste management, and promoting climate-resilient agricultural practices. Addressing the intersection of AMR and CC requires the cooperation of healthcare professionals, veterinarians, environmental scientists, policymakers, and the public.

Environmental changes and antimicrobial resistance spread

CC alters environmental conditions in ways that can enhance the spread of AMR. Rising temperatures can significantly influence the survival, replication, and behaviour of bacteria and other pathogens. As global temperatures increase, many bacterial species find more favourable conditions for growth, leading to higher reproduction rates and, consequently, a greater likelihood of mutations that can result in AMR. Additionally, higher temperatures can extend the survival of pathogens in the environment, including in water, soil, and food, making it easier for them to persist and spread. This enhanced survivability is particularly concerning in regions that were previously too cold to support certain pathogens, leading to the expansion of their geographical range and introducing new public health challenges as these areas become breeding grounds for resistant organisms. Furthermore, elevated temperatures can stress host organisms, potentially weakening their immune responses and making infections more likely to take hold and spread.

Warmer climates foster conditions that enhance the proliferation of AMR by boosting bacterial growth and mutation rates. Extreme weather events, like floods and droughts, exacerbate this issue by disrupting water systems. Floods can overwhelm sewage and wastewater treatment facilities, releasing untreated or partially treated sewage rich in antibiotics and resistant bacteria into rivers, lakes, and coastal waters. This contamination spreads resistant pathogens widely, impacting agricultural fields, residential areas, and drinking water supplies, thereby increasing exposure risks for humans and animals.

On the other hand, droughts intensify water scarcity, leading to a higher concentration of contaminants, including antibiotics and resistant bacteria, in increasingly limited water sources. This phenomenon not only reduces the availability of clean water but also increases the risk of these contaminants accumulating and spreading more easily in the environment. Additionally, droughts often lead to increased reliance on recycled water or alternative water sources, which may not be adequately treated to remove all microbial contaminants. In such conditions, the remaining water bodies can become reservoirs for resistant bacteria, providing ideal conditions for their survival and further spread. The combined effects of these extreme weather events not only compromise the safety and quality of water resources but also facilitate the dissemination of AMR across ecosystems, highlighting the profound impact of CC on public and environmental health. This environmental contamination can spread resistance genes across different ecosystems, creating hotspots of AMR.

Impact of climate change and antimicrobial resistance on agriculture and livestock

Agriculture and livestock farming are critical sectors where the impacts of CC and the growing threat of AMR intersect in complex and significant ways. CC exacerbates challenges in these sectors by altering weather patterns, affecting crop yields, and increasing the prevalence of pests and diseases. These changes can lead to greater reliance on chemical inputs, such as fertilizers, pesticides, and antibiotics, to maintain productivity and protect animal health. In turn, the intensified use of antibiotics in livestock farming contributes to the

development and spread of AMR. This resistance poses a serious threat to both human and animal health, as it can render common infections more difficult or even impossible to treat.
Agriculture is a major source of antibiotics and antimicrobial agents entering water systems, particularly through runoff from livestock farms and fields treated with manure. CC, by altering rainfall patterns and increasing the frequency of extreme weather events, can exacerbate this runoff. Increased runoff can carry higher loads of antibiotics and resistant bacteria from agricultural lands into nearby streams, rivers, and groundwater, where they can persist and spread. The presence of these contaminants in water systems creates environments where resistant bacteria can thrive and exchange resistance genes with other microorganisms. Thus, the intersection of CC and AMR in agriculture and livestock farming creates a feedback loop where efforts to adapt to one challenge can inadvertently exacerbate the other. Sustainable agricultural practices, integrated pest management, and the judicious use of antibiotics are essential strategies to address the complex challenges posed by the intersection of CC and AMR. These approaches are crucial not only for enhancing the resilience of food systems but also for safeguarding public health and preserving the efficacy of antibiotics for future generations. As CC disrupts traditional agricultural productivity through unpredictable weather patterns, shifting growing seasons, and the increased prevalence of pests and diseases, there is a growing dependence on chemical interventions to maintain food production. In particular, intensive farming systems, which prioritize high yields and efficiency, often resort to the extensive use of antimicrobials to prevent and treat infections in livestock. This practice, while essential for sustaining production in the face of climate-related stressors, significantly contributes to the development and spread of AMR. The rising use of antimicrobials in agriculture, spurred by climate change, accelerates the emergence of resistant bacteria. These resistant strains spread through food, water, and populations, making infections more difficult to treat, compromising the effectiveness of antibiotics, posing significant risks to human and animal health, and undermining global efforts to combat AMR.

The impact of antimicrobial resistance and climate change on water systems

Water systems are highly vulnerable to the combined impacts of CC and AMR, which together pose significant risks to environmental and public health. CC raises global temperatures, warming lakes, rivers, and oceans, which promotes the growth of antibiotic-resistant bacteria. In freshwater systems, higher temperatures lower oxygen levels, creating conditions that support resistant bacteria and extend the life cycles of pathogens, increasing their ability to thrive and spread. In addition, rising temperatures and changing precipitation patterns can lead to water scarcity and contamination, creating ideal conditions for the spread of resistant bacteria. Extreme weather events, such as floods, are becoming more common due to CC. Flooding can overwhelm wastewater treatment plants and septic systems, causing untreated or partially treated sewage to enter water bodies. This can introduce a large load of antibiotics, resistant bacteria, and other pollutants into the environment. The resulting contamination can spread AMR more widely, affecting both local and downstream ecosystems and human populations that rely on these water sources for drinking, irrigation, and recreation. Water treatment facilities are critical in reducing the presence of contaminants, including antibiotics and resistant bacteria, in water systems. However, CC-induced challenges, such as increased sedimentation from runoff, can disrupt these treatment processes. This disruption can reduce the effectiveness of treatment plants in removing pathogens and chemical pollutants, leading to the discharge of water that still contains significant levels of contaminants, including AMR-related ones, back into natural water bodies.
In this context, Wastewater-Based Epidemiology (WBE) — which uses wastewater analysis to monitor public and environmental health — is proving to be a powerful tool for understanding and monitoring the relationship between AMR and CC, as well as gaining insights into human populations at the community level. Since

CC affects wastewater quality through extreme weather events such as floods and droughts, which can alter the concentration of contaminants, including antibiotics and resistant bacteria in wastewater, WBE helps to understand how these environmental changes influence the spread of AMR. Wastewater analysis can also provide useful data for adapting water resource management strategies and mitigating AMR-related risks. For these reasons, understanding how precipitation and temperature affect the spread of contaminants in wastewater can guide more effective treatment and management policies.
Water systems are also prone to the formation of biofilms, which are communities of microorganisms that adhere to surfaces within aquatic environments. Biofilms can protect bacteria from environmental stressors, including antibiotics, allowing resistant strains to persist and multiply. The combined effects of CC, such as increased temperatures and nutrient loads from runoff, can promote biofilm formation, thereby enhancing the persistence and spread of AMR in water systems.

The impact of COVID-19 on the relationship between antimicrobial resistance and climate change

The COVID-19 pandemic has significantly influenced the interplay between AMR and CC, acting as a catalyst for their convergence. During the pandemic, the inappropriate use of antibiotics for secondary bacterial infections in COVID-19 patients has accelerated AMR development. Additionally, increased use of disinfectants, sanitizers, and personal protective equipment (PPE) has led to substantial environmental pollution. These products have introduced chemical residues and microplastics into ecosystems, with disinfectants disrupting aquatic life and PPE contributing to microplastic accumulation. CC exacerbates these environmental issues through rising temperatures, altered precipitation patterns, and more frequent extreme weather events. Higher temperatures can speed up plastic degradation, increasing microplastic release, while changes in precipitation affect pollutant distribution in water and soil.
The pandemic has also diverted funding from climate action efforts, worsening CC impacts on health. Studies show that higher temperatures and extreme weather worsen COVID-19 outcomes by increasing mortality and cardiopulmonary issues. Although COVID-19 is viral, it can lead to bacterial pneumonia, with about 50% of patients developing secondary infections, though only 8% actually need antibiotics.
The pandemic has also intensified water contamination with residual antibiotics from various sources, contributing to the spread of antibiotic-resistant bacteria. The increased use of plastics during the pandemic further contributes to microplastic accumulation, providing habitat for microbial growth and the transfer of antibiotic-resistance genes (ARGs). Additionally, the pandemic has strained healthcare systems, reducing focus on AMR surveillance and mitigation. Addressing these interconnected crises requires an integrated approach combining environmental management, public health interventions, and robust policy frameworks.

Global Health implications and future perspectives

The convergence of AMR and CC presents a significant challenge to global health. Both issues transcend national borders, requiring coordinated international responses. However, the resources needed to combat these challenges are often limited, particularly in low- and middle-income countries. CC can exacerbate health inequities, as poorer regions are more vulnerable to both its effects and the spread of AMR. The global nature of these threats necessitates a One Health approach, recognizing the interdependence of human, animal, and environmental health. In this context, AI offers powerful and innovative tools for assessing and understanding the complex relationship between AMR and the climate crisis, providing resources for analysis, prediction, monitoring, and optimization of responses. AI can analyze large datasets to identify correlations between climate factors and AMR, predict how CC will influence the spread of AMR, optimize the allocation of healthcare resources, and enable real-time monitoring of environmental conditions. These capabilities help in identifying high-risk areas, improving prevention efforts, and supporting timely interventions, especially in resource-limited settings. In addition, AI may provide a useful strategy to accelerate the discovery of new antimicrobials by analysing chemical, resistance, and climate data to find effective solutions under changing conditions.

Conclusion

Addressing the link between AMR and CC requires a multifaceted approach that integrates environmental, agricultural, and public health strategies. Efforts to mitigate CC can have a direct impact on reducing the spread of AMR. For instance, reducing greenhouse gas emissions and improving water management can help mitigate the environmental factors that contribute to AMR. Similarly, promoting sustainable agricultural practices and reducing the overuse of antimicrobials in farming are crucial steps in curbing the development of AMR. The combined effects of CC and AMR on water systems highlight the need for integrated management approaches that address both environmental and public health risks. Protecting water quality, improving wastewater treatment infrastructure, and implementing sustainable agricultural practices are essential steps in mitigating these vulnerabilities. Additionally, ongoing monitoring and research are crucial to understanding the evolving dynamics of AMR in water systems in the context of a changing climate.

Although the links between the climate crisis, rising temperatures, the spread of infections, and AMR are clear, the interactions between these two crises are complex, and the current evidence base is still limited. There is a need to intensify multidisciplinary research and surveillance to build a more solid and practical data foundation on the effects of the climate crisis on AMR in various contexts and scenarios. A key challenge is making the science behind these complex issues clear to policymakers, decision-makers, the media, and the public. Coordinated global action is essential to mitigate the impacts of AMR and climate change, protecting future generations' health.

Take home messages

- The climate crisis and AMR are interconnected global threats that influence each other, requiring integrated strategies to address both environmental and public health challenges
- Global events such as the COVID-19 pandemic have diverted crucial resources from AMR monitoring and management, further exacerbating the issue of AMR.
- Rising temperatures and extreme weather events caused by the climate crisis intensify the persistence of pollutants and resistant bacteria in ecosystems, amplifying AMR among humans, animals, and plants.
- Targeted economic and political interventions, including sustainable investments, global policy coordination, and the integration of environmental and public health strategies are needed to address AMR and CC

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 33

Antimicrobial resistance in international travelers

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Introduction

Antimicrobial resistance (AMR) in travelers is a growing and silent public health problem with significant socio-economic impacts worldwide. Current evidence indicates that human movement facilitates the spread of resistant pathogens and resistance genes. Consequently, numerous international institutions and scientific societies have concluded that strategies to control AMR must be transversal, multidisciplinary, longitudinal, and self-sustainable. Global action plans and international coordination are essential to mitigate the spread of AMR, which involves both pathogens and resistance genes and their mechanisms of resistance. This approach requires an interdisciplinary and holistic perspective that integrates interconnected areas such as humans, animals and the environment under the One Health framework.

Knowledge the burden of AMR, including resistant pathogens, resistance genes, entry routes, transmission mechanisms and asymptomatic carriers in different parts of the world, is crucial for directing efforts more specifically and efficiently. Furthermore, migration patterns must be considered to establish new entry and circulation routes for AMR. A recent systematic review from 204 countries worldwide, estimated in 2019 almost 5 million deaths were associated with bacterial AMR including 1.27 million directly attributable to bacterial AMR. The highest rate of deaths attributable to resistance across all ages was found in sub-Saharan Africa (27.3 deaths/100,000) and the lowest in Australasia (6.5 deaths/100,000) with lower respiratory infections being the syndrome with the highest burden. The resistant pathogens associated with the highest death rates were *Escherichia coli*, followed by *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*. Interestingly, these pathogens differed in fatal AMR burden. In high-income countries *Staphylococcus aureus* and *E. coli* were linked with half of the fatal AMR burden and in Sub-Saharan Africa were *Streptococcus pneumoniae* and *Klebsiella pneumoniae*. Furthermore, Methicillin-resistant *Staphylococcus aureus* caused the highest fatal AMR burden and 3.5 million DALYs attributable to resistance.

This chapter specifically addresses bacterial AMR and not fungi, viruses, parasites or any other pathogen species. We will explain the different dissemination mechanisms of bacterial AMR and AMR genes (ARG). One in eight people worldwide is on the move, which equates to one billion people, including 281 million international migrants.

Traveler definition

We define travelers as any group of people traveling via land, sea, river, lake, underwater, air, and/or space for temporary transit or migration for various reasons: Work-related travel: International organizations, government agencies, suppliers, uniformed services, rescue teams, missionaries. Studies-related travel: Short or long-term international studies, annual meetings, scientific or technical congresses. Tourism: Sports competitions (regional, continental, world), vacations, adventure trips, spiritual/religious/seasonal retreats, family reunions, medical tourism. Political: Armed conflict, displaced persons, refugees, asylum seekers, hostages, homeless, nomads, etc. (**Table 1**)

Work-related travel

The need to maintain economic, commercial, technological, and scientific ties dates back to ancient times, with globalization and trade being fundamental elements. International travel plays a crucial role in the geographic translocation and acquisition of AMR. Mellou reported that from 419 fecal samples collected pre- and post-travel from international travelers, 5% (20/419) contained colistin-resistant *Enterobacterales* (MCRE) and 1% (2/419) carbapenemase-producing carbapenem-resistant *Enterobacterales* CP-CRE.

Uniformed services, missions, and rescue teams have historically sought solutions to combat AMR of military relevance. The international deployment of personnel can expose them to new infectious diseases, to which they lack prior immunity, potentially making them carriers of pathogens, especially those involved in non-combat operations, peacekeeping, logistics, humanitarian assistance, and disaster relief, among others.

Space travel is also considered a potential source of AMR infection. Scientific articles have reported the presence of multi-resistant *Enterobacter bugandensis* strains on the International Space Station. Biofilms on its surfaces, subjected to selective pressure in anaerobic conditions, cosmic radiation, and reduced gravity, can generate such multi-resistance. Additionally, *Enterobacter bugandensis* was found in body fluid cultures of astronauts participating in these missions.

Study-related travel

Short trips are not associated with the risk of acquiring AMR. However, up to 35% of health students on international short-term placements have been reported to carry extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (BLEE), with no *Enterobacteriaceae* (CPE) found. Most medium and long-term study programs include pre-trip, semi-annual, and/or annual evaluations.

Tourism

Sports competitions. Events like world championships, where measures are taken to prevent infection risks, including COVID-19 and resistant clones of *Neisseria gonorrhoeae*.

Vacations, adventure, spiritual/religious/seasonal retreats, volunteer work, medical tourism, family reunions. Rupee *et al.* found a 50.8% (292/574) carriage rate of Multidrug-resistant *Enterobacteriaceae* (MRE) among travelers returning from tropical regions, with higher acquisition rates in Asia (72.4%), Sub-Saharan Africa (47.7%), and South America (31.1%). MRE was found up to three months post-return in 4.7% of cases.

Political

Armed conflicts

The TIDOS (Trauma Infectious Disease Outcomes Study) collected over 8,300 samples from military personnel wounded in the Middle East, with nearly a third being AMR-MDR. High MDR rates were found in *Acinetobacter baumannii* (85%) and *E. coli* (79%) from skin and subcutaneous tissue samples. Exposure to heavy metals from armed conflicts also plays a significant role in AMR, particularly in *Acinetobacter*. Furthermore, war wounds are associated with multiple complicating factors, including: 1) polytrauma: multiple severe injuries affecting various parts of the body; 2) severe bone comminution: extensive fragmentation of bones due to the impact; 3) bone contamination: the presence of foreign particles and infectious agents in bone tissue due to high-energy trauma. These factors are the result of high-energy trauma inflicted by various weapons, such as High-velocity firearms, anti-personnel mines, explosive devices, fragmentation grenades, bomb cylinders and various unconventional weapons. Each of these elements contributes to the severity and complexity of treating war wounds.

A special concern has recently arisen for the relationship between exposure to heavy metals used in manufacturing weapons and antimicrobial resistance, specifically in *Acinetobacter baumannii*. It is well known that many bacterial species developed resistance mechanisms against metal toxicity since high concentrations of these metals could damage the bacteria. The heavy metals can induce selective pressure on bacteria when resistance genes for heavy metals and antimicrobial agents are in close proximity to each other on mobile genetic elements such as plasmids, genomic islands, transposons or integrons (co-resistance), when one resistance mechanism causes resistance to heavy metals and antimicrobial agents simultaneously (cross-resistance) and when mutual regulatory protein regulates the resistance to both heavy metals and antimicrobial agents (co-regulatory). These mechanisms are still under study to the extent of contributing to increased antimicrobial resistance, especially in war zones. It is important to take into account different pathways in the emergence of antimicrobial resistance, despite the ones already known such as poor antimicrobial stewardship in humans and animals.

Displaced persons, refugees, asylum seekers, hostages, homeless and nomads

By 2022, there were 84 million forcibly displaced persons, including 48 million internally displaced, 26.6 million refugees, and 4.4 million asylum seekers. As of late 2023, there are over 117.3 million forcibly displaced persons. Of them, 68.9 million were internally displaced, 37.6 millions were refugees, 6.9 millions asylum seekers and 5.8 millions people under the necessity of international protection.

It is noted that AMR prevalence in displaced populations is 33%, higher than in other migrant types. A study with 3960 isolates, including 2,526 (68%) from refugees, found that compared with the general population, 6.7% were asymptomatic AMR carriers, particularly MRSA. Furthermore, a Swiss meta-analysis reported up to 25.4% of AMR in displaced people with a 21% MRSA prevalence among refugees and migrants across Europe. MDR-TB was also reported as a significant concern among displaced persons from endemic TB and MDR-TB regions, such as Asia y/o Sudán to Europe by diverse routes, sharing the “tylA N236K” mutation and the carbapenem phenotype resistance.

Others

*Smuggling, human trafficking, child/adult sexual exploitation, illegal mining, drug trafficking***.** There is no formal data on bacterial AMR studies on these high-risk populations. Because of that, it wouldn’t be noticed as an exponential threat, and seen as the iceberg peak.

Medical team responsibilities

The medical team attending these international travelers should consider the various phases of the itinerary: pre-travel preparation, during travel, and post-travel. Each phase might be affected depending on the traveler group being attending.

Pre travel phase

The main objective of this phase is to prevent the traveler from any illness and/or potential risk of death associated with the travel, as well as minimize the impact of infectious diseases using the available prophylaxis so far. As a consequence, it would protect the general population from pathogens related to travel when the traveler comes back to the origin country. In order to plan this phase, the Medical Officer or Medical Team in charge will make the medical Risk Assessment Process.

According to the Medical Risk Assessment Process, it could be consider the following checklist:

- Clear detail of the travel: Where will you go? What will you do?
- Identification of potential hazards: What are the endemic threats? Environmental hazards?
- Identification of potential exposure routes: Will the trip be exposed by this? If so, how?
- Risk characterization and prioritization: Classify based on severity and probability.
- Identification of prevention and mitigation measures: Apply what we know, what is necessary, feasible and effective?
- Communicate with appropriate staff: Be concise, relevant and realistic.
- When available, vaccinate against bacterial (as well as viral pathogens) (It is well known that vaccines can reduce AMR infections and the use of antibiotics).

It will be helpful to develop a Medical Risk Assessment Matrix. Based on the destination place, ways of travel, the previous epidemiological maps, and relevant dynamic information from reliable sources. It needs to be considered and identified: potential infectious hazards, potential routes of exposure, prioritize risk and then characterize, preventive measurements and mitigating plan.

A pre-travel consultation would be needed in all cases and is easier to conduct in planned and scheduled trips. Including health background, immunization status, travel history, travel risk assessment (itinerary, timing, reasons, activities), and assessment of individual risk. Perform the pre-travel checklist. However, the unexpected human mobilizations lack these pretravel evaluations.

A chance can be during the trip (pilgrimage, refugee camp, shelters etc) or after the trip is finished.

Travel phase

- Ensure basic sanitary conditions:
    - Adequate water flow.
    - Adequate waste disposal.
    - Continuous energy flow.
    - Correct cleaning of common sanitary services.
    - Air conditioning at all times.
    - Cleanliness in the handling, preparation and distribution of meals as well as the kitchen.
    - Vector control and animals native to the area.
- Ensure the provision of 100% medication and prophylaxis.
- Ensure the provision of rapid test strips for rapid detection of possible high-risk diseases in the area, and self-diagnosis equipment.
- Ensure an adequate flow of national and international reference and counter-reference in case of a patient evacuation would be required.

Post-travel observations

The post-travel consultation and evaluation must be performed in order to offer the best diagnosis tool and the opportunity to begin early treatment for an infection or not, as well as keeping under medical follow-up travelers with potential bacterial AMR/ARG carriers.

Consider follow-up: the immediate phase is 1-7 days post travel; the mediate phase is 6 months; the prolonged phase is 1-3 years. The clue is how to proceed in order to control carriers, and how long they will expect to be colonized with AMR or MDR strains. Certainly, the physician needs to individualize every case. All travelers need to take a post-travel consultation. We strongly recommend taking samples after long-term trips.

Upon return, the traveler must be under relative or absolute observation, depending on the places of the itinerary, according to the evaluation of each case. The time of observation will be determined by the average incubation time of the potential pathogen to which the traveler was exposed. The pre-and post-deployment (travel) checklists are quite detailed and meticulous. Obviously, the isolation of multi-resistant strains from body tissues (sputum, blood, urine, feces, CSF, etc.) must be attempted, taking into account the time of exposure and the potential place where it is being disseminated in the traveler's body, as well as the patient age group.

Factors and sources of dissemination

Factors such as the traveler's origin and destination, and endemic conditions from origin countries and travel routes must be considered.

To facilitate the comprehension of factors affecting the transmission of bacterial AMR, we will classify them by intrinsic and extrinsic factors that should be assessed.

Intrinsic factors: Those related to the traveler, such as pre-existing immunizations, need for new immunizations or prophylaxis, and chronic conditions affecting direct or indirect immunity.

It is of note to mention changes in the microbiota of Dutch international travelers. A study from the Netherlands found that from 190 fecal microbiota, 56 were AMR genes including blaCTX-M (extended spectrum beta lactamases - ESBL) and mcr1 (codified for resistance to colistin).

Those who travel for different reasons and are in an immunosuppression state are at high risk of being infected or carrying AMR bacteria. While a healthy person can deal with and confront these microorganisms, an immunocompromised traveler can not, added to the lack of a suited language of the internet and informative platforms in real-time. The risk is even higher when the population is displaced from war to places with deficient microbiological control and surveillance.

Extrinsic factors: Those related to the environmental condition.

Water**.** Human consumption, recreational use, and wastewater are potential sources of AMR exposure (24). High resistance levels have been found in urban water sources, which can serve as reservoirs for AMR distributed globally. It was found in human consumption water, antimicrobial resistance genes (ARG) in plasmids from bacteria, such as the NDM-1 gene which can jump to another bacteria by horizontal genetic transfer, which have already emerged in more than 70 countries globally. It is not surprising then the presence of AMR bacteria and ARG in sewage waters. Although some treatment plants of such waters can reduce the presence of AMR bacteria and ARG, the persistence of these agents has been found in the water and sediments up to 20 km from the treatment plant. Recreational waters also pose risks, both natural sources and hot springs and/or artificial ones (swimming pools, etc.). Thus, in an Irish study of 428 recreational water users, 80 isolates of *Enterobacteria* were found; revealing that 52.5% were MDR, of them

11.25% resistant to ertapenem, but sensitive to Meropenem. Of these, 7.1% were ESBL *Enterobacteria* and 2.2% were carbapenem-resistant *Enterobacteria* (CRE). The activities performed by this population were: surfing, bodyboarding, stand-up paddle boarding or paddle boarding, windsurfing, swimming, snorkeling, scuba, diving and canoeing. Showing that there was no significant difference by activity, intensity or frequency. However, 98% were swimmers.

Food products**:** AMR has been detected in marine biological products under microbiological surveillance. Although it is true that the maritime industry tries to control the survival of a species subject to an outbreak with various antimicrobial agents, it is important to point out that such early exposure contributes to the presence of residual antimicrobials as well as its metabolites. At that level, it will generate secondary resistance to such exposure. Therefore, in the following phases of the biological cycle, this fact may contribute to primary antimicrobial resistance for the new species of diverse marine/river/lake flora and will subsequently become part of this biological cycle. Therefore, it is not difficult to agree that antibiotic resistance must be controlled at all levels, not only in humans, but in various species that serve as food within the biological cycle. The same occurs with the agricultural, wine, and aquaculture industries, among others, if we begin to analyze where de novo or primary antimicrobial resistance comes from or originates.

It is important to know that in various parts of the world, ATB is being used in high concentrations. Long periods of time with high concentrations of ATB, create severe selective pressure, which will lead to increased bacterial AMR. It is therefore striking that tools such as microbiological resistance maps are rarely used in some places, when high-level decisions must be made, such as the national and international purchase of some ATBs. Then comes the dilemma for international travelers, whether or not to eat food (such as vegetables, and fruits, meat, among others), without being sure if they were exposed to high concentrations of antibiotics and pesticides spraying or if they have been properly washed and cleaned. Therefore, there would be a potential risk of subsequent resistance, in another species of the biological cycle, which would manifest itself as primary resistance for that species. On the other hand, it is worth asking about the long-term effects of genetically modified foods and their impact on subsequent bacterial resistance. Consequently, a critical level of anthropogenic waste such as antibiotics, heavy metals, and pesticides can exert selection pressure; while residual microplastics generate a suitable niche for the perpetuation and dissemination of AMR in the environment.

Basic services**:** It is evident that the poor conditions of basic services (water, drainage, toilets, sewerage, solid waste disposal, excrement, inaccessible health services, malnutrition and dehydration, overcrowding, lack of a home or shelter) further aggravate this bacterial AMR situation and will perpetuate it, turning it into a silent pandemic, impossible to control if appropriate measures are not taken. This situation becomes more evident when it comes to displaced populations, refugees, and asylum seekers, as a result of internal and external armed conflicts. One of the darkest scenarios is established when sexual violence becomes a massive weapon of war, leaving countless groups helpless, without early diagnosis and timely treatment, at the mercy not only of the events described above, but of AMR infection and ARG carriers. For this reason, it is important to take into account all these aspects and how the circulation of certain strains becomes perpetuated, without the opportunity to be registered or studied.

As a special note, a study recently published by researchers from Barcelona Spain and Japan found a variety of bacterial pathogens in surveys performed in a tropospheric aircraft over Japan in 2014, at 3,000 m heights and from 2,000 km from the possible sources. Many of them are potential resistant bacteria that infect humans, such as *Escherichia coli*, *Serratia marcescens*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Clostridium difficile*, *Stenotrophomonas maltophilia*, *Shigella sonnei*, *Haemophillus parainfluenzae* and *Acinetobacter baumannii* between others. These groundbreaking findings confirm the presence of bacterial pathogens and resistance genes in a planetary boundary layer, which could become a great concern to mitigate ARM resistance dissemination.

Epidemiological contact

An important point is to establish whether this traveler exposed to this superbug upon returning home will be a source of exposure for his or her closest contacts (family, friends, work or study colleagues) who did not leave home. As a parallel, this fact became evident with the COVID-19 Pandemic due to SARS COV 2, which put into action various epidemiological surveillance systems as well as contact tracing, to try to unify under the same evaluation and analysis criteria, such as those of WHO, CDC, Hopkins, etc. Furthermore, the circulation of *Neisseria gonorrhoeae* MDR strains during large multinational events such as world championships, etc. should be considered. It should be noted that bacterial AMR does not respect borders, nationalities, ethnic groups, religious groups, genders, beliefs, or ages. Therefore, the corresponding precautionary and protective measures must be taken regarding the sexual activity that takes place on such trips. Do not forget that each one of us, our families, friends and the society that surrounds us can become travelers at a certain time and circumstance.

On the other hand, it is important to take the appropriate public health precautions and promote better epidemiological surveillance of the contacts of future space travelers. Since tourist trips on various private airlines have begun to be considered, it is important to remember the great responsibility to humanity that this demands.

Therapeutic options

Therefore, scientific teams are currently investigating new therapeutic options and medical technologies. AMR, whose possibility of being treated with common antibiotics is minimal, should lead us to reflect that after multidrug resistance, there are limited antibiotics that could be used, but after extensively drug resistance or pan-resistance bacteria, there is very limited or no possibility of cure. Recently, a group of scientists and the industrial community have been promoting research into the use of Bacteriophage therapy as a weapon up its sleeve against extremely resistant microorganisms.

From the point of view of the general population who will travel abroad, there are few friendly sources easy to understand that are related to the aforementioned recommendations for international travelers. A very important topic is the International Health Regulations, which should be updated regularly in accordance with the dynamic AMR epidemiological movement globally.

Conclusion

The chance to cut the chain of transmission and the spread of extremely resistant microorganisms should be one of the main strategies in the prevention and control of antibiotic resistance, from the most unusual habitats to the most common sources used temporarily (recreational) by international travelers; as part of the multidisciplinary response of One Health. With the recent advances in possible novel sources of dissemination of resistant bacteria and resistant genes, research in this field is warranted. However, mitigating the spread of this bacteria could be challenging at this moment.

Educating international travelers to check potential places on their itinerary for sources free of outbreaks of infections caused by extremely resistant microorganisms is essential. Promoting the use of user-friendly digital systems with real-time information and preventive guidance (easy for travelers to understand) is a priority. For those without access to digital media or people lacking digital instruction (elderly adults/very young children), visual and/or auditory media should be offered that allow understanding of health regulations during border crossings, and that are continuous.

Promote research on bacteriophage therapy and the growth of the phagosome bank in a decentralized manner, as a strategic weapon for the treatment of extremely resistant infections. Since it seems to be promising to fight against extensively and pan antimicrobial resistance bacteria infections.

Encourage preclinical and clinical studies in search of new molecules that the clinician can count on in the arsenal of anti-infectious treatment.

Promote the research of potential prospects of polyvalent vaccines for multi-resistant microorganisms.

Train the health sector on the existence of this silent pandemic, unifying preventive-promotional criteria and regulations across countries, for the benefit of the health of international travelers.

Special attention should be paid to the itinerant population displaced by armed conflicts since the perfect environmental conditions are generated for the dissemination of new resistant microorganisms as well as the reemergence of others.

Improve epidemiological surveillance to establish the patterns of human movement as well as the patterns of resistance, mechanism of action and molecular sequencing and make this information globally accessible to the scientific community, health sector and general population.

Competing interests

The authors have no financial and non-financial competing interests to declare.

Table 1. AMR studies on international travelers from the last 10 years.

Author	**Population**	**Sample**	**Time of sample taken**	**Resistance genes**	**MDR-mo**	**Setting**
Worby *et al. 2023*	368 international travelers (South Asia, Southern Africa, Western Africa, Central America)	Stool samples	Before and after travel	*Mcr-1, mphA, bacA mdtE, TolC, qnrB41, Qnr48, qnrS8, Ctmx-155*	41% AMR, 41% ESBL-PE, 7% Colistin RE, 1% CRE	US Travel clinics
Mc Gann 2023	Injured soldier Ukraine	Wound debrideme nt	At entry	*bla*IMP-1, *bla*NDM-1, *bla*OXA-23, *bla*OXA-48, *bla*OXA-72 *armA, rmtB4*	ESBL, XDR	Germany
Yıldız *et al. 2023*	3960: 2525 Syrians refugees, 1453 locals	Nasal swabs and stool samples	At entry (once), during Sep 2020 – Mar 2021 (cross sectional)	–	6.7% MRSA, 17.9% ESBL	Refugees camp in Turkiye
Azour *et al. 2021*	250 Syrian refugees	Rectal swap	During Jun – Jul 2019 (cross sectional)	*blaOXA-48, blaNDM-1 Mcr-1, pmrB, phoQ*	25 (10%) MDR: 16 CPE 9 colistin RE: *E. coli/ K. pneumoniae*	2 refugee camp at North Libano
Dao *et al. 2021*	293 international French medical students (Vietnam, North India, Peru, Madagascar, Tanzania)	Nasophary ngeal, rectal, and vaginal swabs	Before and after travel	*blaCTX-M-A, mcr-1, Mcr-3, mcr-8*	29.3% ESBL-E, 2.6% CPE	Travel consultation at mediterranean infectious institute, France
Mellou *et al. 2021*	18 Afghans, Syrian, Palestine refugees	Stool samples	At entry	blaCTX-M-group 1	14 *S. flexneri* 1b & 3 *S. sonnei* phase S(I) MDR ESBLs	Refugees camp in Greece
D'Souza *et al.2021*	190 Dutch travelers (Northern Africa, Eastern Africa, Southern Asia, and South-Eastern Asia)	Fecal swab kits	Before and after travel	*Mcr-1, blaCTX-M*	150 switch metagenomics after travel	Outpatient travel clinics at The Netherlands
Tufic-Garutti *et al.* 2021	210 international travelers (South Sahara Africa, South America)	Anal stool swab	Before and after travel	*blaCTX-M-15, blaOXA-181, mcr-1*	12% MDR-E, 18%ESBL-PE	Travel center Brazil

(cont.)

Table 1. AMR studies on international travelers from the last 10 years *(cont.)*

Author	Population	Sample	Time of sample taken	Resistance genes	MDR-mo	Setting
Rasheed *et al. 2020*	355 Syrians refugees	Nasal swabs	At the entry	*mec*A gene, SCC*mec* group	MRSA: 15.4% host, 13.8% refugee	Refugees camp in Iraq
Mellon *et al. 2020*	412 international travelers (Southeast Asia, Latin America, South Africa)	Stool samples	Before and after travel	*mcr-1, mcr-2, mcr-3 blaNDM-5, blaCTX-M blaCTX-M-55, aac3-IIa, qnrS1*	5% MCRE, 1% CP-CRE	5 sites US health centers
Worby *et al. 2020*	608 international travelers	Stool samples	Before and After Travel	*mcr-E*	37%ESBL-PE, 4.9% mcr-E, 0.4% CP-CRE	5 US travel clinics
Langelier *et al. 2019*	10 International travelers healthcare related workers (Nepal, Nigeria)	Stool samples	Before and after travel	*AmpC*, *CTX-M*, *OXA*, *SHV*	9/10 ESBL-PE, 4 develop sx, 3 carriers 1 m, 2 carriers 6 m	US travel clinic
Aro *et al. 2018*	447 Asylum seekers and refugees (Iraq, Afghanistan, Syria, Somalia)	Nostrils (one swab for both), pharynx and rectum or perineum/wound	After travel	*spa type t-304 t-386, t-223*	45% MDR, 32.9% ESBL-PE, 21.3% MRSA, 0.7% CPE, 0.4% MRPA, 0.4% MRAB	Inpatients at Helsinki university hospital, Finland
Jan Piso *et al. 2017*	261 refugees (Syria, Afghanistan, or Eritrea)	Pharyngeal, nasal, and inguinal swabs rectal swabs and urine	During staying (cross sectional screening)	*PVL gene*	15.7% MRSA, 23.7% ESBL-PE	4 Swiss refugees centers
Angeletti *et al. 2016*	48 Syrian asylum seekers	Blood, rectal, pharyngeal and nasal swabs	At entry	–	*Klebsiella*, *E. coli* ESBL	Asylum seeker center Italy
Angelin *et al. 2015*	99 swedish international travelers healthcare students (Southeast Asia, Africa)	Stool samples	Before and after travel	–	35% ESBL-PE	3 Swedish Universities
Rupee *et al. 2015*	824 international travellers (Asia, Sub-Sahara Africa, Latin America)	Fecal samples	Before and after travel	*CTX-m, OXA-181, NDM-1*	50.9% MRE 33.9% carrier 1 m MRE 4.7% carrier 3 m MRE 0.5% CPE	6 international vaccination center France

Abbreviations. MRSA: meticillin-resistant *Staphylococcus aureus*, VRE: vancomycin-resistant *Enterococcus*, ESBL-PE: extended-spectrum beta-lactamase-producing *Enterobacteriaceae*, CPE: carbapenemase-producing *Enterobacteriaceae*, MRAB: multiresistant *Acinetobacter baumannii*, MRPA: multiresistant *Pseudomonas aeruginosa*, MRE: *Enterobacteriaceae* producing an ESBL, pAmpC, and/or carbapenemase.

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Chapter 34

The burden of infectious diseases in war settings

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Introduction

War and armed conflict cause a significant loss of human life and are a major cause of disability worldwide. In addition to those hurt and killed as a direct result of violent conflict, a vast amount of people are also negatively impacted by the wider effect of war on global health.

The burden of infectious diseases in war-torn regions presents a significant public health challenge, exacerbated by the disruption of healthcare systems and the conditions created by armed conflict. Violence and displacement lead to overcrowded living situations, inadequate sanitation, and limited access to medical care, all of which contribute to the spread of preventable diseases such as cholera and measles. This cyclical relationship between conflict and disease creates a persistent health crisis, complicating humanitarian responses and undermining efforts to control outbreaks. Understanding these dynamics is crucial for developing effective interventions that can mitigate the health impacts on vulnerable populations.

Historical context

The impact of infectious diseases during the World Wars highlights the devastating consequences of conflict on public health. In the aftermath of World War I, the Spanish flu pandemic (1918-1919) emerged, infecting approximately one-third of the global population and resulting in millions of deaths. The conditions of trench warfare, characterized by overcrowding in military camps and hospitals, facilitated the rapid transmission of pathogens. Similarly, World War II saw rampant typhus outbreaks, particularly in concentration camps and among displaced populations in Eastern Europe. The disease, spread by lice in unsanitary conditions, thrived amid malnutrition and poor living environments. Efforts to combat typhus included delousing campaigns and vaccination initiatives, underscoring the critical role of public health measures during wartime.

Factors contributing to infectious disease burden in war settings

Populations in conflict situations present an increased incidence of infectious diseases as a result of a multitude of risk factors that precipitate disease emergence and transmission. Factors contributing to infectious disease burden in war settings are the following.

1. **Displacement of populations**. Conflict often leads to mass displacement, creating overcrowded living conditions in refugee camps where sanitation and hygiene are inadequate. This environment facilitates the spread of infectious diseases. For example, the 2014 Ebola outbreak in West Africa was exacerbated by ongoing conflicts, leading to thousands of deaths and overwhelming healthcare systems. Similarly, cholera outbreaks in Yemen during the ongoing conflict have resulted in hundreds of thousands of cases and significant mortality.
2. **Breakdown of healthcare infrastructure**. Wars typically destroy healthcare facilities and disruption of medical services, limiting access to vaccinations and treatments for infectious diseases.
3. **Poor sanitation and hygiene**. Conflict zones often lack access to clean water and proper sanitation facilities, leading to outbreaks of waterborne diseases such as cholera and dysentery.
4. **Malnutrition**. War can disrupt food supplies, leading to malnutrition, which weakens immune systems and increases susceptibility to infectious diseases.
5. **Increased vector breeding sites**. Destruction of infrastructure and changes in land use during conflicts can create new breeding sites for vectors like mosquitoes, increasing the risk of diseases such as malaria and dengue fever.
6. **Psychological stress and societal disruption**. The psychological impact of war can lead to increased stress and social disruption, which may hinder public health responses and increase vulnerability to diseases.

Impact of infectious diseases in war settings

Infectious diseases in war settings can impact people in different ways:

1. **Increased morbidity and mortality**. Infectious diseases often lead to high rates of illness and death in conflict zones, overwhelming healthcare systems and causing significant loss of life.
2. **The strain on healthcare systems**. The outbreak of infectious diseases during conflicts places immense pressure on already strained healthcare systems, often leading to their collapse.
3. **Economic consequences.** The burden of infectious diseases can hinder economic recovery in war-affected areas, diverting resources from development to emergency health responses.
4. **Long-term health consequences**. Survivors of infectious disease outbreaks may face long-term health issues, including chronic illnesses and disabilities, affecting their quality of life and productivity.
5. **Disruption of education**. Outbreaks of infectious diseases can lead to school closures and interruptions in education, particularly for children in conflict-affected areas.
6. **Social instability**. The health crises caused by infectious diseases can exacerbate social tensions and lead to increased instability and violence within communities.

Case study

The ongoing conflict in Sudan has led to severe public health challenges, particularly the spread of infectious diseases. In 2023, widespread malnutrition and inadequate sanitation resulted in a cholera outbreak, putting millions at risk due to the collapse of healthcare infrastructure and limited access to clean water.

Mosquito-borne diseases. Malaria cases have surged, especially in the Blue Nile and South Kordofan regions, where stagnant water from damaged infrastructure creates favourable conditions for mosquito breeding. The disruption of health services and lack of preventive measures, such as insecticide-treated bed nets, have worsened this situation. Additionally, dengue fever cases have increased due to the failure of vector control programs and rising urban mosquito populations, further threatening public health.

Sanitation-related diseases. Outbreaks of conjunctivitis have been reported, primarily due to poor sanitation and overcrowded living conditions in displacement camps, facilitating rapid transmission. Enterobius vermicularis (pinworm) infections are also prevalent among children in unsanitary environments, highlighting the urgent need for improved hygiene practices).

Vaccination disruptions. The conflict has disrupted vaccination campaigns, leading to a resurgence of measles among children, emphasizing the critical need for comprehensive health interventions.

Addressing these public health challenges in Sudan requires immediate and coordinated efforts to restore healthcare services, improve sanitation, and ensure access to vaccinations and essential health resources. Without decisive action, the health crisis will continue to escalate, further endangering vulnerable populations.

Strategies for mitigating the burden of infectious diseases in war settings

Below we report the strategies to mitigate the burden of infectious disease in war settings.

1. **Improving sanitation and access to clean water**. Enhancing sanitation facilities and ensuring access to clean drinking water are crucial in preventing the spread of infectious diseases. Implementing community-based water and sanitation programs can significantly reduce disease incidence, especially in vulnerable populations.
2. **Strengthening healthcare infrastructure**. Investing in healthcare infrastructure, including the training of healthcare workers and the establishment of functional health facilities, is vital for effective disease management and outbreak response. This includes ensuring that clinics are stocked with essential medicines and supplies.
3. **Implementing vaccination campaigns**. Conducting widespread vaccination campaigns can prevent outbreaks of vaccine-preventable diseases such as measles and polio. Targeted campaigns in high-risk areas can significantly reduce disease transmission and protect vulnerable populations.
4. **Enhancing disease surveillance and response systems**. Developing robust disease surveillance systems helps in early detection and rapid response to outbreaks. This includes training local health workers and utilizing technology for real-time data collection and analysis.
5. **Promoting vector control measures**. Implementing vector control strategies, such as insecticide-treated bed nets and indoor residual spraying, can help reduce the incidence of vector-borne diseases like malaria and dengue fever. Community engagement in these efforts is essential for sustainability.
6. **Raising community awareness and education**. Educating communities about disease prevention, hygiene practices, and the importance of vaccination can empower individuals to take proactive measures against infectious diseases. Community health education programs can lead to better health outcomes.

Infectious diseases in war settings

In war-affected regions, infectious diseases emerge as significant public health crises, exacerbated by disrupted healthcare systems, poor sanitation, and overcrowding.

Cholera has severely impacted countries like Yemen and Haiti. In Yemen, since 2017, there have been over 1 million suspected cases, primarily driven by a lack of clean water and inadequate sanitation facilities. The humanitarian crisis has made it challenging to implement effective control measures, leading to widespread transmission. Cholera is transmitted through contaminated water and food, and the risk factors include poor hygiene practices and overcrowded living conditions. Efforts to combat cholera have included vaccination campaigns, such as the Oral Cholera Vaccine (OCV) initiative, and improvements in water and sanitation infrastructure. However, ongoing conflict hampers these initiatives, making it difficult to sustain long-term solutions. The WHO and UNICEF have collaborated on emergency response efforts, emphasizing the need for rapid access to safe water and sanitation.

Malaria remains a critical issue in South Sudan, Nigeria, and the Democratic Republic of the Congo (DRC). In South Sudan, malaria cases surged due to stagnant water, poor healthcare access, and population displacement resulting from ongoing conflict. Control efforts, such as the distribution of insecticide-treated nets (ITNs), have led to a reported 30% decrease in cases between 2015 and 2017. However, the ongoing instability continues to disrupt healthcare delivery and limit access to preventive measures, making malaria a persistent threat in these regions. The WHO emphasizes the importance of integrated vector management and community engagement in malaria control. In Nigeria, the National Malaria Elimination Program has been working to scale up prevention strategies, including indoor residual spraying and rapid diagnostic testing.

Ebola virus disease has posed severe threats in Sierra Leone and Liberia, especially during the 2014-2016 outbreak, which resulted in over 11,000 deaths. The Democratic Republic of the Congo continues to experience periodic outbreaks, with the most recent one in 2021. The risk factors contributing to the spread of Ebola include poor healthcare infrastructure, cultural practices surrounding burial rituals, and population movement due to conflict. Vaccination campaigns, such as the rVSV-ZEBOV vaccine, along with contact tracing and community engagement, have been vital in controlling outbreaks, though challenges remain due to ongoing instability and mistrust in healthcare systems. The WHO and Médecins Sans Frontières (Doctors Without Borders) have been crucial in mobilizing resources and providing care during outbreaks.

Dengue fever has surged in conflict zones like Myanmar and the Philippines, where the lack of vector control measures has led to increased incidence. The Philippines reported a significant rise in cases in 2019, prompting the government to intensify control measures. Risk factors include urbanization, poor waste management, and stagnant water, which create ideal breeding conditions for mosquitoes. Efforts for control have included community awareness programs, fumigation, and the introduction of a dengue vaccine in some areas. The WHO has emphasized the need for integrated vector management to reduce dengue transmission effectively. In Myanmar, local health authorities have implemented community engagement strategies to promote preventive measures, such as eliminating standing water.

HIV/AIDS remains a critical concern in conflict zones such as the Central African Republic and South Sudan, where ongoing violence disrupts healthcare services and increases stigma around the disease. By 2020, approximately 70% of people living with HIV in the Central African Republic were receiving antiretroviral therapy (ART), a significant improvement from previous years. Efforts to control HIV/AIDS focus on expanding access to treatment, community outreach programs, and education to reduce stigma. The Global Fund and other international organizations have supported initiatives to enhance testing and treatment access in conflict-affected areas.

Hepatitis, particularly Hepatitis B and C, poses additional challenges in these regions. The prevalence of hepatitis is often linked to unsafe medical practices, lack of screening, and limited access to treatments. In conflict zones, the disruption of healthcare services can lead to increased transmission rates. Efforts to combat hepatitis include vaccination programs for Hepatitis B, public health campaigns to raise awareness about transmission, and improving access to antiviral treatments for Hepatitis C. The WHO has emphasized the importance of integrating hepatitis prevention and treatment into primary healthcare services, especially in vulnerable populations affected by conflict.

Tuberculosis (TB) remains a concern in Iraq and Afghanistan, where the incidence of the disease is exacerbated by malnutrition, overcrowding, and lack of healthcare access. Iraq reported a decrease in TB incidence from 40 to 30 per 100,000 population from 2015 to 2019, largely due to free diagnosis and treatment programs. However, ongoing conflict poses challenges in maintaining these efforts, as healthcare facilities are often damaged or destroyed. The WHO advocates for the implementation of directly observed treatment, and short-course (DOTS) strategies to ensure adherence to TB treatment. In Afghanistan, the National TB Control Program has been working to enhance case detection and treatment adherence through community health worker initiatives.

Brucellosis is prevalent in Afghanistan, South Sudan, and Iraq, driven by close contact with infected animals and the consumption of unpasteurized dairy products. The lack of veterinary services in conflict zones has hindered control efforts. Public health education on food safety and vaccination of livestock are essential strategies for reducing the incidence of brucellosis. Efforts to improve veterinary services and promote the pasteurization of dairy products are critical in these regions. The WHO has recommended strengthening food safety regulations to mitigate the risk of zoonotic diseases like brucellosis.

Meningitis has seen significant success in vaccination campaigns in Burkina Faso and Niger, where the introduction of the MenAfriVac vaccine has dramatically reduced incidence rates in the meningitis belt. However, ongoing conflict and instability in the region pose challenges to sustaining these vaccination efforts. Risk factors include overcrowding and poor living conditions, which facilitate the spread of the disease. Continued advocacy for vaccination and surveillance is essential to prevent outbreaks. The African Vaccination Week has been used to promote awareness and increase vaccination coverage in these regions.

Zika virus outbreaks have been reported in Brazil and Colombia, with increased incidence linked to population displacement and poor vector control in conflict-affected areas. The disease poses particular risks for pregnant women, as it can lead to severe birth defects. Control efforts focus on vector management, community education, and surveillance to prevent outbreaks. Collaboration with local health authorities is crucial for effective response strategies. The WHO and PAHO have provided technical guidance to countries on managing Zika virus outbreaks and reducing mosquito populations.

Schistosomiasis remains a health burden in Sudan, Nigeria, and Egypt, where poor sanitation and access to clean water contribute to transmission. Mass drug administration and improved water management are vital for control, but ongoing conflict complicates these efforts. Public health education is also crucial in raising awareness about prevention, including avoiding contact with contaminated water sources. The WHO has emphasized the importance of integrated control strategies that combine treatment with efforts to improve water and sanitation infrastructure.

Leishmaniasis has increased in Syria and Iraq, where conflict has hindered vector control and healthcare access. The disease is transmitted by sandflies and is associated with poor living conditions. Control efforts include vector management, disease surveillance, and treatment programs, but challenges remain due to ongoing violence and instability. Community engagement and education are necessary to raise awareness about prevention and treatment options. The WHO has been involved in providing support for leishmaniasis control programs in conflict-affected areas.

Noma, a disease affecting malnourished children, has seen rising cases in Nigeria and Sudan, particularly in conflict-affected areas. The disease is associated with poor oral hygiene and malnutrition, leading to severe facial necrosis. Efforts to control noma focus on nutritional support, health education, and surgical treatment to address the physical and psychological impacts of the disease. International organizations are working to provide resources and training to healthcare providers in affected areas. The WHO has called for a multisectoral approach to address the underlying causes of noma, including malnutrition and lack of access to healthcare.

COVID-19 has emerged as a global challenge, significantly impacting conflict-affected countries such as Ukraine, Syria, Yemen, and Afghanistan. The pandemic has strained already fragile healthcare systems, leading to increased morbidity and mortality. In Yemen, the health system was already under severe stress due to war, and the arrival of COVID-19 exacerbated existing vulnerabilities. Risk factors include overcrowding, lack of access to healthcare, and misinformation about the virus. Efforts to control the spread of COVID-19 have included vaccination campaigns, public health messaging, and the establishment of quarantine measures. However, ongoing conflict and instability hinder these efforts, making it difficult to achieve widespread vaccination and public compliance with health guidelines. The WHO and various NGOs have worked to provide vaccines and medical supplies to these regions, but access remains a challenge.

Measles outbreaks have been reported in war-torn countries like Syria and Yemen, where vaccination coverage has plummeted due to conflict. Measles is highly contagious and can lead to severe complications, especially in malnourished children. In Yemen, the ongoing humanitarian crisis has resulted in low immunization rates, contributing to significant outbreaks. The risk factors include displacement, lack of healthcare access, and misinformation about vaccines. Efforts to control measles outbreaks have included mass vaccination campaigns and community education about the importance of immunization. Organizations like UNICEF and the WHO have been crucial in implementing these campaigns, but challenges remain due to access restrictions in conflict zones.

Diphtheria, although rare in many parts of the world, has re-emerged in conflict-affected areas such as Yemen and Syria. In Yemen, a diphtheria outbreak was reported in 2017, with hundreds of cases due to weakened healthcare systems and low vaccination coverage. Diphtheria is a bacterial infection that can cause severe respiratory issues and complications. The risk factors include poor sanitation, malnutrition, and lack of access to preventive healthcare. Control efforts focus on vaccination and treatment of infected individuals. The WHO has assisted in providing diphtheria vaccines and establishing treatment protocols in affected regions, but ongoing conflict complicates these efforts.

These interconnected challenges underscore the urgent need for comprehensive public health strategies in conflict-affected areas, addressing both immediate health concerns and the underlying factors exacerbating the spread of infectious diseases.

Contribution of wars to the development of antimicrobial resistance

Wars can accelerate the spread of multidrug-resistant organisms, driving antimicrobial resistance (AMR) worldwide in different ways.

- Damage to infrastructure that provides water and sanitation can accelerate AMR development.
- Damage to laboratory infrastructure, which may be already underdeveloped in many conflict areas, can limit any ongoing testing for pathogens (microbiological and antimicrobial susceptibility testing).
- Disruption to healthcare can disrupt infection prevention and control and public health activities, such as vaccination programmes.
- Traumatic bone and soft-tissue injuries in people exposed to the conflict can necessitate damage-control surgery, which is often delivered in informal facilities lacking appropriate infection control. It can result in wounds being more easily contaminated with environmental organisms.

- More recently, conflict-related heavy metal contamination of the environment has been raised as a possible driver for the emergence of novel mechanisms of AMR.

Conclusion

Conflict within or between countries adversely affects population health. In conflict circumstances, affected populations are at an increased risk of infectious disease outbreaks. Infectious diseases have a significant impact on the population's health, thus understanding the link between conflict and infectious diseases is essential. Overall, major overarching pathways reported include displacement of populations, breakdown of healthcare Infrastructure, poor Sanitation and hygiene, malnutrition, increased vector breeding sites and psychological stress and societal disruption.

Competing interests

The author has no financial and non-financial competing interests to declare.

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Chapter 35

One Health approach

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Introduction

The One Health approach is an integrative and holistic vision that recognizes that the health of humans, animals and our environment is interconnected and interdependent. This multidisciplinary perspective is essential for understanding and managing health risks at the interface of these three components. In a world where the boundaries between natural ecosystems and human societies are increasingly blurred and porous, the One Health approach offers a framework for addressing the complex health challenges of our time.

Human health is profoundly influenced by animal health and the state of the environment. Zoonotic diseases, which spread from animals to humans, represent a growing threat, as recent outbreaks have demonstrated. Furthermore, environmental degradation can compromise the health of ecosystems on which both animals and humans depend for their well-being. The One Health approach emphasizes the importance of protecting and promoting health across all species and environments to prevent disease and maintain ecological balance.

A crucial aspect of One Health is the fight against Antimicrobial Resistance (AMR), a global public health problem that threatens the ability to effectively treat infections in humans and animals. Inappropriate use of antimicrobials in the human health, livestock and agriculture sectors has accelerated the emergence and spread of resistant microorganisms. The One Health approach calls for the prudent and coordinated use of antimicrobials and integrated strategies to monitor and control AMR.

This article explores the One Health approach by highlighting the interconnectedness between humans, animals and the environment, and demonstrating how this perspective can help control AMR. By taking a holistic view of health, we can identify sustainable solutions that benefit all living beings and the planet we share.

Interconnection between human, animal and environmental health

The health of our planet is a delicate balance between ecosystems, the species that inhabit them, and the environments in which they exist. This interdependence is at the heart of the concept of "One Health", which recognizes that human and animal health are intrinsically linked and depend on that of the environment.

Ecosystems and health

Healthy ecosystems are essential for the health of animals and humans. They provide clean air, clean water, medicine, shelter, healthy food and more. Biodiversity plays a crucial role in regulating disease and providing ecosystem services such as purifying air and water and sustaining and improving pollination of crops.

However, environmental degradation can lead to an increase in communicable (inter and intra-species) and non-communicable diseases, thereby affecting overall health. According to the World Wildlife Fund (WWF) report, there has been an average decline of 68% in populations of birds, amphibians, mammals, fish and reptiles since 1970. This loss of biodiversity affects our health and well-being, with catastrophic impacts on people and the planet coming closer than ever.

Zoonotic diseases

Zoonotic diseases, which spread from animals to humans and vice versa, account for a large portion of new infectious diseases as well as many existing diseases. More than 60% of emerging infectious diseases reported worldwide are of animal origin. Veterinary surveillance and wildlife management are therefore essential to prevent epidemics. Examples include avian influenza and Ebola virus disease, both of which have animal reservoirs. Many of these diseases are 100% preventable through vaccination, biosecurity and other methods, as in the case of rabies, avian flu, and tuberculosis.

Climate change

Climate change directly contributes to humanitarian emergencies such as heat waves, wildfires, floods, tropical storms and hurricanes, and they are increasing in scale, frequency and intensity. It is estimated that between 2030 and 2050, climate change could cause around 250,000 additional deaths per year, due to undernutrition, malaria, diarrhoea and heat stress.

Climate change is altering ecologies, allowing certain diseases to spread to new regions. For example, warming temperatures can expand the range of disease vectors like mosquitoes, increasing the risk of diseases like malaria and dengue.

Biodiversity

Biodiversity, all living beings as well as the ecosystems in which they live, is the variety of life on Earth. The concept of biodiversity refers to the components and variations of living things and scientists distinguish three levels of organization: ecological diversity (ecosystems); specific diversity (genes); and genetic diversity (genes). It is crucial for the balance of ecosystems and the survival of species. However, human action has led to a very significant decrease in biodiversity. WWF's Living Planet Report 2020 indicates an average decline of 68% in wildlife populations since 1970. This loss of biodiversity has direct and indirect repercussions on human health because it affects the ecosystem services on which we depend.

In conclusion, the concept of “One Health” highlights the importance of an integrated and unified approach to optimize the health of people, animals and ecosystems. It uses the close and interdependent connections between these fields to create new methods of disease surveillance, control and management. By addressing the connections between human, animal and environmental health, One Health is considered a transformative approach to improving global health.

Importance of the One Health approach

The “One Health” approach is much more than just a concept. It embodies a holistic vision that recognizes the deep interconnection between human, animal and environmental health. Here’s why this approach is crucial for people's collective well-being:

Multidisciplinary collaboration

The "One Health" approach brings together experts from various fields such as human medicine, veterinary medicine, ecology, biology, agriculture and many others. By working together, these professionals can anticipate, detect and manage health risks more effectively.

Pandemic prevention

The One Health approach can help prevent pandemics by promoting integrated disease surveillance and improving communication between sectors. This enables early detection and rapid response to health threats. The COVID-19 pandemic has highlighted the importance of prevention rather than reaction. The One Health approach helps identify transmission hotspots between animals and humans, reducing the risk of future pandemics.

Food security

Food safety depends on the health of farm animals and the environment. The One Health approach can help ensure that animal-based foods are safe, nutritious and sustainably produced. This approach shows that sustainable agricultural practices and food security are closely linked.

Animal welfare

Healthy animals contribute to food security and human health. The One Health approach promotes animal welfare because it is essential for overall health.

Several infectious diseases, such as brucellosis, avian influenza, toxoplasmosis or other zoonoses, circulate between animals and humans. A healthy animal is less likely to be a carrier and transmit these zoonotic diseases.

Animals raised in good sanitary conditions produce food that is safer for human consumption: this is a factor in reducing the risks of contamination by pathogens and contributing to food safety.

A stressed or sick animal is more likely to develop infections and require antibiotic treatment. Excessive and inappropriate use of antibiotics, antiparasitic, and antifungals in animals contributes to the emergence of resistant bacteria, parasites and fungi, which poses a major public health problem.

Animals play a vital role in maintaining the balance of ecosystems because healthy animals contribute to biodiversity and ecosystem health, which is beneficial for the entire planet.

In short, the One Health approach is an essential investment for the future. It allows to prevent health crises, protect our food and guarantee a healthier world for all.

One Health and Antimicrobial Resistance (AMR)

Antimicrobial resistance (AMR) is a major challenge for global public health. The One Health approach, which links human, animal and environmental health, is essential to combat this phenomenon. Here is how this approach can be applied to manage AMR:

Monitoring AMR

Effective AMR surveillance requires systems to track resistant pathogens in humans, animals, and the environment. This allows trends to be identified and control measures to be implemented.

Monitoring is crucial to understanding and managing AMR. According to the World Health Organization (WHO), effective monitoring of antimicrobial agents, antimicrobial residues and the spread of AMR through food chains is necessary. Monitoring programs integrated into food production are key to stopping AMR. For example, as part of a large international study, researchers from the Pasteur Institute, INRA and the Health Surveillance Institute tracked the sudden and worrying emergence of *Salmonella* which had become resistant to almost all antibiotics. Here are the key points of this study:

- Resistant bacteria. The bacteria, called *Salmonella* Kentucky, has become resistant to almost all antibiotics, including fluoroquinolones, which are essential for treating severe *Salmonella* infections.
- Chronology of emergence. The study traced the evolution of this bacteria over the last 50 years. It made it possible to determine the chronology of the appearance of different resistances and to decipher their mechanisms.
- Main vector. Poultry has been identified as the main vector of this multi-resistant strain.
- Surveillance and rationalization. The study highlights the importance of close monitoring of these bacteria responsible for food infections and the need to rationalize the use of antibiotics in livestock sectors on a global scale.
- The study highlights the importance of monitoring in poultry production.

Research and development (R&D)

Research and development are vital to combating AMR. The WHO has published a global research agenda to combat AMR, highlighting 40 priority research topics that need to be addressed by 2030. This includes the discovery of new diagnostic tests and improved treatment regimens, as well as cost-effective methods for collecting data and translating it into policy.

R&D must be closer to communities to better understand their needs and habits so that these communities are stakeholders in research against AMR, according to the "One Health" approach. The reasons that justify this approach arise from:

- In-depth understanding of the needs of communities. By being in direct contact with communities, researchers must seek to better identify the specific problems related to AMR that they face. This will allow them to adapt their research work more precisely and effectively.
- Identification of local practices. Researchers will therefore have to identify local practices that promote or, on the contrary, limit the spread of AMR. This knowledge is crucial for implementing appropriate and sustainable interventions.
- Improving adherence to prevention measures. By involving communities from the beginning of the research process, they are more likely to adhere to the AMR prevention and treatment measures that will be proposed and these proposed measures are more likely to become habits.
- Strengthening local ownership. By making communities research partners, we strengthen their sense of ownership of the solutions implemented. This promotes their long-term involvement in the fight against AMR.

To facilitate the implementation of this rapprochement, we will have to consider several actions:

- Creating dialogue platforms. Setting up spaces for exchange between researchers and community members to encourage exchanges and the co-construction of research projects.
- Training local stakeholders. Training local stakeholders (health workers, community leaders, etc.) on AMR issues and participatory research methods.
- Integrating traditional knowledge. Taking traditional knowledge and local practices into account in the design of research projects.
- Adapted communication. Use communication tools adapted to different communities to disseminate research results and encourage their appropriation.

Breeding practices

Breeding practices can influence AMR. Judicious use of antimicrobials and the adoption of better hygiene practices can reduce selection pressure for resistant bacteria.

Breeding practices have a significant impact on AMR. Inappropriate and excessive use of antimicrobials in livestock production may contribute to AMR. It is therefore crucial to adopt breeding practices that minimize the need and use of antimicrobials. For example, a meta-analysis showed a 24% absolute reduction in the prevalence of antibiotic-resistant bacteria in humans with interventions that reduce antibiotic use in animals.

Public policies

Public policies play a key role in combating AMR. The European Union has identified AMR as one of the three major health threats and has adopted recommendations to strengthen EU actions to combat AMR in a One Health approach. These policies aim to strengthen national One Health action plans on AMR, improve surveillance and infection control, and promote prudent use of antimicrobials.

A One Health approach is essential for effective management of AMR. It requires cross-sectoral collaboration and coordinated action to monitor, research and develop solutions, improve livestock practices, and implement strong public policies. Only by working together can we overcome the challenges posed by AMR and protect the health of all living things on our planet.

Conclusion

The One Health approach is more than a concept; it is an imperative necessity for global health. It recognizes that human health is intrinsically linked to that of animals and the environment. This interconnection highlights the importance of transdisciplinary collaboration to anticipate, prevent and respond to health threats. Antimicrobial Resistance (AMR) is a prime example of a challenge that can only be addressed through a One Health strategy, involving prudent use of antimicrobials across all sectors.

The data presented in this chapter highlights the urgency with which we must act. With 60% of emerging infectious diseases originating from animals and an alarming increase in AMR, it is clear that our individual and collective actions have direct consequences on overall health. Integrated disease surveillance, responsible breeding practices and effective public policies are essential components of a One Health response.

The One Health approach is not only relevant for healthcare professionals; it is crucial for everyone. Farmers, decision-makers, educators and the general public must be informed and engaged in this process. By adopting sustainable practices and supporting research and monitoring efforts, we can all contribute to a healthier future for humans, animals and our planet.

The approach to AMR by healthcare professionals has been biased towards adherence to human antimicrobials. In terms of a One Health approach, this needs to change and as community outreach takes place, they need to educate the community on AMR from a One Health perspective.

Now is the time for action. We have a collective responsibility to promote and implement the One Health approach to protect and improve health globally. This article hopes to inspire change, encourage collaboration and encourage the adoption of concrete measures to address the health challenges of our time. Together, we can make a significant difference in preserving the health of current and future generations.

Competing interests

The author has no financial and non-financial competing interests to declare.

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Chapter 36

Controlling emerging infectious diseases at the human-animal interface

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Introduction

Over the past half-century, 75% of the Emerging Infectious Diseases (EIDs) had an animal origin. For this reason, a thorough understanding of the human-animal interface is pivotal to preventing and controlling them.
This chapter provides an overview of the mechanisms behind the transmission of zoonoses, highlighting the importance of the anthropogenic determinants that play a crucial role in their spread. Through a global health lens, particular attention is given to the role of wildlife, farm animals and also companion animals as members of families, because the human-animal relationships can influence the bidirectional transmission of pathogens, whether through increased interaction or changes in the type of contact.
Even if this interface provides a path for disease transmission, it also presents opportunities for effective prevention and disease control. Owners, farmers, and health professionals can create synergies to implement biosecurity measures and cost-effective strategies for the prevention, early detection, and control of emerging diseases.
Moreover, ensuring animal welfare and health contributes to the reduction in the use of antimicrobials and to contrast the phenomenon of antimicrobial resistance eventually.
Preventing and controlling the spread of emerging zoonotic pathogens requires a holistic One Health approach that integrates human, animal, and environmental health sectors. This chapter calls for an enhanced global perspective, underpinned by a commitment to translating knowledge into locally tailored actions, especially when dealing with infectious diseases with a potential global impact.

Emerging zoonotic diseases

The context
The World Organization for Animal Health (WOAH, founded as OIE) defines emerging infectious diseases (EIDs) as “A new occurrence in an animal of a disease, infection, or infestation, causing a significant impact on animal or public health resulting from a change of a known pathogenic agent or its spread to a new geographical area or species; or a previously unrecognized pathogenic agent or disease diagnosed for the first

time”. As over the past half-century, 75% of the total EIDs had an animal origin (zoonoses), in this complex epidemiological framework, a thorough understanding of the human-animal interface in the specific environmental contexts where they may occur is crucial to prevent them properly.
Moreover, when epidemics and pandemics originate, their assessments and response measures require a holistic approach involving the main multidisciplinary and multisectoral stakeholders. This integrated approach to dealing with health challenges is perfectly summarized in the One Health concept and, ideally, it should be applied with a global mindset.

A global health perspective on zoonotic diseases

Zoonotic diseases, derived from the Greek words "zoon" (animal) and "nosos" (disease), represent a significant and complex category of illnesses. These diseases and infections can be transmitted between vertebrate animals and humans under natural conditions, creating intricate webs of interaction between hosts, pathogens, and the environment. The occurrence of zoonotic diseases is multifactorial, influenced by various dynamic factors that include the host's biology, the characteristics of the infectious agent, and environmental conditions.
Infectious diseases can be transmitted via direct contact with animals, through ingestion of contaminated food of animal origin or water, but also indirectly through vectors, which can carry pathogens from a reservoir to a host. Often, invertebrate arthropods act as vectors. When invertebrates act as intermediate hosts and can transfer pathogens between different species these are referred to with the term "bridge vector". For example, mosquitoes are vectors for the West Nile Virus (WNV) and ticks can transmit the tick-born-encephalitis virus (TBEV). In these cycles, animals can act as dead-end hosts, which, due to the low pathogenic load in the bloodstream, do not efficiently transmit the pathogens to other susceptible hosts. However, from a public health perspective, in this occurrence, animals can also be considered important sentinels for detecting emerging health threats before they impact human populations.
Additional relevant actors in the transmission cycle are reservoirs, which can be either symptomatic or asymptomatic hosts that harbor the pathogen and serve as sources of infection to other potential hosts.
Inanimate objects are capable of transmitting infectious agents as well. Contaminated medical equipment, for instance, can spread viruses like Ebola and these are defined as fomites.
Zoonotic diseases might be enzootic, emerging, or re-emerging in an area. Enzootic diseases are consistently present within a specific animal population or geographical area while emerging zoonotic diseases are those that have been newly recognized or have evolved recently. Conversely, re-emerging zoonotic diseases are those that were previously controlled or eradicated but are showing a resurgence in incidence or geographical spread, affecting new hosts or species, or expanding their vector range.
Zoonoses can negatively impact various aspects of society, and, in terms of human health, they can contribute to increased death and disability, while among livestock and other animals, they can cause increased mortality and morbidity rates.
In the zootechnical sector, zoonotic diseases can cause severe direct losses due to the culling of entire herds of livestock, animal deaths, and decreased production. Additionally, indirect costs may arise due to implementing control programs for trade and travel. Trade implications are also significant, as outbreaks can lead to restrictions and losses in international food trade and animal import and export. One of the diseases that creates the highest losses in agribusiness is African swine fever (ASF). In fact, in case of ASF outbreaks, significant trade bans on pork products from affected regions are applied, consequentially disrupting global pork markets, and leading to substantial economic losses.
Importantly, zoonoses can have profound indirect effects on people as well, including psychological trauma from the loss of pets or valuable animals, and disruptions to cultural traditions that revolve around animal

keeping and husbandry. The holistic impact of zoonotic diseases highlights the critical need for integrated control and prevention strategies to safeguard both human and animal health and mitigate economic and social repercussions.
Adopting a global perspective to understand the dynamics behind EIDs' spread is essential to designing effective strategies to tackle them.
Frequently, hotspot areas for zoonotic diseases are predominantly found in developing regions and areas characterized by strong socioeconomic contrasts and inequalities. These territories are often more vulnerable to outbreaks due to factors such as limited healthcare infrastructures, high population density, and close interaction between humans and animals. The processes of recombination and spillover predominantly occur with wildlife species, which are often migratory and reproduce rapidly, elements that challenge the implementation of effective surveillance, preventive, and control measures. Indeed, the migratory nature of many wildlife species means that they traverse various regions, potentially spreading pathogens over large distances. Additionally, their rapid reproduction rates can lead to quick changes in population dynamics, making it difficult to predict and manage outbreaks. This situation underscores the importance of understanding the ecological and biological behaviors of wildlife, as long as robust surveillance systems and international cooperation in monitoring and responding to zoonotic threats effectively.
Also in high-income countries emerging zoonotic diseases should not be underestimated. An example comes from New York City, one of the most advanced and rich metropolises in the world. In 1999, a mysterious illness caused fever and neurological symptoms in the city area, where an abnormal number of crows were also dying at the Bronx Zoo. A veterinary pathologist noticed similarities between the symptoms in birds and humans and necropsies of the birds revealed signs of viral infection, sparking concerns of a zoonotic disease. Collaboration with the public health sector's agencies identified the cause as the WNV, a previously unseen pathogen in the Western Hemisphere. This incident highlighted a critical gap in communication between the veterinary and human medicine fields, as the lack of an integrated animal and human disease surveillance system prevented early detection. Post-outbreak, policies were reformed to foster better collaboration between veterinarians and physicians, emphasizing a united front against zoonotic diseases. Importantly, humans can serve as "canaries in the coal mine" for re-emerging diseases, indicating the need for vigilance and cooperative strategies in health surveillance and response.

The role of preparedness

Capacity building for the surveillance and control of zoonoses must be prioritized and planned well in advance of any emergency. These efforts are a crucial component of preparedness strategies that should be established during peacetime, ensuring they can be quickly activated in response to an outbreak. Such preparedness is essential to prevent outbreaks from spreading beyond national borders and potentially escalating into epidemics with global impacts.
Preventive and preparedness measures are more cost-effective than response ones for controlling EIDs' spread and mitigating their impact on human and animal health. The sooner a zoonotic pathogen is detected in the environment, wildlife, or domestic animals, and the more effectively human, animal, and environmental surveillance systems communicate to prevent an outbreak, the lower the overall costs.
Some scenarios might be complicated for multiple factors, prevention is not always applicable and, sometimes, it is essential to apply mitigation strategies that might also be adapted from similar diseases to react to the unforeseen still in an efficient way. However, effective preparedness strategies that allow the early detection and a coordinated response to an emergency significantly reduce by far the cumulative financial, health, and social impacts of potential outbreaks.

As emerging diseases with pandemic potential, like the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and avian influenza, are most often zoonotic, awareness among the people who work and have contacts with animals is pivotal. Exposed individuals are at the driving seat of implementing effective biosecurity measures at the human-animal interface. These measures aim to reduce the risk of zoonotic disease spread to, from, and within animal populations and to humans. Moreover, when supported by veterinarians and trained in disease prevention and detection, animal owners and farmers can strengthen the local early warning systems for timely detection of EIDs.
As already mentioned, an added layer of this topic's complexity is due to the linkage between animal welfare, health and production. From an animal production perspective, maximizing animal growth and minimizing disease rates are crucial. When a single farm animal becomes infected, the entire herd is at risk, together with the farmer's livelihood, which depends on it. Farmers often resort to increasing antibiotic use in animals when resources are scarce, and farms have low biosecurity measures and poor management systems. To reverse this trend, the implementation of biosecurity measures is strongly recommended in every setting where the human-animal interface may enhance the interactions among people and animals, like in live animal markets, farms (both small size and intensive), wildlife environments, but also in the family contexts.
Of course, animals are not only a source of revenue. The growing global trend of forming close relationships with companion animals often humanized them as family members. If the enhanced interactions with animals within the household might increase the chances of zoonotic disease transmission, this interface might also be seen as an opportunity to design effective preventive strategies. Owners, together with health professionals, can play a crucial role in implementing measures that reduce the risk of disease transmission and in the early detection of the diseases. Responsible animal ownership also means that animal welfare should be preserved in order to minimize the use of drugs and improve the prudent use of antimicrobials when necessary and prescribed by the veterinarian. This approach can also contribute to the contrast of antimicrobial resistance, a tremendous burden for both human and animal health.

Antimicrobial resistance: a human-animal challenge

Worldwide, antimicrobial drugs (AMDs) are extensively used to treat or prevent infectious diseases in both humans and animals. Data shows that the incidence of antimicrobial resistance (AMR) significantly increased between 2000 and 2015, with projections suggesting it could double by 2030.
Veterinary medicine, particularly in livestock production, accounts for a large portion of AMD usage and the currently available data, indicate that AMD use in livestock plays a critical role in the emergence, amplification, persistence, and transmission of resistance determinants across all involved ecosystems.
In livestock, antibiotics are not only used to treat sick animals but are also used preventively for metaphylaxis and prophylaxis purposes of entire herds. Metaphylaxis involves the collective treatment of all animals in a group when a certain percentage show signs of infection, while prophylaxis refers to the preventive administration of AMDs in the presence of infection risk factors, even when no animals are currently infected. These treatments can be applied to protect the health and welfare of the herd at various stages of animal development and production cycles, for example, during the weaning period in piglets, the transportation of calves, and the drying off of dairy cattle. When combined with the substantial quantities used in human healthcare, this contributes significantly to the emergence and spread of AMR genes across humans, animals, and the environment they share.
Low- and middle-income countries (LMICs) report the highest levels of resistance prevalence which can be in part explained by the black market which further enhances the risk of unregulated access to AMDs. This

aspect complicates the ability to accurately quantify and monitor actual antimicrobial use (AMU) levels, can cause the underestimation of the drugs' consumption, and thus lower the risk perception.
Although global collaboration to reduce AMU is encouraged, many local factors hinder its successful implementation, for instance, inadequate motivation, limited awareness, malpractice, and insufficient regulations. Additionally, due to resource constraints and higher barriers to access it, developing countries often adopt and implement evidence-based scientific advancements more slowly. Involving experts from human and social sciences is therefore essential to strategically facilitate the adoption of new approaches at the community level.
In order to operationalize this approach in an integrated matter across sectors and disciplines, in 2015 a Global Action Plan on Antimicrobial Resistance was adopted through decisions in the World Health Assembly, the Food and Agriculture Organization of the United Nations (FAO) Governing Conference and the World Assembly of WOAH Delegates. Countries that agreed to have a national action plan on AMR consistent with this Plan, are currently implementing policies, interventions, and initiatives at the national level. The degree of implementation of each national plan can be tracked and is available online. This strategy is pushing toward a more comprehensive vision of AMR, helps to raise awareness, and brings health professionals together to achieve shared goals.
To effectively reduce global antibiotic consumption and to promote its appropriate use, it will be crucial to scale up antibiotic stewardship plans, transitioning from a local sectoral approach to an international intersectoral one. Implementing antibiotic stewardship at the community level can help address the AMR crisis effectively by ensuring that practices are tailored to local contexts and resources. In turn, this approach will lay the groundwork for a more coordinated and comprehensive strategy to tackle AMR globally.
Furthermore, pathogen transmission can be bidirectional, and pathogens can spill over from animals to humans and back, increasing the risk of new and more virulent strains. There is a growing scientific interest in investigating and monitoring reverse zoonoses. In particular, the methicillin-resistant form of *Staphylococcus aureus* (MRSA) exemplifies this risk, as it can spread between humans and animals, including through direct contact in various environments like healthcare facilities and farms. Although further research on MRSA's prevalence in animals is needed, evidence already shows that it may carry antimicrobial resistance traits derived from human strains.
Awareness of emerging reverse zoonoses is critical for pet owners, farmers, veterinarians, and clinicians, who are often the first who make a crucial contribution to the prompt integrated detection and report of the unexpected emergence of infectious diseases.

An integrated cost-effective approach to prevent and control infections at the human-animal interface

The integrated approach advocated in this chapter to preventing and controlling infections at the human-animal interface is not a new framework, but it has deep roots in health science history. However, it was not until recent highly impacting zoonotic outbreaks such as SARS-CoV1 and SARS-CoV2 raised general public interest that this holistic perspective gained more significant momentum in both scientific and political agendas. As a matter of fact, the concept of One Health (OH), defined as the "integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals, and ecosystems," has increasingly been recognized as vital.

Given that OH operates within One World, epidemiological evaluations and interventions must be developed based on biological and socioeconomic evidence. Efficient and effective trans-sectoral approaches must be targeted and well adapted to the context to allow effectiveness at the local level that can be later scaled up at the global one. This exercise led to identifying opportunities for creating additional value in interdisciplinary cooperation and reducing the shared burden of complex health challenges. One of the most compelling examples of added value is the economic benefit that OH integration can bring. Indeed, to demonstrate the impact of interventions and secure stakeholder interest in structured collaborations, it is essential first to prove their added value, which can be more frequently assessed as earlier disease detection or higher cost-effectiveness.

By understanding the societal and ecological ramifications of health crises and interspecies risks, stakeholders can coordinate interventions across sectors and share costs. This approach helps reduce the financial burden on individual sectors, even if the overall cost to society remains constant. Additionally, it promotes a fair distribution of responsibilities and resource preservation, while reinforcing the understanding that health is a systemic outcome, shaped by the complex interactions between human, animal, and environmental factors.

Demonstrating the added value of human-animal programs' integration

Successful examples of integrating human and veterinary medicine have already shown clear benefits in various settings, for instance, in the strategy to tackle dog-mediated rabies.

The Quadripartite Regional Coordination Group composed of Representatives/Directors of the FAO, the United Nations Environment Programme (UNEP), the World Health Organization (WHO), and the WOAH, together with the Pan-African Rabies Control Network (PARACON) of the Global Alliance for Rabies Control (GARC), made a joint appeal to eliminate human deaths from dog-mediated rabies by 2030 and developed a Global Strategic Plan.

The efforts of a coordinated strategy to eliminate rabies in the African subregions, including dog mass vaccination campaigns and pre-exposure-prophylaxis (PEP) in humans, already allowed to reduce the burden of the disease in both animal and human populations, resulting in billions of dollars saved. Considering the dimension of the problem, which causes about 59,000 deaths yearly (at least 36% notified in Africa), and the role of the dogs (as most cases are dogs mediated), an integrated approach is pivotal.

Overall, the OH approach offers significant advantages in controlling EIDs at the human-animal interface and contributes to global health security.

Conclusion

A thorough understanding of the human-animal interface is crucial to grasp the dynamics that can influence the spread of EIDs, address their determinants, promote preventive measures, and implement cost-effective control strategies.

This chapter has outlined how zoonoses emerge and spread due to anthropogenic factors and the interactions among humans, wild, farmed, and companion animals. The One Health approach, which promotes cooperation across human, animal, and environmental health disciplines, is essential in developing robust prevention and control mechanisms.

This mental framework should be reflected when designing emerging diseases' preparedness strategies, which must be prioritized over responsive ones. Indeed, focusing on early detection systems, biosecurity protocols, and enhanced communication between human and veterinary medicine helps mitigate the

financial, social, and health impacts of EIDs. Merged with responsible animal ownership and welfare practices, this approach is also pivotal in reducing the misusage of drugs, especially antimicrobials, eventually contributing through their prudent use to tackle AMR.
The added value of an integrated approach becomes evident when examining practical successful initiatives, such as the rabies control one presented. By fostering collaboration and sharing resources, these initiatives reduce the burden on individual sectors and enhance global health resilience.
Controlling infections at the human-animal interface is crucial to prevent the spread of future emerging diseases with pandemic potential. The most effective strategies rely on integrated preventive measures that reduce the risk of spill-over and spill-back and foster multisectoral cooperation. To do so, a broad global mindset is required, together with a solid willingness to and capability of putting knowledge into locally feasible, cost-effective and practical actions.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 37

One Health and antimicrobial resistance

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Introduction

Inappropriate use of antibiotics in human health, animal health and agri-food sectors has contributed to the phenomenon of Antimicrobial Resistance (AMR). Additionally, the waste generated from these sectors can contaminate the environment if not treated appropriately. The environment (including water pathways, soil, and land) acts as a reservoir, playing a crucial role in the development, transmission, and spread of AMR. Several other factors influence the AMR landscape in different settings. These include factors involving access to effective antimicrobials, market practices, the pharmaceutical industry, health systems, socio-behavioral, Infection Prevention and Control (IPC) and Water Sanitation and Hygiene (WASH), livestock and animal husbandry practices, policy implementation and political will. AMR is also intricately linked to the triple planetary crisis of climate change, pollution and biodiversity loss, and is situated at the human-animal-environment interface.

If left unaddressed, AMR could have adverse consequences on human health, animal health and food security. It could also adversely impact productivity, cause economic losses, affect farmers' livelihood, worsen poverty and hinder the achievement of several Sustainable Development Goals (SDGs). Studies suggest that low-income and low-middle-income countries will be disproportionately affected. The problem is further compounded by limited research and development of new antimicrobials. Due to its multi-factorial, multi-sectoral nature, AMR is now considered a global public health threat requiring a 'one health' approach.

Even though 'One Health' is an old concept, it has gained immense attention since COVID-19. 'One Health' is defined as an "integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals, and ecosystems". It recognizes that the health of humans, domestic and wild animals, plants, and the wider environment (including ecosystems) is closely linked and interdependent. The approach is based on the principles of equity across sectors, socio-political and multicultural parity, socioecological equilibrium, broader societal stewardship, and transdisciplinary and multi-sectoral collaboration (**Figure 1**). Given the complex nature of AMR, the 'One Health' approach has been adopted in AMR mitigation efforts and for multiple global governance mechanisms such as the Global Action Plan on AMR and the One Health High-Level Expert Panel (OHHLEP).

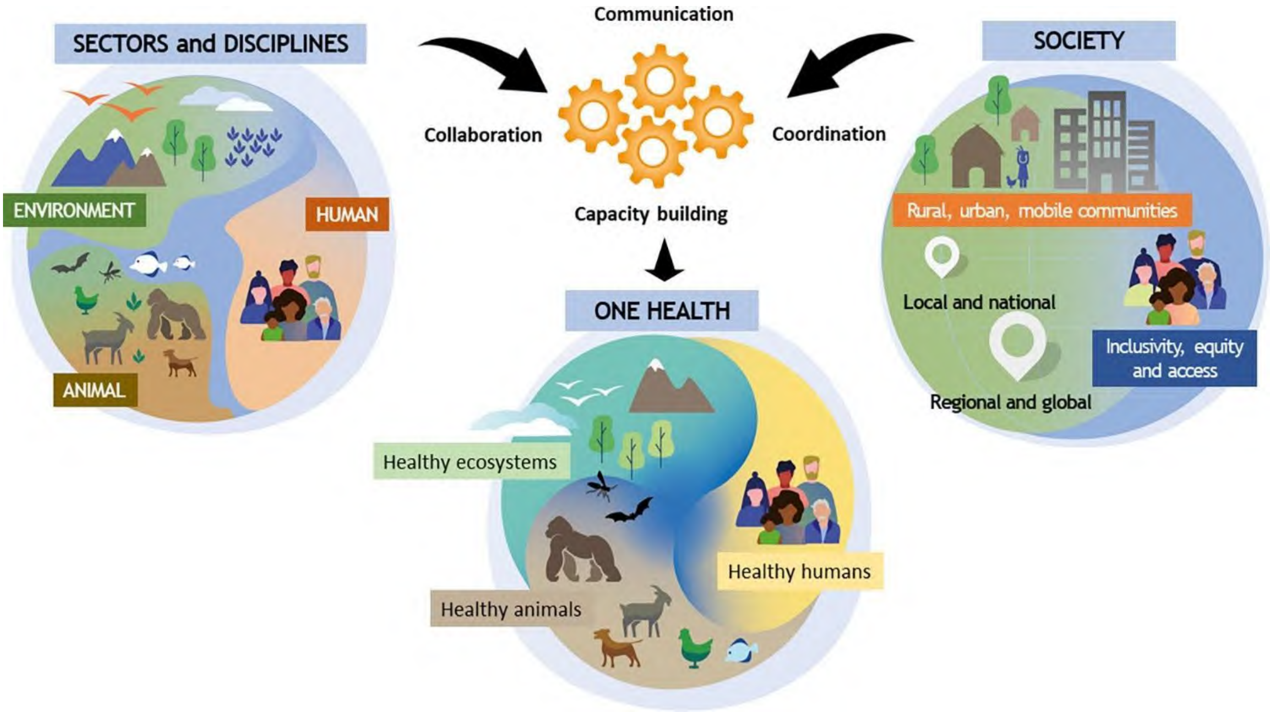

Figure 1. Multi-sectoral collaboration in One Health (Adapted from: One Health High-Level Expert Panel, *et al.* 2022).

This chapter discusses the 'One Health' aspect of AMR and its importance in tackling AMR through a brief overview of the drivers of AMR and contributory roles of each sector, the current ongoing measures to address AMR and potential recommendations to further strengthen these measures.

Role of the human sector

Innumerable lives have been saved by using antibiotics since the discovery of penicillin. Antibiotics have been the cornerstone of the modern medical era, not just in the treatment of infections, but in the management of cancers, organ transplantations and complex surgeries. Over the years, pathogenic organisms have developed resistance to almost all groups of antibiotics resulting in significant morbidity and mortality. A significant number of deaths also happen because of a lack of access to effective antibiotics.

Towards a more focused approach, the World Health Organization (WHO) has formulated the 'Bacterial Priority Pathogen List (BPPL). The list includes 24 pathogens from 15 families (including Gram-negative bacteria resistant to last-resort antibiotics, drug-resistant Mycobacterium tuberculosis, and other high-burden resistant pathogens such as *Salmonella, Shigella, Neisseria gonorrhoeae, Pseudomonas aeruginosa, and Staphylococcus aureus*). These pathogens exhibit high rates of multidrug resistance and are associated with significant mortality and morbidity.

Multiple systematic analyses have shown that antibiotic consumption and inappropriate use drive AMR. The Global Research on Antimicrobial Resistance (GRAM) project highlighted a significant increase in antibiotic consumption over time. Multiple factors drive inappropriate antibiotic use in the human health sector. Although some factors are common across the globe, other factors are more pronounced in low-middle-income countries (LMICs). These include challenges at different levels of healthcare systems; perceptions and practices of patients and communities; gaps in regulations or implementing regulations; over-the-counter antibiotic use; inappropriate treatment practices by healthcare workers, difficulties in implementing stewardship programs, gaps in infection prevention and control both in healthcare setups and in communities, lack of access to clean water and WASH facilities, and effective antibiotics. A lot more can be said about the drivers of AMR and challenges in the human health sector, but other chapters of this book have elaborated a great deal, and hence we will now move on to other sectors.

Role of the animal sector

Soon after antimicrobials started being used for humans, they were introduced into the animal sector. The use was for multiple purposes, including for therapeutic (treating animals for a diagnosed infection), for prophylactic (preventing infection in animals at risk of infection), and for growth promotion (Antibiotic Growth Promoters/AGPs). Such use for growth promotion was mainly to improve the feed conversion ratio, facilitate earlier weaning, increase the growth rate and reduce morbidity and mortality. Initially, though many antibiotics were common to both sectors, some were found unsuitable for human use and therefore used specifically for animals (for example bacitracin, avoparcin and colistin).

In 1951, the US Food and Drug Administration (FDA) approved the use of AGPs in animals. Over the past 70 years, there have been significant changes to the way antibiotics are used in the food-animal sector. Parallel to this, rising global population has resulted in increased demand for animal products for protein requirements resulting in more intensive farming practices. The Organization for Economic Co-operation and Development (OECD) suggests that meat from poultry, followed by pigs, accounts for a large proportion of protein sources. Aquaculture (including fisheries) also contributes to 19% of total edible protein for 40% of the population worldwide. Studies also suggest that climate change could adversely affect animal health and welfare, making them more susceptible to infections and in turn increase the demand for effective antibiotics.

Challenges in the animal sector

Multiple factors drive the inappropriate use of antibiotics in the animal sector (especially in LMICs). These include feeds premixed with antibiotics, lack of proper labelling of feeds, ignorance among farmer/farmer associations regarding the consequences of misuse, lack of veterinary/para veterinary services, failure to adhere to infection prevention and control practices, over-the-counter availability of bulk antibiotics, failure to follow withdrawal periods and absence of antibiotic residues monitoring. Withdrawal period is defined as the time that must elapse between the last administration of a veterinary medicine and the slaughter or production of food from that animal, to ensure that the food does not contain levels of the medicine that exceed the maximum residue limit. In many LMICs, poor biosecurity measures (such as overcrowding), lack of infection prevention measures and unhygienic conditions, and a lack of access to diagnostics, vaccines and veterinary services have prompted the indiscriminate use of antibiotics for prophylactic and metaphylactic purposes. This use in animals has contributed to the emergence of drug-resistant strains, with the potential for transmission from animals to humans through specific pathways (most crucial being food-borne). Resistant bacteria can transfer resistance genes to gut commensals, interact with them and spread further. Studies have also suggested that antibiotic residues could have other harmful effects such as promoting allergies and alteration of gut microbiome. Unsafe food causes 600 million cases of foodborne diseases and 420,000 deaths each year. Thirty percent of these foodborne deaths occur among children under 5 years of age.

Recent studies have shown that similar to humans, AMR in animals (including aquaculture) is rising. Studies have also reported high rates of resistance in poultry and swine industries. Such high rates of resistance could potentially result in production losses and threaten food security.

Surveillance and regulatory measures

As early as the 1960s, concerns about potential harm resulting from antibiotic use in the animal sector and the need for regulations were raised, based on the potential for resistant bacteria to transfer from animals to humans. The Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine (UK) referred to as 'Swann 1969', was one of the first groups that suggested avoiding the use of overlapping antibiotics for growth promotion purposes. Later, many others voiced these concerns too. Evidence of the potential harm to humans and the environment is now well documented.

Although regulations vary, more countries are now in the process of adopting stringent regulations to use antibiotics appropriately in the animal sector. The majority of high-income countries (HIC) have banned antibiotic use as growth promoters/feed additives and for mass prophylactic use in line with WOAH and WHO recommendations. Many have also banned the use of critically important antimicrobials with the highest priority in the animal sector. Some LMICs have banned the use of antibiotics for growth promotion, but implementation of these regulations remains a challenge. Many HICs have well-established surveillance systems to measure AMU and AMR in animals, but most LMICs are yet to have these systems in place. Progress has been slow, (as evident from the WOAH report, where many countries continue to use antibiotics for growth promotion purposes) mainly due to the fear of losing crop and livestock with ensuing economic losses.

Civil society and consumer groups have played a crucial role in raising awareness and advocacy regarding this issue. For example, in December 2018, nearly 40 civil society organizations met in Bangkok to address the issue of misuse of antibiotics on farms. The resulting 'Bangkok Declaration' on AMR has several strong recommendations to guide global action to address antibiotic misuse in animals and promote sustainable food systems. Studies have shown that interventions restricting antibiotic use in food-producing animals are associated with a reduction in antibiotic-resistant bacteria in these animals. There are also examples from both HICs and LMICs suggesting that the implementation of good biosecurity practices drastically reduces the requirement of antibiotics without causing significant economic loss.

Role of environment

After decades of 'being in the shadows', the role of the environment in contributing to the AMR threat has been increasingly recognized. The effluents generated from the pharmaceutical industry, and waste generated from healthcare delivery systems and food production systems (containing antibiotics and antibiotic residues) contaminate the environment. Although experts have highlighted critical gaps in the literature and areas where more research is warranted, it is now well established that the environment serves as a reservoir for interactions between different microorganisms, the emergence of drug-resistance strains and the transfer of resistance genetic materials among different microorganisms (**Figure 2**).

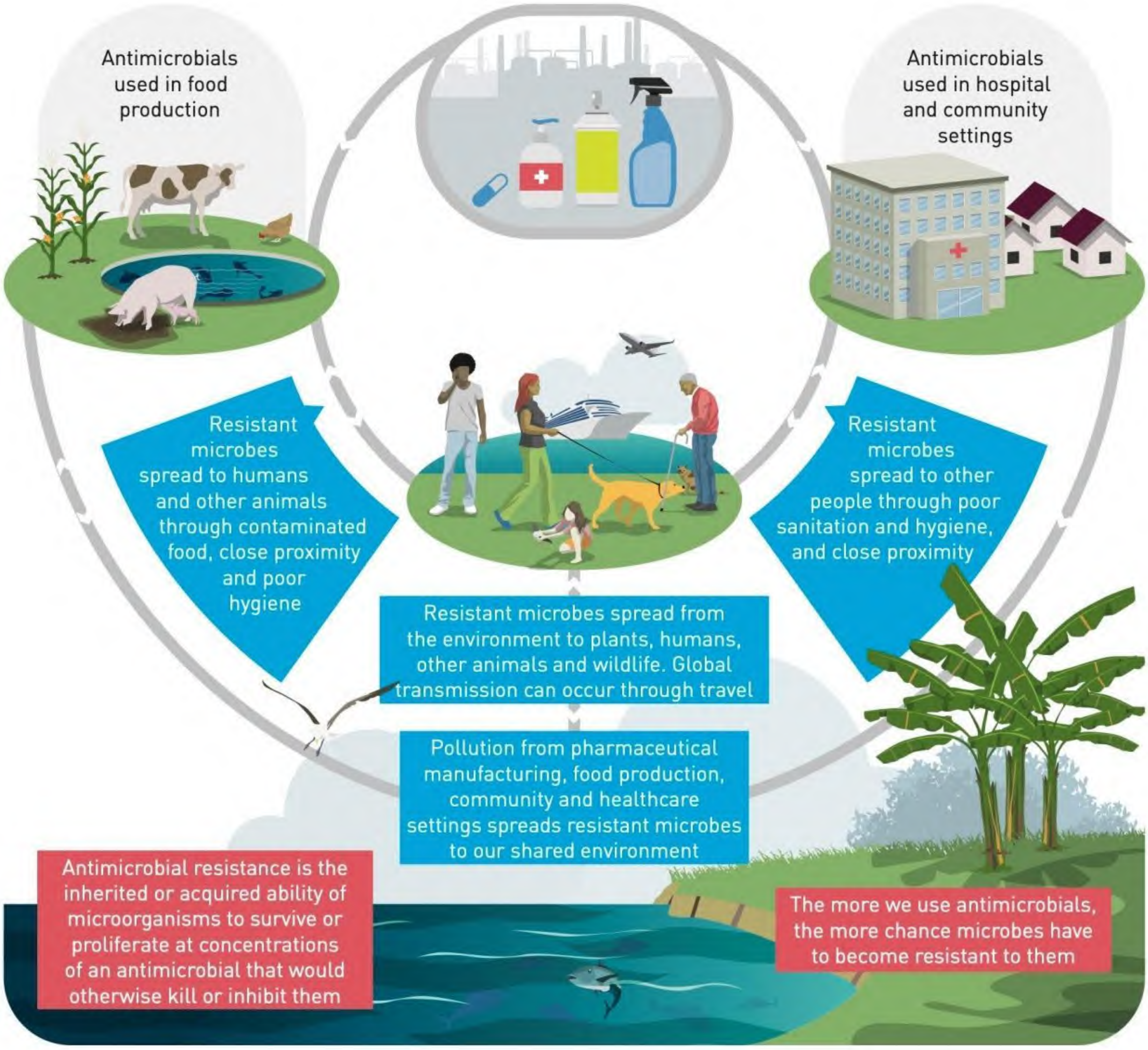

Figure 2. Environment and AMR (Adapted from United Nations Environment Programme, 2023).

Larsson *et al.*, have extensively worked on different aspects of pharmaceutical pollution of the environment. Unfortunately, in many LMICs, there are no strict government regulations determining the discharge limits for different antibiotics in effluents. The pharmaceutical industry, through the ‘AMR Industry Alliance’, has however voluntarily developed and published standards to manufacture antibiotics responsibly along with predicted no-effect concentrations for discharge limits and reduce the environmental impact of AMR.

Inadequately treated waste from healthcare sectors (hospital effluents), waste from wastewater treatment plants (WWTPs), and effluents from the animal sector and agriculture are other important contributors to environmental contamination. Improper disposal of used and expired antibiotics is another factor. Further in-depth understanding of which factors and their extent favor the evolution of resistance genes in the environment will greatly help in designing preventive strategies.

Similar to other sectors, better infrastructure facilities are needed to handle wastes before disposal in the environment, improved WASH facilities to prevent fecal waste contamination, and appropriate disposal of unused and expired antibiotics. Climate factors, and pollutants in the environment such as heavy metals, pesticides, and microplastics, will continue to be challenges that influence these complex dynamics.

Why AMR needs a One Health approach

As seen from the above sections, it is clear that AMR cuts across human, animal and environment interfaces. The indiscriminate use of overlapping antibiotics in human health, animal health (including aquaculture and fisheries) and crop production has resulted in the emergence and spread of resistant genes and mobile genetic elements from humans to animals and vice-versa through different pathways. In many countries, industrial effluents, inappropriately treated waste from communities, healthcare systems and animal husbandry, inadequate infrastructure to manage waste, gaps in WASH and IPC across sectors, inappropriate handling of unused or expired antibiotics, climate change and pollution have all resulted in the environment being a reservoir for the emergence and transmission of resistance. Globalization has contributed to the transfer of resistant bacteria from one region to another. In addition to these, the majority of emerging infectious diseases are zoonotic in origin. Hence among many of the world's problems, AMR is truly a 'One Health' problem. Therefore, experts have repeatedly advocated for adopting 'One Health' as a guiding principle in AMR mitigation efforts. Similar to any other complex societal problem, AMR requires a multisectoral, collaborative (both within and across sectors) and transdisciplinary approach. An inherent principle shift in focus is needed from the human-centric approach (anthropocentric) to a broader holistic perspective of planetary health, giving appropriate importance to humans, animals and nature.

A prerequisite for success on the ground, therefore, is to have coordination through governance mechanisms, synergies in policies, advocating guiding principles, practicing antimicrobial stewardship across sectors, developing common integrated surveillance systems, and monitoring use and resistance across sectors. Using Intervention and Implementation Research with a One Health approach to generate context-based evidence for sustainable and cost-effective solutions involving key stakeholders would be key to have sustained contextual solutions.

Overview of key initiatives as part of AMR mitigation efforts

This section highlights a few milestones in AMR mitigation efforts (these are only examples and non-exhaustive).

Global Action Plan on AMR

The Global Action Plan (GAP) on AMR which was adopted in 2015 had tripartite organizations WHO, FAO, and WOAH (formerly OIE). Realizing the important role of the environment, the tripartite was expanded to the quadripartite with the inclusion of the UN Environment Programme (UNEP) in 2022. Many countries have adopted their respective National Action Plans (NAPs) on AMR using a One Health approach. Continued efforts and guidance of the quadripartite organisations over the years with efforts from countries and various stakeholders have resulted in better awareness of this issue, improvement in surveillance capacities (as seen from the GLASS enrolment), countries adopting regulatory measures for appropriate use of antibiotics and fewer countries using antibiotics for growth promotion purposes. Countries have faced varying challenges though in implementing various components of NAPs. Sustained financing, intersectoral co-ordination, governance issues and involvement of all stakeholders have been consistently identified as key challenges.

United Nations high-level meeting on AMR

A one-day high-level meeting (HLM) on AMR was held on September 21st, 2016, in UN New York, which served as a major turning point in the AMR landscape. Besides, increased political action and countries committing to adopting NAPs, led to the establishment of the Interagency Coordination Group on AMR (IACG) which published several important recommendations in its report in 2019. The HLM in September 2024 gives another opportunity for countries to increase their level of commitment to action on AMR through optimal implementation of NAPs, one health governance and coordination, adoption of targets in different sectors and sustainable financing.

Muscat manifesto

The third high-level ministerial conference on AMR hosted by Sultanate of Oman in 2022 was one of the major meetings in which more than 47 countries have committed to various measures on AMR. Some of the notable points include the following:

- Eliminate the use of medically important antimicrobials for human for non-human purposes.
- Ensuring access group comprises at least 60% of overall antibiotic consumption in humans by 2030.
- Reducing the total amount of antimicrobials used in the agri-food system by at least 30- 50% from the current level by 2030.

Formation of One Health global leaders group on AMR

To increase political will and action on AMR, the quadripartite launched the One Health Global Leaders group (GLG) with high-level representations from governments, different ministers, the private sector and civil society. The GLG has senior political dignitaries and key representatives from one health sector. Since its establishment, the group has provided several recommendation documents that have shaped the AMR landscape.

World AMR Awareness Week (each year between 18th-24th November)

Formally called World Antibiotic Awareness Week, this was a campaign launched by WHO aiming to increase awareness among the general public on the need for rational use of antibiotics and also share best practices. Most of the countries have adopted this campaign through various activities. In addition to these, other measures towards engaging various stakeholders to improve awareness have been established. This includes platforms for engaging youth and media professionals.

In addition to the above, multiple guidance documents have been developed over the last decade, such as costing and budgeting tools for NAPs, handbooks for NAPs implementation, and developing NAP monitoring and evaluation plans. Other key milestones have been highlighted in **Table 1**.

Table 1. Overview of other key initiatives as part of AMR mitigation efforts.

Year	Description
2005	WHO published the list of critically important antimicrobials. The 6th revision was published in 2019 titled, 'Critically important antimicrobials for human medicine, 6th revision'. The list was further updated in 2024 as 'Medically Important Antimicrobials List'
2015	Establishment of Global Antimicrobial Resistance and Use Surveillance System (GLASS) by the WHO, which is a global platform for monitoring data on AMR and AMU from different countries.
2019	AMR Multi-Partner Trust Fund for Countering antimicrobial resistance with a 'One Health' approach which is a pooled funding mechanism for various countries.
2020	Global Leaders Group (GLG) on AMR
2021	Establishment of One Health High-Level Expert Panel (OHHLEP) by the Quadripartite organizations i.e., FAO, UNEP, WHO and WOAH
2022	WOAH adopts ANIMUSE in (animal antimicrobial use global database) which is a global platform for data on antimicrobial use in animals)
2022	Quadripartite launches Multi-stakeholder Partnership Platform
2022	Third level Ministerial Conference on Antimicrobial Resistance in Oman
2022	Establishment of InFARM -International FAO Antimicrobial Resistance Monitoring (InFARM) system that supports countries in AMR surveillance data generation and analysis mainly from livestock, fisheries, and aquaculture and associated food products.
2023	1st Global Joint Summit of Human and Veterinary Medicines Regulatory Authorities to Preserve Antimicrobials
2023	Quadripartite published the One Health Priority Research Agenda for AMR research agenda which also serves to help policymakers, researchers, and a multidisciplinary scientific community work together on solutions to prevent and mitigate AMR within the One Health approach.
2024	FAO launched the "Reduce the Need for Antimicrobials for Sustainable Agrifood Systems Transformation (RENOFARM)" which is a ten-year global programme by FAO for sustainable food systems.

Barriers and enablers in implementing One Health

Multiple studies from different contexts have shown the value of one health approach, especially with respect to building surveillance capacities, adopting policies and frameworks that promote multi-sectoral collaboration at national and sub-national levels, and overall better health systems. Studies from different LMIC contexts have also documented challenges and facilitators concerning the One Health approach for the management of zoonoses or emerging infectious diseases. One study has identified that One Health calls for more than just policy frameworks and includes complex factors that could either act as barriers (e.g., technical, institutional, contextual) or enablers (e.g., existing policy frameworks, platforms for sharing data across sectors, inter-sectoral coordination mechanisms). Competing priorities, lack of adequate funding mechanisms and limited institutional capacities continue to be the main barriers, however.

In addition to these, some of the common challenges while implementing one health NAPs on AMR include lack of financial sources, lack of skilled human resources, infrastructure, skilled human resources, lack of surveillance systems, political commitment, working in silos among sectors without cross-sectoral coordination, poor regulatory implementation, geographical disparities over access to medicines, access to diagnostics access to vaccines, to name a few.

Conclusion

Complex factors such as urbanization and globalization have shaped the ways humans interact with other living beings and broader ecosystems. The emergence of zoonotic diseases such as H1N1, H5N1, Nipah virus, Eblola virus and other coronaviruses (including COVID-19) is a clear example of the increased risks. AMR is a complex global health phenomenon that occurs at the interface of humans, animals and the environment and interacts with broader ecosystems. It is a cross-cutting problem that transcends borders and could have devastating consequences in addition to impacting livelihoods and economies. On the other hand, climate change, pollution and loss of biodiversity impact the way different microorganisms interact, evolve and adapt. All these are in a sense, interdependent, meaning that progress in one sector will not be achieved without progress in the others. An inherent principle shift in focus is needed from the human-centric approach (anthropocentric) to a broader holistic perspective of planetary health, giving appropriate importance to humans, animals and nature. A broader whole-of-society and a whole-of-government approach based on One Health principles is essential to manage this complex problem. It is imperative that measures to raise awareness about this complex problem and promote a sense of responsibility among sectors is the need of the hour. Good collaboration both within and across sectors, synergies in policies and guiding principles, antimicrobial stewardship across sectors, developing and implementing common integrated surveillance systems across sectors, and having appropriate targets and indicators for monitoring and evaluation are essential for ensuring forward momentum and on-the-ground impact. For better coordination, the creation of One Heath Secretariats would be important with transdisciplinary teams across human, animal and environmental sectors. Other stakeholders such as donors, professional associations, food safety organizations, consumer groups, civil society groups and private organizations should be involved. Measures to address barriers and challenges must be taken to achieve forward momentum. Finally, generating context-specific data, piloting novel projects through implementation research, and creating both global and domestic finance mechanisms are needed to address the unique needs of LMICs with a One Health focus. A roadmap incorporating these plans with appropriate timelines and sustainable financing will go a long way to ensure that the One Health approach remains a viable pathway to address AMR.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 38

The role of the environment in the emergence and spread of AMR

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Introduction

Antibiotics have been essential in reducing the burden of infectious diseases in humans, animals, and plants for decades. The effectiveness of antibiotics is recently at risk because several of them, antivirals, antiparasitics, and fungal treatments no longer work because of antimicrobial resistance (AMR). The World Health Organization considers AMR in humans and animals to be one of the top ten threats to global health. Estimates suggest that by 2050 up to 10 million deaths could occur annually. AMR also poses economic challenges, leading to at least USD 3.4 trillion annually by 2030 of GDP drop and increasing by 24 million the number of those living in extreme poverty, the low-income and middle-income countries will bear most of the burden.

The environment and the AMR are strictly linked. The environment acts as a vehicle for the spread of antimicrobial-resistant microbes and a reservoir for antimicrobial pollutants, which negatively affect biodiversity and ecosystems.

The environmental aspects of AMR encompass pollution from hospitals and community wastewater, as well as runoff from pharmaceutical production and agricultural practices involving plants and animals. Water can also be an important source of antimicrobial residues, (ARBs) antimicrobial-resistant bacteria and (ARGs) antimicrobial-resistant genes. There is a direct link between water quality used for irrigation and antimicrobial-resistant bacteria in foods. Effluent from municipal sewage can harbor ARGs and ARBs. Wastewater and fecal sludge create a reservoir for antimicrobial substances, residues, and pathogenic genes in the environment. This can create selective conditions for the development and proliferation of AMR strains. Bacteria in water, soil, and air can acquire resistance following contact with resistant microorganisms.

Chemical disinfectants are commonly used in food production and processing to ensure hygiene and environmental sanitation. However, bacteria that exhibit increased tolerance to biocides have been found in these environments.

Therefore, environmental degradation and pollution factors connected to the crisis of climate change, and biodiversity loss are the very same ones that alter microbial diversity and facilitate the development, transmission, and diffusion of AMR.

The "One Health" approach, recognizes that the health of the people, animals, plants, and the environment are closely linked and interdependent, and can successfully address the AMR.

AMR as a global threat

While some progress has been achieved over the past years, The World Health Organization considers (AMR) antimicrobial resistance a significant health and developmental challenge, being listed as one of humanity's top 10 global public health threats. In 2016, (AMR) was gaining political attention at the highest levels. At a UN high-level meeting, UN member states pledged to take a coordinated approach to address the root causes of antimicrobial resistance across human health, animal health, agriculture, and environmental health. The estimates on antimicrobial resistance (AMR) projected that 10 million deaths caused by AMR could occur by 2050.

A 2022 study estimated that almost 5 million deaths per year are associated with drug-resistant bacteria, with a higher burden among low-income and middle-income countries (LMICs). It emphasizes the effects of bacterial AMR across the life course: newborns, older people, and people with chronic illnesses are particularly susceptible. Treating resistant bacterial infections is estimated to cost US$412 billion annually, and productivity losses due to AMR could account for $443 billion per year. AMR is a natural response that is both intrinsic and genetically acquired and various factors favor its increase. The main drivers for AMR are:

- Poor infection prevention and control in health-care facilities and food production systems.
- Inappropriate use of antimicrobials in health and food-producing animal sectors.
- Lake of access to water, sanitation, and hygiene (WASH) in healthcare facilities.
- Lake of collection, treatment, and disposal of municipal and livestock production wastewater, and solid waste management including pharmaceutical waste.
- Poor housing and occupational conditions including food animal production, and meat-processing sectors (a high-risk group for AMR).
- Lake of access to basic health services for refugees and migrants.

All these factors have an important role in spreading and increasing the AMR in the environment (water, soil and air).

AMR is linked to the environment

The environment and the AMR are strictly linked. The environment is a vehicle for spreading AMR microbes and a culprit of antimicrobial pollutants, negatively impacting biodiversity and ecosystems. The spread of the antimicrobials increases the AMR through the release of residues into the environment. Growing antimicrobial resistance linked to the discharge of drugs and particular chemicals into the environment is one of the most worrying health threats today, according to new research from the UN Environment that highlights emerging challenges and solutions in the environmental space.

The crises of climate change, biodiversity loss, and pollution are the very same ones that alter microbial diversity and facilitate the development, transmission, and diffusion of AMR. Antimicrobials have eco-toxicological effects that can disturb soil and plant health, reducing soil microbial diversity. Soil microbial diversity is an essential shield for the spread of AMR, as well as a main source of pharmaceutical discoveries. Chemical disinfectants are frequently used in the food production and processing environment and are critical for food hygiene and environmental sanitation. Bacteria with increased tolerance to biocides have been recovered from food production environments. Adding to these health hazards, the changing environmental conditions are also increasing the suitability for the transmission of many water-borne, air-borne, food-borne, and vector-borne pathogens.

AMR in agriculture and animal farming

AMR is also affected by land use changes to agriculture. Antimicrobial agents are often overused and misused in human and veterinary medicine, animal farming and industrial settings. Antibiotics are commonly added to animal feed for therapeutic/prophylactic use or growth promotion, and are excreted in urine and faeces. This results in residues of antibiotics, bacteria and antimicrobial-resistant metabolites and AMR genes, which accumulate in wastewater, agricultural fields and agricultural runoff. Plants grown in soil with applied animal manure were found to absorb chlortetracycline antibiotics. Antimicrobials used in crops can be additional sources of resistance evolution.

Figure 1 illustrates a simplified framework that describes how AMR can develop and spread, particularly in the context of environmental and agricultural interactions. It identifies four key stages.

- *Stressor.* This stage highlights environmental sources of stress that contribute to the spread of AMR. For example, agricultural and wastewater runoff may contain antibiotics, which when released into the environment, increase selective pressure for resistant bacteria.
- *Reservoir.* Antibiotics and antimicrobial-resistant pathogens or genes can accumulate in certain "reservoirs" like soil, water, or organisms. These reservoirs serve as sources from which resistance can spread. Wastewater and runoff can carry antibiotics and resistant bacteria into natural environments, such as soil and water systems.
- *Process.* Once antibiotics and AMR genes are introduced into the environment, processes like fixation to soil and plants, horizontal gene transfer (where resistance genes move between different organisms), and AMR evolution (where bacteria evolve to become resistant) can occur. These mechanisms help to sustain and spread resistance across different bacterial populations and environments.
- *Health mediator.* Ultimately, these processes lead to the proliferation of antimicrobial resistance (AMR) in ecosystems, affecting human and animal health by limiting the effectiveness of antibiotics used in medical treatment.

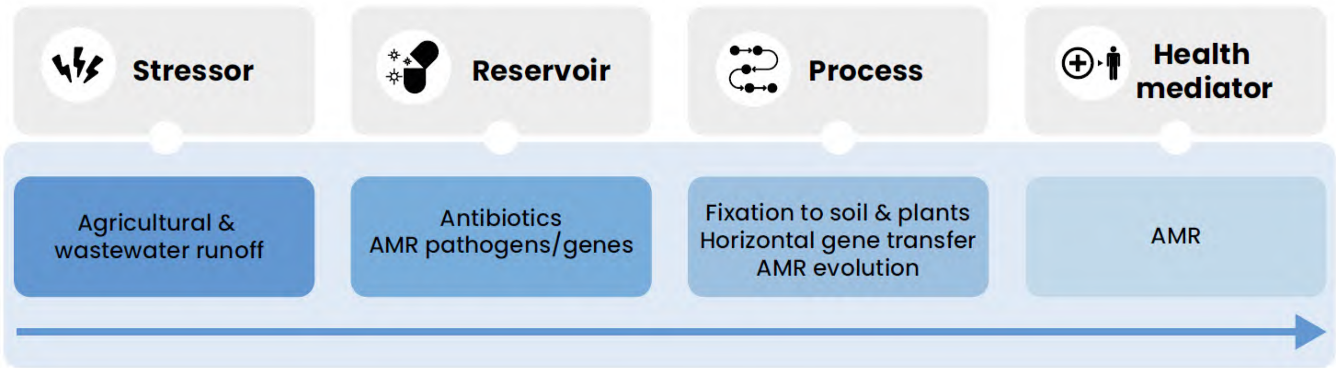

Figure 1. How AMR can develop and spread (Adapted from: World Health Organization, 2022).

The figure shows the progression from environmental factors to the eventual development of AMR, demonstrating how ecological contamination (such as agricultural runoff) contributes to the persistence and spread of resistant genes and pathogens in the environment.

As antibiotics are more frequently used in animal husbandry, resistance is rapidly developed and spread through the environment in the shape of unmetabolized antibiotics. The transmission of diseases from animals to humans through zoonotic pathogens bears the risk of communicating also antibiotic-resistant genes (ARGs) through contact or consumption of animal products. Therefore, people working in or living close to livestock facilities are disproportionately at risk.

Many classes of antimicrobials critically important for human health are also used for crop and food animal production. There is a risk of resistance against these drugs spreading from food production to humans, making it more difficult to treat some infections.

In recent years, ESBL/AmpC-producing *Escherichia coli* (ESBL/AmpC-EC) have been isolated with increasing frequency from animals, food, environmental sources and humans (e). Food-producing sectors are linked with human, animal and environmental sources of AMR (ARBs and ARGs) cyclically. These ARB and ARGs (as well as substances with antimicrobial activity) are introduced to animal- and plant-based food production environments, mostly through fecal waste (human and animal). Most of the sources identified also play a role as transmission routes. Fertilizers of fecal origin (e.g. manure), irrigation and surface water were identified as transmission routes of fecal ARB/ARGs of animal and human origin for plant-based food. Potential sources for this sector include soil, dust, farm animals, wildlife, arthropods, workers, equipment and process water.

Water can also be an important source of antimicrobial residues, antimicrobial-resistant bacteria and ARGs. There is a direct link between water quality used for irrigation and antimicrobial-resistant bacteria in foods. Wastewater effluent recovered from municipal sewage may contain (ARGs) antimicrobial resistant genes and (ARBs) antimicrobial-resistant bacteria.

One Health approach to AMR

Given the interconnectedness of humans, animals, and the environment in the development and spread of AMR, a One Health approach is essential for effectively tackling this issue.

Conclusion

Strengthen environmental governance, planning, and regulatory frameworks

Environmental stakeholders play crucial roles in addressing AMR, by developing strong and achievable regulatory frameworks aimed at reducing AMR related to antimicrobial manufacturing, water, sanitation and hygiene standards (WASH), agricultural standards, solid waste management and infrastructure should be ensured. The implementation of AMR One Health National Action Plans (NAPs) is vital for effectively tackling AMR.

Identify and target priority AMR-relevant pollutants

Reduce releases of chemical and biological pollutants affecting AMR in the environment and address their origins. There should be a focus on prevention and control measures, as well as on innovation, to reduce the

AMR burden by curbing releases of pollutants into urban and rural environments including from important value chains.

Wastewater treatment and management at known sources of contamination (e.g. sewage systems, livestock production, hospitals and pharmaceutical manufacturing sites) can reduce the number of antimicrobial-resistant microbes and gene concentrations. The environmental application of antimicrobials such as fungicides, antibiotics and antivirals in plant-based food production systems needs to be reduced through measures such as integrated pest management.

A greater understanding of the role of food production environments in the transmission of foodborne antimicrobial-resistant bacteria and ARGs, and the role of agricultural use of antimicrobials and potential co-selective agents (e.g. copper ions, and potentially other antimicrobials) will lead to the development of additional tools and strategies to reduce foodborne AMR.

Improve reporting, surveillance and monitoring

As part of plans to mitigate discharges of antimicrobials into the environment, is essential to measure the impact of antimicrobial pollution on biodiversity and integrate environmental monitoring data (e.g. from monitoring of surface water, solid waste and airborne particulate matter) with existing AMR surveillance and pollutants data.

One Health integrated surveillance for AMR included the environment one is the instrument that offers two useful perspectives: (i) knowledge of how resistant organisms and genes present in humans and animals are contributing to environmental contamination, through sewage discharge; and (ii) knowledge of the resistant organisms that human beings and animals may encounter through exposure to that environment.

Innovation and capacity development on One Health AMR

New scientific tools and technologies have the potential to illuminate the connections across various scales—ranging from the genetic evolution of emerging pathogens to the global ecological processes that facilitate their spread.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 39

Potential causes of antimicrobial resistance spread and preventive measures from One Health perspective

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Introduction

Annually, approximately 700,000 individuals globally succumb to infections attributable to antimicrobial-resistant pathogens, a figure projected to escalate to 10 million by the year 2050 if proactive measures are not implemented. The repercussions of this crisis will be particularly severe for resource-limited countries, resulting in significant economic ramifications. By 2050, the financial consequences of inaction against antimicrobial resistance (AMR) could amount to $100 trillion, with a potential reduction of 3.5% in global GDP, and an estimated 28 million individuals may be driven into poverty owing to AMR. Additionally, food security is likely to be compromised, with a projected 7.5% decline in the population of food-producing animals. Patients hospitalized with resistant infections typically experience prolonged stays, necessitate more extensive diagnostic evaluations, and are subject to expensive and occasionally toxic treatment regimens. This situation places considerable strain on healthcare systems, patients, and society. Consequently, governments may be compelled to reallocate resources from other initiatives to address healthcare needs. Furthermore, patients suffering from AMR infections can serve as reservoirs for pathogens, thereby perpetuating the cycle of AMR. AMR is a major One Health issue which encompasses the biological factors influencing AMR evolution, such as microorganisms, vectors, hosts, environment, and socioeconomic elements that facilitate its emergence and spread. Reduced biodiversity and increased human-animal interactions may result in the merging of similar microorganisms and gene exchange among them. AMR can emerge and spread across the different microbiomes residing in the one health framework, human, animal and environment and alter bacterial population genetics, potentially altering the genetic makeup and population dynamics of microbiomes. Changes in habitats, like pollution by antibiotics or antibiotic-resistant organisms (AROs), can influence the structures of bacterial populations and hasten the spread of AMR among the microbiomes. A comprehensive review is needed to address these aspects within the One Health framework. Thus, this review aims to outline potential causes of AMR and preventive strategies from a One Health perspective.

Potential causes for the emergence and spread of AMR from One Health perspective

AMR is affected by human activities such as the overuse and misuse of antimicrobials, inadequate infection control, and a lack of awareness. It is also influenced by practices applied on animal health and production, including the heavy use of antibiotics in farming and aquaculture, as well as the spread of AROs through food chains and direct interactions. Environmental aspects play a role too, with antibiotics and AROs being released into water, soil, and waste systems. Additionally, wildlife factors contribute to AMR through contact with wildlife and encroachment into their habitats.

Human activities: health and non-health related factors

Antimicrobial overuse and misuse in human health management

The misuse of antibiotics has played a substantial role in the worldwide challenge of AMR. Research indicates that our extensive dependence on these medications has facilitated the emergence and dissemination of AROs. As a result, numerous antibiotics that are frequently employed in clinical settings are increasingly losing their efficacy in the treatment of infections. The excessive utilization of pharmaceuticals, including self-medication, dispensing of antibiotics without prescriptions, and the over-prescription of medications by healthcare providers, in conjunction with patient expectations and concerns regarding liability significantly contribute to AMR. These practices facilitate the survival of resistant pathogens in/on human body by eliminating susceptible strains, thereby promoting AMR. While antimicrobials are effective in eradicating harmful microorganisms, they also adversely affect beneficial microbes that play a crucial role in protecting against infections. As a result, AROs proliferate and disseminate resistance genes through their genetic material to other microbial populations.

The inappropriate utilization of antimicrobials within community settings has been recognized as a significant contributor to the emergence and dissemination of multidrug-resistant (MDR) organisms. It can facilitate the development of AROs as susceptible bacterial populations are eradicated, allowing resistant strains to proliferate unchecked. Additionally, the underutilization of antibiotics characterized by improper prescriptions or non-adherence to recommended dosages can result in suboptimal treatment outcomes and recurrent infections. Likewise, inadequate prescription of antibiotics results in the presence of subinhibitory and subtherapeutic concentrations. This scenario may necessitate the administration of additional antibiotics, further exacerbating the issue of AMR. The use of broad-spectrum antibiotics indiscriminately targets both pathogenic and normal flora, thereby disrupting the normal microbiota and fostering an environment conducive to the growth of AROs. Moreover, using second-line antimicrobials for the treatment of acute self-limiting infections or infections amenable to treatment with first-line agents can impose selective pressure on microbial populations. This selective pressure is a critical factor in the development of AMR.

Nosocomial infections

The inadequate maintenance of hygiene and the failure to adhere to infection prevention and control protocols in health care settings have significantly contributed to the proliferation and dissemination of AROs. Hospitals have emerged as significant reservoirs for AROs, primarily due to the frequent and extensive use of antimicrobials within these settings, coupled with the presence of patients and visitors, which increases the likelihood of microbial exchange. Ultimately, these factors facilitate the ongoing propagation and spread of AROs, posing a substantial threat to public health. In certain instances, the degree of transmission between patients is directly correlated with the level of contamination present in the hospital environment. Furthermore, insufficient cleaning and hygiene practices within healthcare facilities contribute to the persistence of AROs in the healthcare surrounding. Each day, hospitals receive thousands of patients, staff, and visitors from various regions, each carrying unique microbiomes and colonizing microbes with diverse genotypes and phenotypes on their clothing and within their bodies. The potential for microbial transmission increases in the absence of adequate strategies and protocols to maintain cleanliness in hospital settings, which may ultimately lead to the further development and dissemination of AMR.

Using antibiotic-incorporated cosmetics and detergents, and biocides

Everyday grooming and hygiene products, including lotions, creams, shampoos, soaps, shower gels, toothpaste, and fragrances, contain additives designed to enhance product preservation and provide disinfection properties. However, these additives can infiltrate ecosystems, where they interact with microbial communities, where active ingredients present in them induce the development of AMR in the microbes. The limited solubility of these compounds exacerbates their role in AMR as they tend to accumulate and contact microbes in the environment for prolonged periods.

Biocides, such as chlorine, iodine, and alcohols, which are commonly utilized in disinfectants to manage infections in critical healthcare environments and household, can contribute to the development of AMR in microorganisms. Furthermore, microorganisms that exhibit tolerance to biocides may also develop resistance to antimicrobials. This can be attributed to the similarities in the mechanisms of action and microbial insusceptibility between biocides and antibiotics.

Social, economic and political factors

In addition to medical issues, social, cultural, and economic elements contributing to the misuse, overuse, and abuse of essential antimicrobial drugs can promote AMR. Factors such as poverty and lack of resources significantly increase the risk of AMR development and spread. Poorer socioeconomic conditions are reported to be linked to higher rates of AMR. Socioeconomic and environmental elements like insufficient water, sanitation, and hygiene (WASH) systems, poor living conditions, waste disposal practices, levels of education and awareness, economic activities, as well as factors like climate, the quality of healthcare, and migration influence the rise and spread of AMR. In addition, war and national conflicts are also the driving forces as both cause displacement, economic disaster, increased susceptibility to the disease, inadequate diagnosis and treatment of the diseased people, consumption of contaminated feed and water, transfer of the patients harbouring AROs across the globe and the like phenomenon. This all culminate in the emergence and spread of AMR directly or indirectly.

Animal health management and animal production factors

Prophylactic and therapeutic antimicrobial misuse in animals

Antimicrobials utilized in animals, such as pets, farmed fish, bees, and farm animals play a crucial role in animal production. Their usage surpasses that of antimicrobials in humans on a global scale. Many of the same classes of antimicrobials that are essential for human medicine are also used for animals. However, the misuse of antimicrobials in animals and the resulting AMR is an escalating issue worldwide, impacting not only humans but also livestock and the entire food supply chain in nearly every country. ARGs and AROs can transfer from food-producing animals to humans through direct contact or the consumption of animal products, particularly if these products are not properly handled or cooked (**Figure 1**).

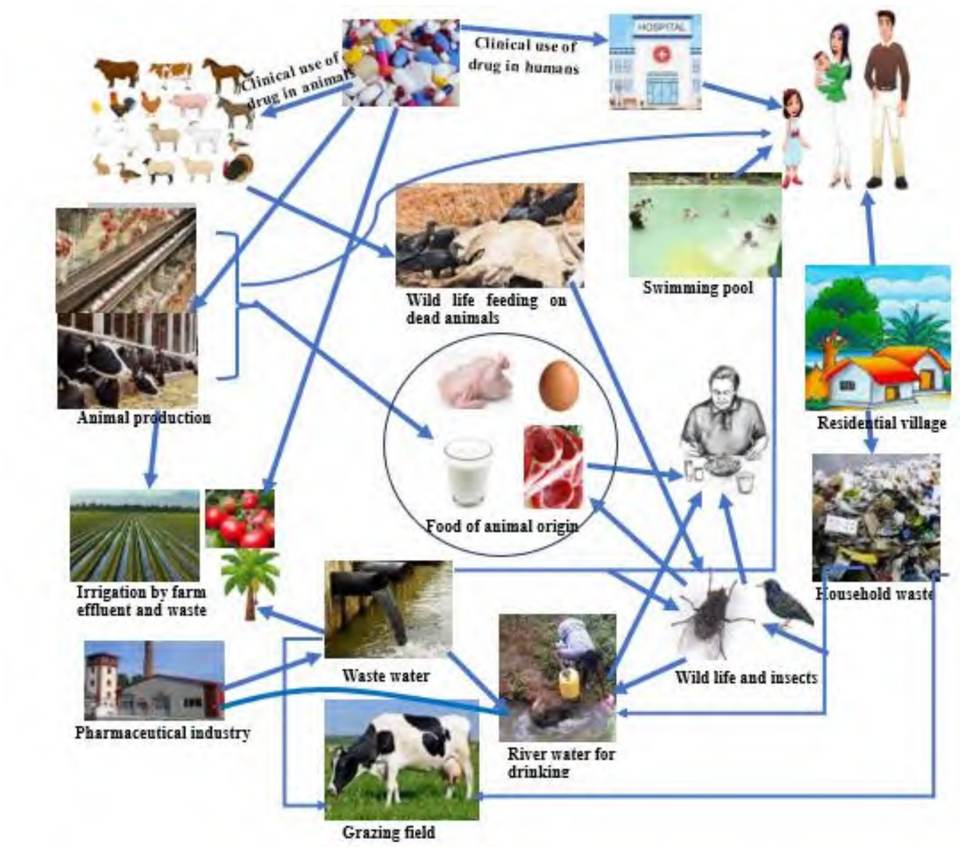

Figure 1. Emergence and dissemination of AMR within one health framework.

Additionally, the off-label use of antimicrobials can lead to variations in the absorption, distribution, or excretion of the active ingredient. As animal size increases, the ratio of body surface area to body weight decreases, which results in slower physiological processes compared to smaller animals. These elements affect how drugs are absorbed, distributed, metabolized, and eliminated across different species. Using antibiotics that are ineffective against the bacteria specified on the label, or administering insufficient doses due to AMR, leads to unnecessary exposure to antibiotics and triggers the development of AMR. Animal-derived foods throughout the food processing stages contain significant levels of AROs. It is crucial to recognize that consumers may come into contact with or consume animal products that carry AROs, increasing their exposure to these microbes (**Figure 1**).

Antimicrobial residue in food of animal origin

Intensive farming practices, which involve housing large numbers of animals in confined spaces under stressful conditions, have heightened the risk of infectious diseases, leading to an increased reliance on antibiotics for treatment. Antibiotics have also been widely used at lower doses for preventive measures and to promote growth in livestock. These results in antibiotic residues in food products like chicken, milk, eggs, and meat even after cooking the food. This subinhibitory or sublethal concentration of antibiotics present in food can enter the human body when consumed, either in raw or cooked form. Once inside, the microbes within the human body are exposed to these concentrations, which can stimulate the development of various resistance mechanisms against the antibiotics present in the feed.

Antimicrobial-resistant microbe and resistance gene in animals' excreta

The improper use of antimicrobials in animals, such as under-prescribing, infrequent use, or using the wrong administration route, leads to the emergence of AMR in the microorganisms living in the animals' intestines and on their skin. These AROs can then be transmitted to humans and the environment through direct contact and fecal contamination. AROs from the animals' gut are expelled in feces, potentially contaminating the environment and infecting other animals and farm workers. Antibiotics not only target harmful bacteria but also disrupt the natural microbiota, resulting in an animal gut that is rich in AROs and a diverse range of microbes, some of which may be pathogenic. This situation facilitates the selection and transfer of AMR-related genes within the microbial community in that environment.

The existence of AROs and drug residues in waste further contributes to the development and dissemination of AROs. The use of untreated animal waste (manure) for fertilization and irrigation, as well as the discharge of livestock farm waste into water bodies, significantly facilitates the spread of ARGs and AROs in irrigated vegetables and aquatic food. Humans can be exposed to these AMR microbes and ARGs by consuming plant-based foods, especially those eaten raw, as well as aquatic food (**Figure 1**).

Environmental and climatic factors

The environmental microbiome is particularly notable for its vast diversity, which presents a wide range of genes that pathogens can acquire to resist antibiotics. ARGs can originate from environmental bacteria that generate and release antimicrobial substances to compete with other microbes for resources. This inherent resistance may have played a role in the emergence and dissemination of AMR in pathogens. Beyond this, different contaminants from different sources can reach the environment from where they transmit to humans, animals and wildlife and then circulate within.

The impact of climate change on human health is extensive and is worsening as the rate of change accelerates. One area that has received less attention is the relationship between climate change and infections, especially those that are resistant to antibiotics. Temperature plays a crucial role in bacterial activity and infections. Higher temperatures enhance horizontal gene transfer, a key process in the development of AMR. Additionally, warmer temperatures generally boost bacterial growth rates. As the climate heats up, the atmosphere's ability to retain moisture increases significantly, resulting in more intense storms and heavier rainfall. This increased precipitation can lead to flooding, which in turn causes flood-related infections, population displacement, and overcrowding, all of which contribute to higher infection rates.

Mismanagement of leftover and expired antimicrobials

The incorrect disposal or management of unused and expired medications is a significant way that antibiotics can spread into water and other environmental areas where microorganisms may encounter them. A rise in antibiotic usage is consistently linked to the easy availability, accessibility, and inappropriate use of these drugs, which contributes to the development of AMR. Not every product that patients or clients receive is fully utilized; a large amount remains unused or expires. As a result, the disposal of unused medications has emerged as a global issue, drawing the interest of policymakers, healthcare professionals, pharmaceutical companies, and the public. The improper disposal of pharmaceuticals is a major concern, as many users are unaware of the correct disposal methods, causing them to discard their unused or expired medications by flushing them or throwing them away. This practice ultimately leads to contamination of landfills, water sources, and drainage systems, harming the environment (**Figure 1**).

Pharmaceutical industrial, public setting and animal farm effluents as deriving factors for AMR

Wastewater contains a variety of pollutants, such as pharmaceuticals, personal care items, disinfectants, and pesticides, which are gathered from homes, industries, and healthcare facilities by urban wastewater systems. The presence of antibiotics and similar chemicals in wastewater presents a significant health threat due to their ability to promote AMR when microorganisms are exposed to these substances. Wastewater serves as a critical reservoir for both antimicrobials and clinically significant AROs and ARGs, highlighting its significant role in the dissemination of AMR. These AROs and ARGs can spread to the environment, animals, and humans through various direct or indirect interactions and food chains.

Antibiotic residues are often released into and disposed of with agricultural waste, creating a selection pressure on environmental microbes. Many antimicrobials given to animals are not well absorbed in their digestive systems, leading to the excretion of up to 90% of the active antimicrobial compound in urine and as much as 75% in feces, with variations among different animal species. When animal waste containing these residues is spread on land, it can contaminate the surrounding air, water, and soil, which may be accessed by other animals or humans. In these environments, the presence of antimicrobial residues in feces promotes the development of AMR, as microbes are ubiquitous.

Using antimicrobials as a feed additive in livestock production

Antibiotics are commonly used in livestock farming as feed additives to improve nutrient absorption, support animal health, and enhance overall performance. However, this practice has contributed to the development of AMR. The use of antibiotics creates selection pressure that leads to the formation of ARGs in bacteria, as sub-therapeutic doses are often included in feed. In some cases, exposure to low levels of antibiotics can result in the production of reactive oxygen species, which may increase mutation rates and lead to the emergence of multidrug-resistant strains. Furthermore, antibiotics in animal feed can aid in the transfer of resistance genes via bacteriophages, facilitating the spread of AMR. It is important to note that low concentrations of antibiotics also promote horizontal gene transfer, which is a key mechanism behind the proliferation of AMR.

Wildlife and insects associated factors

As human populations grow and natural habitats diminish, wildlife is increasingly encroaching to humans and livestock. The presence of ARGs and bacteria in wild animals suggests that pollution from human activities, rather than natural selection, is to blame. Once AMR develops in the wild, wildlife can help spread it across various ecosystems. This wildlife contribution to AMR transmission occurs on two levels. First, in non-migratory species, AMR transfer primarily takes place within local environments. Non-migratory animals like cockroaches, fleas, and rats, which often coexist with humans, can act as reservoirs and carriers of AMR, aiding its spread. Second, migratory species such as gulls, fish, and turtles can facilitate the movement of AMR across different geographic regions, potentially even between continents. The occurrence of AROs in wildlife can be linked to two primary reasons. First, the introduction of ARGs through pollution from human activities leads to the contamination of their natural habitats. Second, AMR arises from natural selection, as bacteria gain resistance in reaction to environmental pressures (**Figure 1**).

One Health approach for the prevention of the emergence and spread of AMR

Multilevel antimicrobial stewardship and community awareness

Antimicrobial stewardship (AMS) is a strategy adopted by healthcare organizations to promote the responsible and effective use of antimicrobial medications. AMS was originally developed to coordinate efforts to improve the use of antimicrobial agents by choosing the appropriate drugs and establishing the correct dosages, administration methods, and treatment durations, all while focusing on positive patient outcomes. Evidence-based policies should guide the "one health" approach, vaccination recommendations, training for healthcare professionals, and public awareness initiatives regarding AMR.

AMS initiatives in animal husbandry successfully decrease AMR while ensuring productivity levels are upheld. This approach will facilitate the evidence-based use of antimicrobials in animals and foster responsible practices regarding their use. To effectively implement AMS, promoting an interdisciplinary approach, monitoring AMR and healthcare-associated infections, tracking antibiotic usage, educating staff, utilizing the shortest evidence-based duration for antibiotics, reevaluating treatment once culture results are received, prescribing suitable antibiotics at the correct dosages, only prescribing antibiotics when necessary, managing source control, and improving infection prevention and control measures are milestones (**Figure 2**).

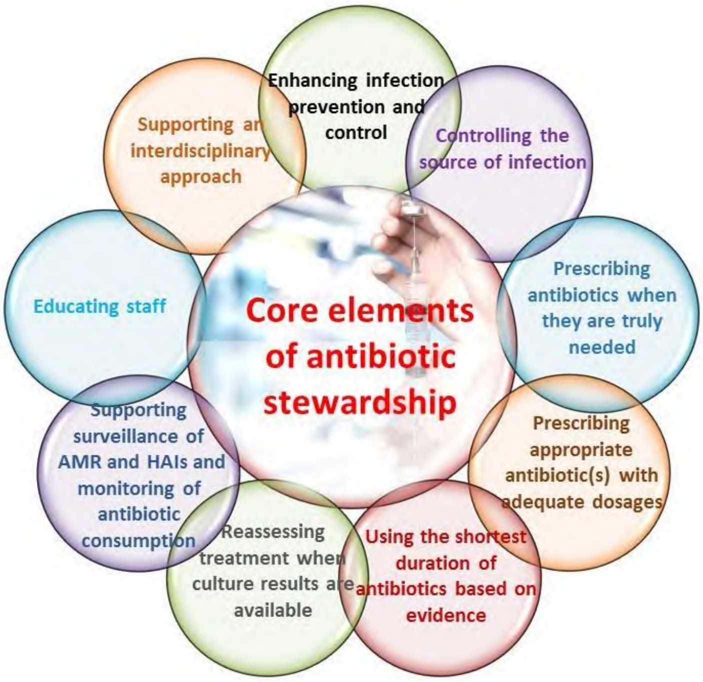

Figure 2. Core elements of antibiotic stewardship (Adapted from The Global Alliance for Infections in Surgery). *Abbreviations*. AMR: antimicrobial resistance, HAIs: healthcare-associated infections.

Environmental sanity and hygiene in public settings and human residential area

To reduce the development of new resistant strains, it is essential to improve hygiene practices, prevent the spread of infections, enhance healthcare systems, and better living conditions. These actions can lower the reliance on antimicrobials, which in turn helps to reduce the risk of AMR. Research shows that maintaining clean hospital environments and encouraging hand hygiene can lead to less surface contamination, which decreases the transmission of microbes to patients. Therefore, minimizing surface contamination is a crucial factor in preventing the spread of MDR bacteria and managing hospital-acquired infections that contribute to the rise of AMR.

Environmental health practices include ensuring access to clean water, sanitation, and hygiene (WASH); effectively containing, treating, and disposing of human waste; maintaining good personal hygiene, such as washing hands with soap at critical times to reduce the transmission of AROs; properly disposing of solid waste, including unused and expired antimicrobials; and following appropriate food hygiene practices aid in the prevention of AMR. Effective waste management in homes, public spaces, and livestock farms and treating wastewater properly (as wastewater is a source and breeding ground for AROs.

Antibiotic alternatives based on community health improvement

Encouraging the creation and use of vaccines and alternative therapies for infections by AROs is essential for lowering the incidence of severe infections caused by AMR. By focusing on innovations like phage therapy, probiotics, antibodies, and lysins, we can lessen our dependence on conventional antimicrobial treatments. This strategy will aid in fighting AMR and reduce the number of patients needing antimicrobial interventions. Other options include phage therapy, immunotherapy, and the use of plant extracts such as essential oils. Phage therapy involves using bacteriophages, which are viruses that specifically target and destroy bacteria. This method has been practiced in some countries for many years and shows promise as a replacement for antibiotics. Immunotherapy is another potential alternative, as it leverages the body's immune system to fight infections. By boosting the body's natural defenses, immunotherapy may provide a viable substitute for antimicrobial treatments. Furthermore, essential oils have demonstrated antimicrobial properties, indicating that they could be investigated as a future alternative to conventional antimicrobial.

Antibiotic-free animal health management and animal production

The significant rise in global food demand has led livestock producers to increasingly rely on antibiotics to produce large amounts of animal protein at a lower cost. Enhancing animal welfare and health could help reduce this reliance on antibiotics while maintaining productivity and cost-effectiveness. To prevent infections in animals, it is advisable to utilize vaccines and implement strong biosecurity measures. This approach can lower the need for antibiotics and boost productivity. Timely and effective vaccination of animals can decrease disease incidence, thereby reducing the dependence on antimicrobials for prevention or treatment. Integrated biosecurity measures in animal production initiatives significantly lower the incidence of diseases in livestock, which in turn reduces the reliance on antimicrobials. Which in turn decreases the presence of AROs on farms and their dissemination to the environment and humans. A comprehensive strategy is employed to tackle this issue, incorporating practices such as proper agricultural methods, hygiene, veterinary care, hazard analysis and critical control points (HACCP) protocols. If AMR arises, effective safeguards like good agricultural practices and HACCP-based strategies can help prevent its spread, thereby ensuring food safety, security, and public health. Additionally, utilizing effective and commercially available alternatives to antibiotics, such as herbal extracts, probiotics, enzymes, antimicrobial peptides, and phages, to minimize antibiotic use in livestock production campaigns.

Tackling access of wildlife and insects to the AMR contaminants and spread by them

The main approach to curbing the spread of AMR in wildlife involves reducing the transfer of AROs and ARGs from humans and animals to environments where wildlife can access them since these sources significantly contribute to AMR in wildlife. Additionally, preventing the transmission of AMR or ARGs among humans, animals, and wildlife can be achieved by focusing on two important factors. First, it is essential to ensure the proper and safe disposal of deceased animals. Second, efforts should be made to increase the distance between wildlife and livestock, as well as humans, to reduce interactions that could facilitate the spread of AMR or ARGs. Beyond these, proper disposal of the pharmaceutical containing wastes out of reach of wildlife and insects is also paramount.

Conclusion

The One Health framework, encompassing public health, animal health, and environmental health including wildlife has an interconnected role in the emergence and spread of AMR. Addressing this issue requires a comprehensive One-Health approach involving governmental, human, and animal health professionals, farmers and the public. By preventing and controlling AMR in key areas globally and regionally, we can mitigate the threat of AMR. Raising awareness about the causes and risks of AMR in remote areas of developing countries is crucial for prevention.

Competing interests

The author has no financial and non-financial competing interests to declare.

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Chapter 40

Zoonoses as an essential cause of hospital admission and a source of antimicrobial resistance for humans in Romania

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Introduction

Zoonoses are a significant threat to public health worldwide, as most pandemics originate in animals. The transmission of zoonotic diseases is associated with environmental factors, climate change, animal health, human activities, and behaviors, including globalization, urbanization, and travel. These diseases at the human-animal-environment interface pose a risk to animals and humans, inducing significant mortality and morbidity; it is estimated that of 1,400 infectious diseases known to affect humans, 60% of them are of animal origin, and 75% of the emerging infectious diseases have a zoonotic nature, worldwide.
The global impact of zoonoses on the health systems, healthcare services in general, and especially on the hospital environment is unknown. The frequency of some zoonotic diseases appears to be increasing, although the overall prevalence of zoonoses in general, as well as in the hospital environment, is also unknown. Often, cases of zoonotic diseases are admitted to hospitals that should be technically equipped and prepared in terms of evidence-based guidelines and procedures to diagnose, treat, and prevent the transmission of zoonotic agents. Nevertheless, human-to-human transmission has been demonstrated only for a limited number of zoonotic diseases; some can be transmitted to hospital personnel, and the staff who are unaware of or need to implement proper disease prevention and control measures may facilitate the spread of zoonotic pathogens. Thus, hospitals themselves may even unknowingly transfer zoonotic pathogens to patients during different procedures and interventions, such as organ transplantation. Data, information, and knowledge on zoonoses cases admitted to hospitals are essential to understand the impact, undertake decisions on isolation and precautions measures, and administer preexposure prophylaxis to prevent and control the diseases. Many countries still need to implement an integrated human, veterinary, and environmental surveillance system based on one health. The knowledge about the consequences of the hospitalizations of patients with zoonotic diseases is the evidence for the basis of health policies not only at the national level but also regional and global, regarding health care services, health protection, promotion, and illness prevention.

We analyzed the discharges of patients identified as the main cause of admission, the diseases considered zoonotic in the scientific literature, from all public and private hospitals in Romania where the Unique National Social Health Insurance Fund reimburses health services.

Objectives

The magnitude of public health problems caused by diseases caused by zoonotic infections in humans is variable. This chapter's main contribution is to develop knowledge and better understand the impact on hospital activity of zoonotic disease cases discharged.

The specific objectives were to a) characterize all the hospitalizations produced by zoonotic diseases as the main cause of admission between the years 2017 and 2023, regarding gender, age, year, level of education, health insurance availability, continuous hospitalization, the character of emergency at the admission, the need of long-term care, the source of referral to hospital, length of stay, mechanical ventilation required during hospitalization, the surgical procedures performed in the hospital, the readmissions by disease, the cases that received both continuous and day hospitalization, the status at the discharge, and mortality. b) Describe the annual trend of continuous hospitalizations by zoonotic disease group in the context of the COVID-19 pandemic and analyze the regional distribution of the overall admissions burden.

Methods and sources of data

A retrospective analysis at the national level was performed using the information from a database of the National Institute of Public Health -National Centre for Statistics in Public Health that collects data about discharges on continuous and day hospitalizations from all Romanian public and private hospitals, where the Unique National Social Health Insurance Fund reimburses health services. The analysis was performed on anonymized data and included information from 2017 to 2023 about the year of hospitalization, continuous and day-hospitalization, gender, age, health insurance status, source of referral to hospital, district, department of the hospital where the patient was admitted, the emergency admissions, length of stay, surgical procedures performed, mechanical ventilation hours, the need of long-term care, the aggravated status at discharge from hospital, readmission, death and several 158 variables representing different zoonoses and its corresponding ICD-10 codes. Each entry in the database relates to a hospital discharge, implying that a single patient can be counted several times if they have been readmitted in the same year in a hospital for the same zoonotic disease. The diseases were coded by qualified personnel from hospitals using the International Classification of Diseases – 10th Revision (ICD-10). The database was assessed and confirmed from the point of view of clinical and medical data at the patient level by external referees, according to legal requirements in Romania.

To analyze the features of the hospitalizations recorded between 2017 and 2023, the selection included all the cases with continuous hospitalizations in which the main diagnosis at discharge was a zoonotic disease by ICD-10 codes. This resulted in a final database with 37,218 records, representing 0.154% of the total number (24,205,603) of all discharges of all causes of diseases between 2017 and 2023. There was no evidence in the database that cases of human infection had originated in animals. This selection excluded influenza, tuberculosis, Creutzfeldt-Jakob disease, and COVID-19 infection, as the human infection might not have an animal origin. No antimicrobial resistance (AMR) data in the database corresponded to ICD-10 codes for zoonotic diseases.

ICD-10 codes organized the 158 diagnoses of zoonoses identified in the database, in 18 groups of zoonotic diseases (**Table 1**): intestinal infectious diseases; echinococcosis; another helminthiasis than echinococcosis; Lyme disease; relapsing fever; acariasis, and other infestations; certain zoonotic bacterial diseases; protozoal diseases; dermatophytosis; rickettsioses; rabies, contact and need for immunization against rabies; listeriosis; arthropod born viral fevers and viral hemorrhagic fevers; other orthopoxvirus infections; mpox; tick-borne viral encephalitis; histoplasmosis; and chlamydia psittaci infection. Of all the 158 zoonotic diseases identified as the main cause of admission, cases have been reported in the statistical system of communicable diseases for 32 diseases. For each of the selected groups of diseases, presented by descending order of the number of hospitalizations, we performed a descriptive analysis for 2017-2023, evaluating the frequencies by gender, mean age, level of education, health insurance availability, length of stay and other characteristics summarized in **Table 1**. The time trend of the number of hospitalizations by groups of diseases at the national level is presented in **Figure 1**. We also evaluated the total hospitalizations by region in all years as the number of hospitalizations per region divided by the average population size in each area multiplied by 100,000. The National Institute of Statistics provided the populational data.

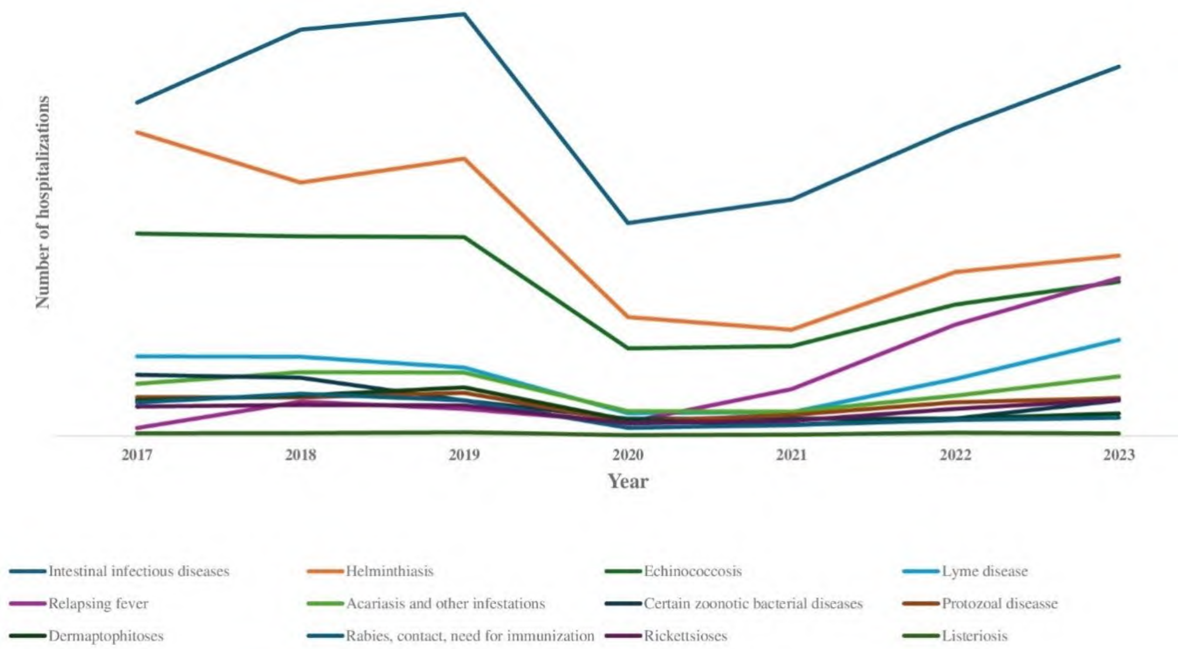

Figure 1. Evolution of the number of hospitalizations by groups of zoonotic diseases, Romania.
(Data from: The National Institute of Public Health-National Center for Statistics in Public Health; The National Institute of Statistics, Romania).

Results

Between 2017 and 2023, 37,218 continuous hospitalizations with a main cause of admission confirmed at discharge from the hospital, a zoonotic disease, were registered in hospitals in Romania where the unique national social health insurance fund reimburses health services. An analysis by regions considering different population dimensions illustrates that the number of hospitalizations per 100,000 inhabitants is the highest in the Bucharest -Ilfov 241.1 (6,248), Center 226.3 (4,690), and Nord West 216.3 (5,983) of the country. Of the 37,218 records, 3.1% (1156) also had, in addition to continuous hospitalization, a day of hospitalization caused by the same zoonotic disease, and 4.82% (1,796) of the patients had at least a continuous hospitalization readmission for the same disease. Of all the hospitalizations caused by zoonoses, 18,590 (49.9%) were male and 18,628 (50.1%) female patients. The mean age was 28.7 ± 26.3 years, with a minimum of 0 and a maximum of 101 years; 7,653 (20.6%) patients did not have any education, and most of them, 36,473 (98%) had health insurance, either voluntary or within national health insurance fund. Of all the hospitalizations, 17,069 (45.9%) had been admitted in infectious diseases and similar departments of hospitals, 4,407 (11.8%) in surgical departments, 15,742 (42.3%) in internal medicine and similar departments, 23,362 (62.8%) were emergency admissions, 179 (0.5%) had been declared cases with endemic epidemic potential and 3,492 (9.4%) as needing long-term care. Regarding the source of referral toward the hospital, out of all 37,218 hospitalizations, in most of the cases, 23,149 (62.2%) of the patients had no referrals, 9,848 (26.5%) had referrals from family doctors, 3,768 (10.1%) from other doctors and 413 (1.1%) from other hospitals. The average length of stay was six days. During the hospitalizations in 2017-2023, 386 cases needed 18,048 hours of mechanical ventilation, and 2,923 (7,9%) cases a surgical procedure. Among all the admissions at the discharges, 76 (0.2%) of the cases were in an aggravated status, and death was the outcome for 114 (0.3%) cases.

Table 1 summarizes the results from all hospitalizations due to the 18 groups of zoonotic diseases by ICD-10 codes, in the descending order of the number of hospitalizations and their characteristics. 80% number of hospitalizations were due to intestinal infectious diseases (12,226), other helminthiasis (7,502) than echinococcosis (5,688), Lyme disease (2,283) and relapsing fever (2,136). Among intestinal diseases, 99% of cases were due to *Campylobacter* enteritis (6,363), salmonellosis (4,727), and giardiasis (1,051), while 62.5% of helminthiasis were due to unspecified helminthiasis (2,981) and visceral larva migrans toxocariasis (1,709). The highest percentages of continuous hospitalizations of all cases that also had in addition to continuous hospitalization a day-hospitalization were for rabies, contact, and need for immunization against rabies (53.1%), followed by Lyme disease (26.2%) and echinococcosis (1.1%).

Zoonoses that showed the most significant difference between genders in continuous hospitalized cases are *Chlamydia psittaci* infection 100% male, mpox 92.3% male, tick-borne viral encephalitis 75.0% female, and Lyme diseases 60.62% female.

Adult patients represented 61.3% of hospitalizations, and patients with a mean age under 18 years were those with intestinal infectious diseases (32.8%), relapsing fever (5.7%), and other orthopoxvirus infections (0.1%). The highest percentages of patients without education were 51,5% from those with other orthopoxvirus infections, 35,7% with intestinal infectious diseases, and 25% with tick-borne viral encephalitis and histoplasmosis. Of all the admissions of patients without health insurance, 11.9% were from those with rabies, contact, and need for immunization against rabies, 6.3% from admissions with certain zoonotic bacterial diseases, and 5.7% with rickettsioses.

Regarding the departments of hospital admissions, the highest percentages of the admissions in the departments of infectious diseases were for chlamydia psittaci infection (100%), rabies, contact and need for immunization against rabies (98%), rickettsioses (93.6%), mpox (92.3%), arthropod born viral fevers and viral hemorrhagic fevers (87.1%), dermatophytosis (85.9%), Lyme disease (84.8%), listeriosis (80.9%), protozoal diseases (73.3%) certain zoonotic bacterial diseases (60.3%). The highest percentages of admissions in the surgical departments were for echinococcosis (65.5%), certain zoonotic bacterial diseases (20.1%), and dermatophytosis (9.4%), while in internal medicine and similar were for relapsing fever (93.7%), histoplasmosis (75%) tick-borne viral encephalitis (66.7%).

Most of the emergency admissions were for 92.3% of mpox, 91.9% of arthropod-born viral fevers and viral hemorrhagic fevers, 89.6% of rabies, contact and need for immunization against rabies, 88.8% of intestinal infectious diseases, 87.7% of the relapsing fever, 87.5% of the histoplasmosis, 87.2% of the listeriosis and 84.6% of the rickettsioses. There was a need for long-term care in 43.9% of admissions of protozoal diseases, 24% of cases of helminthiasis, and 19.7% of echinococcosis.

Admissions for 100% of cases of chlamydia psittaci infection, 92.3% of cases of mpox, 90.3% of cases of arthropod-born viral fevers and viral hemorrhagic fevers, and 88.3% of cases of listeriosis were without any referral from medical doctors or at the patients' request. Family doctors referred 62.1% of admissions with protozoal diseases, 58.4% of those with dermatophytosis, and 56% of echinococcosis. An essential impact of hospital activity measured by the admissions with a higher average length of stay than the overall average length of stay (6 days) had the admissions of cases with listeriosis (20.1 days), histoplasmosis (11.4 days), tick-borne viral encephalitis (9.9 days), echinococcosis (9.0 days), arthropod born viral fevers and viral hemorrhagic fevers (8.9 days), certain zoonotic bacterial diseases (8.8 days), Lyme disease (8.8 days), rickettsioses (8.8 days), mpox (6.2 days) and dermatophytosis (6.2 days).

One of the indicators of the severity of the cases, also measuring the resources needed in hospitals, the mechanical ventilation hours, displayed that for 1% of all the admissions, such support was delivered. 95% of all mechanical ventilation hours were for cases of listeriosis (4,565 hours), echinococcosis (4,438 hours), Lyme disease (4,403 hours), leptospirosis (1,656 hours), rickettsiosis (925 hours), West Nile virus infection (448 hours), salmonellosis (355 hours), and anthrax (346 hours). During the hospitalization, as a measure of the complexity and severity of the diseases, the data analysis disclosed that, in cases of the admissions of 45.8% (2,605) of echinococcosis cases, 9.5% (124) of certain zoonotic bacterial diseases, 9.1% (3) of orthopoxvirus infections and 6.7% (69) dermatophytosis were performed surgical procedures.

Out of all the 76 admitted cases with aggravated status at the discharge, the most numerous cases were with intestinal infectious diseases (19), certain zoonotic bacterial diseases (15), echinococcosis (12), relapsing fevers (10) and protozoal diseases (8). In descending order, the most numerous readmissions were registered in the database in numbers for echinococcosis (683), helminthiasis (326), Lyme disease (252), intestinal infectious diseases (174), and relapsing fever (117).

The highest death percentage of all the hospitalizations was in cases of echinococcosis 0,10% (37), certain zoonotic bacterial diseases 0,07% (26), and listeriosis 0,05% (20). Of all admissions with listeriosis, 21.3% had as outcome death.

We assessed the burden of hospital admissions by the ratio (R) of the number of discharged cases to those reported in the statistical system for communicable diseases. For 19 out of the 32 zoonoses with statistically reported diseases (yellow fever, leptospirosis, tick-borne encephalitis, spotted fever due to Rickettsia conorii, listeriosis, Lyme disease, salmonellosis, rabies, cryptosporidiosis, mpox, Chikungunya virus disease, scabies, erysipeloid, chlamydia psittaci infection, West Nile virus infection and other mosquito-borne viral fevers, yersiniosis, hemorrhagic fever with renal syndrome, giardiasis and tularemia), R values have been between 1 and 0.01, meaning that the number of cases managed in hospitals was equal or lower than those statistically reported. For the other 13 diseases (rickettsioses, echinococcosis, toxoplasmosis, trichinellosis, filariasis, other specified arthropod-borne viral fevers, leishmaniasis, brucellosis, amoebic dysentery, malaria, campylobacteriosis, Q fever and anthrax) the R values were in the interval 50 -1.11, denoting that the number of cases managed in hospitals was higher than those statistically reported.

The trend between 2017 and 2023 for the first 12 groups of zoonotic diseases, with the most numerous cases admitted to hospitals, is displayed in **Figure 1**. The trend for all 18 groups of zoonotic diseases displays a specific pattern, considering the pre-COVID-19 pandemic period 2017-2020 and the pandemic one extended until the end of 2023. The number of cases admitted increased between 2017 and 2019 for nine groups of diseases (intestinal infectious diseases; relapsing fever; acariasis and other infestations; protozoal diseases; dermatophytosis; rabies, contact, need for immunization; rickettsioses; listeriosis; arthropod born viral fevers and viral hemorrhagic fevers) while for the other nine groups decreased or remained the same. In 2020, the beginning year of the COVID-19 pandemic, the number of cases admitted decreased for all the groups of zoonoses at values representing, on average, 49.3% of those in 2017. From 2021, the trend for almost all the groups of diseases, the number of cases admitted began to increase, except for helminthiasis, acariasis and other infestations, dermatophytosis, and other orthopoxvirus infections, which continued slightly the decreasing trend to then increase again until 2023. At the end of 2023, the number of cases admitted was higher than in 2017 for intestinal infectious diseases, Lyme disease, relapsing fever, acariasis and other infestations, rickettsioses, arthropod-born viral fevers and viral hemorrhagic fevers and tick-borne viral encephalitis, while for the others was lower or the same as in 2017.

AMR zoonotic-related information shows a statistically significant ($p<0.05$) increasing trend in resistance to Ampicillin and Tetracycline and an increasing trend to Ciprofloxacin/quinolones for *Salmonella* spp. in humans in 2013–2021 in Romania.

Conclusion

1. The indicators and measures of the impact of zoonotic diseases on hospital activity might be complex. They should be developed ahead, data collected, monitored, and evaluated in a particular framework for the impact of zoonotic diseases on hospitalizations. The measures could include several characteristics to develop valuable knowledge for optimizing health services planning and delivery, such as type of hospitalization needed continuously or day, department of hospital delivering services, number of patients, health insurance availability, emergency character of the admissions, the need for long term care, length of stay, mechanical ventilation hours and surgical procedures needed, status at the discharge, readmissions and mortality data. The source of referral of patients to hospitals, even the lack of a referral, measures the connection of hospitals with other facilities of the health systems. Data about the epidemic and endemic potential of zoonotic diseases is valuable, also concerning pandemic threats such as the current mpox outbreak, which is a public health emergency of international concern. Sociodemographic data about patients, including education, is evidence-based on which health professionals should plan health promotion and education for health interventions.
2. In hospitals, surveillance of zoonotic diseases, including AMR-related data and integration with hospitalization and statistics data collection databases, might offer more complete and timely information to prevent and manage cases and potential epidemics. Data on epidemics or pandemics due to diseases other than zoonotic ones are also relevant to the impact of zoonotic diseases on hospitals. The decreasing trend during the COVID-19 pandemic of zoonotic cases admitted to hospitals in Romania is mainly due to isolation and other general preventive measures applied by the population, such as more frequent hand and personal hygiene, undertaken. It was also due to the overloading of infectious diseases hospitals and departments with COVID-19 cases and, in general, to hospitals' limited activities for other diseases than COVID-19.
3. Although human-to-human transmission has been confirmed for a limited number of zoonotic diseases, nosocomial-associated risks were identified, and surveillance data might be the evidence basis for isolation precautions preexposure and postexposure prophylaxis regimens. Surveillance of nosocomial zoonoses in hospitals might deliver valuable data.

Competing interests

The authors have no financial and non-financial competing interests to declare.

Table 1. Summary of hospitalizations' characteristics, 2017-2023, hospitals in Romania.

	Group number	Patients with continuous hospital Numbers	Patients with continuous and day hospital %	Male %	Female %	Age, years, (mean ± SD)	Without education %	Health insurance %	Department of hospital: Infectious diseases %	Department of hospital: Surgery %	Department of hospital: Internal medicine %
Intestinal infectious diseases A02.0-A02.2+, A02.8, A02.9, A04.5, A06.0, A07.1, A07.2, A07.8, A07.9	1	12226	0.1	51.8	48.2	14.6±22.9	35.7	98.7	41.5	0.3	58.1
Helminthiasis B65.0,B65.8, B65.9, B66.0, B66.3, B66.8, B66.9,B68.0, B68.1, B68.9, B69.0,B69.8, B69.9, B74.0, B74.8,B74.9, B75, B78.0, B78.9, B81.0, B81.1, B81.4, B81.8,B82.0, B82.9, B83.0, B83,1,B83.2, B83.4, B83.8, B83.9, H45.1	2	7502	0.1	43.1	56.9	26.8±24.5	22.6	99.2	41.4	1.7	56.9
Echinococcosis B67.0 -B67.9	3	5688	1.1	48.0	52.0	45.8± 19.5	3.5	97.7	25.3	65.5	4.9
Lyme disease, A69.2	4	2283	26.2	39.4	60.6	44.3±19.7	6.5	98.4	84.8	0.5	14.8
Relapsing fever A68.0, A68.1, A68.9, A69.8, A69.9	5	2136	0.0	53.4	46.6	9.8±16.5	22.2	99.6	4.6	1.7	93.7
Acariasis and other infestations, B86, B87.0-B87.2, B87.9, B88.0, B88.8, B88.9, B89	6	1756	0.3	51.8	48.2	27.6±26.7	23.6	97.0	51.7	1.2	47.2
Certain zoonotic bacterial diseases A20.1, A21.0, A21.9, A22.1, A22.0,A22.7, A22.9, A23.0, A23.3,A23.8, A23.9, A24.0, A25.9,A26.0, A26.7, A26.8, A26.9,A27.0, A27,8, A27.9, A28.0-	7	1298	0.1	58.5	41.5	55.1±20.9	3.9	93.7	60.3	20.1	19.6
Protozoal diseases B50.0, B50.8, B50.9, B51.0, B51.8, B51.9, B52.0, B52.8, B52.9, B53.0, B53.8, B54, B55.0, B55.1, B56.9, B57.4, B58.0, B58.1, B58.2+, B58.8, B58.9, B60.1, B60.2, B60.8, B64	8	1219	0.3	43.9	56.1	44.1±21.1	5.3	95.9	73.3	6.1	20.6
Dermatophytosis B35.0- B35.6, B35.8, B35.9	9	1028	0.1	74.5	25.5	43.2±20.9	7.1	99.1	85.9	9.4	4.7
Rickettsioses A75.1, A77.0, A77.1, A78, A79.1, A79.8, A79.9	10	976	0.1	66.1	33.9	51.8±15.7	1.1	94.3	93.7	0.1	6.3
Rabies, contact, and need for immunization against rabies A82.9, Z20.3, Z24.2	11	883	53.1	58.1	41.9	32.9±24.8	15.7	88.9	98.0	0.3	1.7
Listeriosis A32.1+, A32.7, A32.8, A32.9	12	94	0.0	55.3	44.7	55.6±19.1	7.5	97.9	80.9	4.3	14.9
Arthropod born viral fevers and viral haemorrhagic fevers A92.0, A92.2, A92.3, A92.8, A92.9, A93.8, A95.0, A98.5	13	62	0.0	64.5	35.5	49.7±20.7	4.8	98.4	87.1	0.0	12.9
Other orthopoxvirus infections B08.0	14	33	0.0	48.5	51.5	18.1±22.1	51.5	97.0	45.5	6.1	48.5
Mpox, B04	15	13	0.0	92.3	7.7	30.5±8.1	0.0	100.0	92.3	0.0	7.7
Tick-borne viral encephalitis A84.1, A84.8, A84.9	16	12	0.0	25.0	75.0	39.1±25.4	25.0	100.0	33.3	0.0	66.7
Histoplasmosis B39.0-B39.3, B39.9	17	8	0.0	50.0	50.0	35.1±35.3	25.0	100.0	25.0	0.0	75.0
Chlamydia psittaci infection, A 70	18	1	0.0	100.0	0.0	54.0	0.0	100.0	100.0	0.0	0.0

(cont)

Table 1. Summary of hospitalizations' characteristics, 2017-2023, hospitals in Romania *(cont.)*

Group number	Emer-gency ad-missions %	Cases long-term care %	Source of referral				Length of stays, days (mean ± SD)	Mechanical ventilation hours (mean ± SD)	Cases with surgical pro-cedures %	Status at discharge		Cases with re-admissions %
			Family doctors %	Other doc-tors %	Without re-ferral %	Other hospitals %				Aggra-vated %	Deaths %	
1	88.8	0.0	6.7	6.3	85.3	1.7	4.4±3.1	0.1±3.3	0.2	0.2	0.1	1.4
2	50.4	24.2	37.0	11.6	51.1	0.3	4.4±2.8	0.2±4.7	0.7	0.1	0.0	4.4
2												
3	28.4	19.7	56.0	12.1	30.7	1.1	8.9± 8.8	4.6±29.1	45.8	0.2	0.7	12.0
4	28.4	0.8	32.6	14.5	51.6	0.7	8.8± 7.4	8.6± 194.8	0.3	0.1	0.0	11.0
5	87.7	0.0	7.4	4.8	87.4	0.3	4.9± 5.1	0.1± 0.1	0.5	0.5	0.0	5.5
6	52.5	0.0	25.4	25.1	48.6	0.9	4.9±3.6	0	0.4	0.0	0.1	2.5
7	66.6	0.1	16.4	16.6	64.3	2.3	8.8± 5.8	4	58.7	1.2	2.0	4.1
8	29.1	43.9	62.1	6.0	31.5	0.3	5.4± 4.7	2.6±20.1	1.5	0.7	0.4	5.9
9	11.0	0.1	58.5	20.6	19.5	0.8	6.2±5.0	0.00	6.7	0.1	0.0	3.2
10	84.6	0.0	10.4	10.4	85.6	0.9	7.4± 4.8	11.7±66.5	0.2	0.1	0.5	2.6
11	89.6	0.0	4.2	2.8	90.6	2.4	2.1± 1.8	0.00	0.2	0.0	0.0	1.0
12	87.2	0.0	3.2	2.1	88.3	6.4	20.1±15.1	190.5±255.8	6.4	0.0	21.3	7.4
13	91.9	0.0	6.5	0.0	90.3	3.2	8.9±6.4	49.8±87.1	0.0	0.0	9.7	1.6
14	69.7	0.0	6.1	27.3	66.7	0.0	3.9±2.6	0	9.1	0.0	0.0	0.0
15	92.3	0.0	7.7	0.0	92.3	0.0	6.2±4.8	0	0.0	0.0	0.0	0.0
16	66.7	0.0	0.0	16.7	75.0	8.3	9.91±7.4	0	0.0	0.0	0.0	0.0
18	87.5	0.0	0.0	12.5	87.5	0.0	11.4±8.3	0	0.0	0.0	0.0	0.0
19	0.0	0.0	0.0	0.0	100.0	0.0	6	0	0.0	0.0	0.0	0.0

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