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The interrelationships between antimicrobial resistance, COVID-19, past, and future pandemics

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ABSTRACT

The COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 was first reported in Wuhan, China in December 2019 and is associated with high levels of morbidity and mortality. Various types of bacterial and fungal infections occur in patients with COVID-19 with some resistant to antimicrobials that are associated with significantly worse outcomes and deaths. Besides, antimicrobial-resistant (AMR) co-infections are responsible for clinically significant mortality in past pandemics. There is evidence to suggest that factors such as the proliferation of adulterated antimicrobials in some developing countries, international travels, issues with healthcare financing, use/misuse by humans, and in agricultural production and climate change are determinants of AMR at various levels of society. These complex interrelated determinants intersect with AMR in current and past pandemics and could amplify the potential of a future antimicrobial resistance pandemic. Therefore, global concerted interventions targeted at all levels of society to reduce the use/misuse of antimicrobials and disrupt these multifaceted, interrelated, and interdependent factors are urgently needed. This paper leverages prior research to describe complex major determinants of antimicrobial resistance and provides fresh insights into possible intervention strategies to tackle antimicrobial resistance including in the current and future pandemics.

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Introduction

Antimicrobials such as antibiotics have increased the average life expectancy worldwide. In 1920, people in the United States (U.S.) were expected to live up to 56.4 years. The average U.S. life expectancy has increased to 78.6 years in 2017 [1,2]. In developing countries where sanitation is still poor, antimicrobials are responsible for decreasing the morbidity and mortality associated with infectious diseases [3,4]. However, trends in prevalence, incidence, and the global burden of disease suggest that the battle to conquer infectious diseases is far from over. The approximate estimation is that bacterial infections kill 17 million people each year [5]. Sadly, within several years of the introduction of antibiotics, bacteria began to develop resistance to the available medications. Fungus has equally developed resistance [6]. All antimicrobials in common use in the human population have been more or less affected by superbugs [7]. The term 'superbugs' or antimicrobial-resistant infections commonly describes virulent species of pathogens that have become resistant to antibiotics, antifungals, antivirals, antimalarials, and anthelmintics. Each year, about 2.87 million people are infected with antibiotic-resistant bacteria and fungi in the United States, and 35,900 individuals die because of these infections [8]. However, other research estimates the number may be much higher, perhaps as many as 162,000 deaths in the U.S. annually [9]. Globally, antimicrobial resistance (AMR) is responsible for an estimated 700,000 deaths per year and 25,000 deaths per year in the European Union. Lack of concerted efforts to curtail AMR is likely to cause millions of deaths per year worldwide and by 2050, AMR has the potential to become a more common cause of death than cancer [10]. AMR in developing countries often leads to death because of a lack of access to more affordable and effective antimicrobials [11]. Resistant bacteria are becoming just as virulent as non-resistant bacteria but the ability to modify their genes provides an extra edge over humans [12]. Diseases such as tuberculosis (TB), malaria, acute respiratory infections (ARI), sexually transmitted infections (STIs), bacillary dysentery, and HIV/AIDS are developing resistance and becoming much more costly to treat. Additionally, life-saving healthcare interventions, such as organ transplants, which rely on antimicrobials to prevent surgical site infections, are threatened by AMR [8]. The World Bank Group suggests AMR could cause low-income countries to lose more than 5% of their GDP and push up to 28 million people, mostly in developing countries, into poverty by 2050 [13]. Yet the World Health Organization reported that there are significant gaps in the information available on the development of antimicrobial resistance [14]. Therefore, the purpose of this review is to comprehensively explore the factors influencing the emergence of "superbugs" and summarize findings from the current literature on the determinants of antimicrobial resistance, to contribute to the knowledge base. An understanding of the determinants of antimicrobial resistance is critical to explain current patterns and provide new insights to reduce AMR.

Materials and methods

Ebscohost and Cochrane databases, DARE, EBM reviews, HTA Database via Ovid were searched with the following keywords in all combinations and without date restrictions until May 2020: "superbugs", "drug-resistant", "resistant bacteria", "determinants", "risk factors", "resistant pathogens" "antimicrobial resistance". The titles of articles resulting from these searches were appraised for relevance. Relevant full-text articles in English and reference lists were reviewed. Studies on determinants of antimicrobial resistance in developing and developed countries are included. However, studies focused on AMR laboratory investigations or treatments are excluded.

Results

Poor regulation and enforcement

Dispensing antimicrobials is regulated in developed countries, and a prescription is usually required. However, the ability to purchase antimicrobials online has made them accessible in developed countries [4,15]. In many developing countries, access to antimicrobials is uncontrolled, can be purchased from street vendors and available over the counter without a prescription. This poor regulation results in antimicrobials that are easily available and accessible, encouraging self-medication and inappropriate administration [16]. Furthermore, poor regulation and enforcement of antimicrobial policies are associated with weak pharmaceutical management systems presenting as inappropriate selection, use, and poor storage practices facilitating the ability of microbes to develop and spread resistance [17].

Overuse and misuse of antimicrobials

Increased antimicrobial consumption is significantly associated with the emergence of global AMR [18]. In many countries, some patients insist on antimicrobials and others appear to have more motivation to overuse and misuse antibiotics than to preserve and use them only when prescribed. Often, patients in developing countries resort to self-treatment because they think public hospitals are overcrowded or will encounter greater financial burdens or they simply administer antimicrobials to see if they get better. Therefore, the high incidence of patients requesting for antimicrobials directly can have a huge impact on antimicrobial use rates and the development of resistance [19]. Unfortunately, the motivation to misuse antimicrobials also applies to manufacturers, distributors, doctors, hospitals, and clinics. Furthermore, direct to consumer advertising, pharmaceutical industry promotion targeted at healthcare providers, and competition among pharmaceuticals producers commonly bias patients and providers towards using new drugs when standard treatments are still effective. These influences on providers and patients result in greater use of new antimicrobials which could lead to resistance sooner [17]. The competition has also kept prices of many common antimicrobials low, leading to more motivation for misuse and overuse, both in animals, plant production, and in humans [11,13]. Other factors contributing to antimicrobial resistance are a lack of compliance with appropriate antimicrobial therapy, such as missing doses or stopping antimicrobial treatment early and prolonged use of prophylactic antimicrobials [7]. Patients' nonadherence to antimicrobial treat-

ment plan is still the main reason for the emergence of AMR. Multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB), the most dangerous forms of TB, are mainly caused by the patient's failure to complete therapy [20]. XDR-TB is resistant not only to the two major first-line drugs used in tuberculosis treatment, but also to many of the second-line drugs, and the mortality rate is 85%, highest among immunocompromised HIV/AIDS patients [21,22].

Health-care providers

Some pharmacists perceive their role as part of for-profit healthcare institutions, rather than as a part of the healthcare system [19]. This belief creates an ethical dilemma within the healthcare system, which adversely affects the provider-patient relationship and diminishes the provider's clinical autonomy to advise patients that the requested antimicrobial is unneeded. However, many pharmacists may be unaware of the influence of antimicrobial use on resistance. Sometimes, physicians misdiagnose and prescribe antimicrobials for conditions caused by viruses such as the common cold. Moreover, physicians may not have time to explain to patients why antimicrobials are not required, whilst some physicians err on the side of caution [23]. In developed countries, healthcare providers frequently write prescriptions for antimicrobials in a bid to cover all infection-related exposures. Usually, a combination of broad-spectrum antimicrobials is recommended for bacterial infections when a single narrow-spectrum antimicrobial could effectively cure the disease [24]. Some physicians will not wait for culture and sensitivity results when a patient is critically ill and in many cases administer broad-spectrum antimicrobials. Moreover, the duration of antimicrobial treatment is not evidence-based but most physicians follow general guidance that emphasizes playing safe. Existing research demonstrates that short-course treatment is just as effective as a long-course treatment of bacterial infections [25]. However, the optimal duration of treatment is still under debate. Lastly, physicians encounter different stimuli in healthcare settings, which frequently support needless antimicrobial treatment. For example, targets linked to pay-for-performance, which encourage physicians to use specific evidence-based guidelines that result in improved patient outcomes. However, when the duration for achieving a benchmark excludes the possibility of performing diagnostic examinations, providers are not motivated to conduct diagnostic tests on patients presenting with atypical signs and symptoms.

Diagnostic tests

Although rapid diagnostic investigations of bacteria are becoming more widely available, currently the generally accepted effective and accurate method of identifying bacterial infections involves microscopy, culture, and sensitivity in a biomedical laboratory. However, these procedures are time-consuming, requiring 36–48 h to produce results [26], which may be a deterrent to physicians in public and private requesting for laboratory tests. Therefore, health-care providers infrequently test whether patients have viral or bacterial infections before prescribing antimicrobials. Besides, rapid, real-time, and reliable point-of-care diagnostic devices are not always available and the cost of such advanced diagnostics could be expensive [27]. Therefore, the lack of quick and readily accessible diagnostic investigation leads to cost and time-related misuse of antimicrobials [11].

Livestock and agriculture

Interestingly, more than half the amount of antimicrobials produced worldwide are used in livestock production [28]. The approximate calculation per year of antimicrobial use in agriculture varies significantly from 63,000 tons to over 240,000 tons worldwide. About 700 tons of antimicrobials are imported each year into Australia, and 550 tons (78%) are used in animal production to increase feed efficiency, rate of weight gain and to prevent and treat infections [7,28]. Animals are administered antimicrobials in low doses over a prolonged period as growth promoters but this procedure expedites the emergence of AMR. Yet antimicrobials have minimal impact on animals' growth and the European Union outlawed this practice in animal production in 2006. Farmers contend that the application of growth-promoting antimicrobials greatly reduces production costs, however, analysts [29] found that withholding growth-promoting antimicrobials improve the net value of livestock. The United States allows antimicrobials in livestock production but the Center for Veterinary Medicine (CVM) and the Food and Drug Administration (FDA) carefully monitor how they are administered [11,30]. About 17 classes of antimicrobial drugs such as tetracycline, penicillin, and macrolides are approved growth promoters in the US. Yet the exact number of antimicrobial drugs used in agriculture is uncertain. Notably, during an infectious disease outbreak, farmers commonly treat all the animals rather than only those infected, thus escalating the emergence of AMR. Unfortunately, some AMR organisms present in animals are transmitted to humans, mainly in meat and other products of animal origin, or through direct contact in the production process [31], which adversely affects the health of individuals with reduced immunity such as children and the elderly.

Lack of new antimicrobials

The recent discovery that reengineered vancomycin derivatives were effective against vancomycin-resistant enterococci and could be administered without fear of resistance emerging is a significant development [32]. However, research and production of new antimicrobials by pharmaceutical companies have frequently encountered financial and regulatory barriers [33]. Several large pharmaceutical industries have either scaled back or completely abandoned innovative antimicrobial research and production [34]. Large and small pharmaceutical companies that are interested in pursuing the discovery of new antimicrobials encounter barriers and obtaining regulatory approval is often difficult. Barriers include bureaucracy, absence of clarity, differences in clinical trial requirements among countries, changes in regulatory and licensing rules, and inadequate channels of communication [13]. Besides, mergers between pharmaceutical industries have substantially reduced the number, variety of research and development teams, and innovation incentives of competitors. Return on investment in research and development is considered poor because antimicrobials are used for relatively short periods. They are often curative and not as profitable as drugs for chronic conditions, such as diabetes and mental disorders [2,33]. Moreover, most antimicrobials are currently off-patent and supplied by manufacturers of generic drugs. The result is access to cheap and generally effective drugs, which is good for the public. The downside is that many payers including governments expect all antimicrobials to be priced similarly, including expensive new antibiotics that target multidrug-resistant (MDR) bacteria [4,35]. The pharmaceutical industries have also taken a more active interest in developing antimicrobials for Methicillin-Resistant *Staphylococcus aureus* (MRSA), rather than gram-negative bacteria. This is not unconnected with the fact that MRSA is a major problem worldwide, whereas the demand for gram-negative antibiotics is low and somewhat more unstable given that resistance is rapidly acquired [4,36]. Compounding this problem, new antimicrobials are often treated as "last-line" drugs to combat serious diseases leading to reduced use of new antimicrobials and diminished return on investment [2]. Pharma-

ceutical companies that invest a considerable amount of financial resources into antimicrobial development may discover that profits quickly roll back when resistance develops. Consequently, many large pharmaceutical companies fear a potential lack of return on the millions of United States dollars required to develop new antimicrobials [2,4,36]. A recent report [37] indicates some of the pharmaceutical industries involved in the production of new antibiotics are bankrupt.

Lack of new vaccines

Vaccines are specifically for disease prevention. They contain either killed or weakened microbes. When administered to recipients, vaccines stimulate the immune system to produce antibodies before the individual contracts infection or at the beginning of an infection. Importantly, antimicrobial resistance mechanisms occur randomly among billions of bacteria; therefore, it is unlikely to arise in vaccinated individuals. In addition, vaccines have several targets provoking specific antibodies/t-cell immune responses. In vaccinated individuals, more bacteria mutations would be required for the development of resistance to vaccines making the occurrence difficult [38–40]. Research suggests from 2010 to 2013, the PCV13 vaccine prevented more than 30,000 cases of invasive pneumococcal disease and 3000 deaths [8]. However, as with antimicrobials, the pharmaceutical industry does not produce vaccines at a socially optimal level. Forecasting future demand for vaccines is proving difficult in comparison to antibiotics. Further, the vaccine market represents only 1.5% of pharmaceutical sales. Consequently, these factors could lead to a reduction in revenue and certainty compare to drugs, and reinforces the belief that vaccines are low-profit margin, single or limited-use products [41]. Besides, the development of new vaccines is on hold because of the current focus on COVID-19 vaccines and therapy.

Environmental determinants

The inordinate application of antimicrobial agents to cure patients with infectious diseases and in livestock production has led to the accumulation of these agents in the environment. The effects of this environmental stockpile on the emergence of antimicrobial resistance should not be underestimated [42]. Metabolites and excess antimicrobials are excreted and can enter the environment through poor wastewater and sewage treatment from the community or hospitals, agricultural manure, and water bodies [43]. The common route by which antimicrobials from human waste enter the waterway is through wastewater treatment outflows. Healthcare settings may also send antimicrobials and resistant microbes to landfills, which subsequently contaminates the natural body of water. These antimicrobials are non-biodegradable whether in sediment or water. Some antimicrobials are completely stable in liquid, and some are resistant to heat. For example, a small amount of the antibiotic neomycin in eggs is quite resistant to normal cooking temperatures. Ironically, chlorination of drinking water and wastewater markedly increases the concentration of antimicrobial-resistant bacteria even though it decreases the original bacterial counts [44]. Substances such as household disinfectants and other antimicrobial agents can increase AMR by killing helpful bacteria. The increase in the application of these agents have dramatically altered the balance of microorganisms in the environment. Disinfectants are crucial for sterilization but they may also be selecting for resistant strains and therefore contributing to the rise of resistant microbes [45]. A commonly overlooked cause of AMR is the discharging of pharmaceutically active compounds (PhACs) effluent into the environment from the production of raw materials used to make antibiotics [46]. Yet the contemporary governance on water quality majorly targets the presence of index microorganisms but does not focus on the antimicrobial concentrations in sewage, the influents, and effluents of wastewater treatment plants. Approaches to decrease the hazards of environmental exposure should be directed at improving industrial systems for sanitation and decontamination of hospital sewage water [47].

Drug quality

Counterfeit medicines are partly responsible for AMR because they contain and deliver sub-optimal doses of the active ingredient in antimicrobial drugs. The implication is that when patients and healthcare providers use antimicrobials appropriately, counterfeit drugs will undermine their efforts and AMR would develop. The WHO suggests 10.5% prevalence of medicines available in Low and Middle Countries is counterfeit [48]. This evaluation was corroborated by a study that reported that about half of the counterfeit drugs present worldwide are antimicrobials, mainly generic [13]. Additionally, there is reduced drug quality because of poor storage conditions, age, having none, too little, or too much of the active ingredients. This may be premeditated or the consequences of poor manufacturing practices. Adulterated inactive "excipients" in drugs can also be dangerous to those who consume them. China and India hold the unenviable record of being the main sources of counterfeit drugs [49]. To complicate issues, governments and pharmaceutical companies are reluctant to report counterfeit drugs, in order not to create trepidation among consumers [50]. Moreover, in India, drugs at higher-level health centers are less likely to be expired, but many rural clinics dispense obsolete medicines, especially in areas plagued by violence [51]. Additionally, there are currently no guidelines for maintaining medicines at safe temperatures in retail pharmacies, other than that they must have a refrigerator [19]. The ramification of administering inferior and imitation antimicrobials is grave. The condition of the patients taking the medications is worsened because the drugs contain a sub-therapeutic amount of the active ingredient are ineffective in treating the infections, however, the sub-optimal level contributes to the emergence of resistance [13].

Healthcare financing

The lack of universal coverage for essential medicines in public healthcare settings may cause individuals to patronize less well-regulated informal health providers in low and middle-income countries because of high co-payments. However, health providers in the informal private sector perform prescribing and dispensing activities and quality controls on medications are often absent. Also, many of them are poorly trained and unlicensed. Therefore, attracting patients into a well-regulated public health sector for the treatment of infectious diseases could reduce the use of inappropriate or low-quality antimicrobial drugs and thus decrease the spread of resistant organisms [52]. Moreover, the absence of universal coverage for drugs in some developed countries creates problems in terms of the accessibility of medicines, high copayments, and overall system costs. Some patients cannot afford to take their medicines as prescribed, which in the case of antimicrobials, would contribute to resistance [53].

International travel

A determinant of antimicrobial resistance is the ease of worldwide travel. An individual with a highly contagious disease but with no signs or symptoms, could board an airplane, and be almost anywhere in the world. The case of a U.S. attorney with a tentative diagnosis of XDR-TB, who boarded commercial flights with several passengers from Atlanta to Paris, and returned to the U.S. through

transits in Prague and Montreal, highlights this issue. However, a definitive diagnosis of MDR-TB was later made in this case [21,54]. Research also suggests that fecal colonization rates of Multidrug-Resistant Enterobacteriaceae (MRE) vary from 1 to 12% before travel and travel-related acquisition of MRE range from 21% to 51%. The risk of acquisition of MRE varies between geographical regions. Travel to southern Asia constitutes the greatest risk (29–88%), other Asian countries (18–67%), and Northern Africa (31–57%). Acquisition of MRE after traveling to sub-Saharan Africa varied from 0 to 49% or to South and Central America 0 to 33%, but there are no reported acquisition of MRE after traveling to South or Central America. Acquisition of MRE after traveling to North America, Europe, and Oceania are rare [55,56].

Commensals

Finding resistance genes in microorganisms within antimicrobial-free environments suggests that the characteristics occurred spontaneously and most likely precede industrial-scale pharmaceutical production and distribution of antimicrobials. Indeed, diverse and universally dispersed soil microorganisms carry resistance to virtually all natural produced antimicrobials, including synthetic antimicrobials, some at clinically significant levels. These soil microorganisms are genetically diverse, and some of the bacteria have genetic traits that are remarkably close to bacteria that infect humans. Therefore, based on these reasons, the naturally occurring soil-dwelling bacteria, with their repository of antimicrobial-resistant genes, could be contributing to the increasing levels of resistance now seen among bacteria that infect humans and other animals [57,58].

Cross-resistance and co-selection

Several genetically altered or single transferable antimicrobial resistance traits accord resistance to some or all classes of an antimicrobial family [59]. Exposure to one antimicrobial can select for resistance to other antimicrobials of the same class (cross-resistance). Interestingly, resistance occurs across structurally unrelated antimicrobial classes by co-selection. The chunk of genetic material that carries the antimicrobial resistance nucleus commonly contain several resistance traits and determine resistance to more than one antimicrobial group. When this genetic trait moves from one bacteria to another, all the resistance traits are transferred together (co-transfer) [60]. Exposure to one class of antimicrobial may then select for resistance to an unrelated class [7].

Climate change

The planet is getting warmer resulting in increasing local temperature, and in conjunction with population density, is linked with increasing antimicrobial resistance in regular infectious agents. An increase in temperature of 10 °C across regions leads to increase antibiotic resistance by 4.2%, 2.2%, and 2.7% for regular infectious agents such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus*. The relationship between increasing temperature and antibiotic resistance is uniform across most groups of antibiotics and infectious agents and may be intensifying with time [61–63].

Influenza, SARS, MERS, COVID-19, and healthcare-associated infections

Severe acute respiratory syndrome coronavirus 1 (SARS), Middle East Respiratory Syndrome (MERS), and severe acute respiratory syndrome coronavirus 2 (COVID-19) have also been associated with bacterial resistance coinfections [64–66]. Most deaths in the 1918 influenza pandemic were due to secondary bacterial infections, predominately *Streptococcus pneumoniae* [67–69]. During the 2009 H1N1 influenza pandemic, 29%–55% of worldwide mortality was associated with secondary bacterial coinfections with AMR contributing a clinically significant percentage. Mortality due to penicillin-resistant *Streptococcus pneumoniae* was estimated at 2060–5392 (1.8%) and erythromycin resistance 2551–6679 (2.2%). Analysts project a three to four times increase in deaths as a result of increased pneumococcal coinfections in future influenza pandemics [68,70]. In the severe acute respiratory syndrome coronavirus 1 (SARS) pandemic in 2003, there were reported increased prevalence of Methicillin-Resistant *Staphylococcus aureus* (MRSA), *Stenotrophomonas* species, and *Acinetobacter baumannii* (resistant to some antimicrobials) in treated individuals. This included the occurrence of ventilator-associated pneumonia and MRSA transmission associated with remarkable increases in antimicrobial administered in the intensive care unit [71–73]. Besides, during the Middle East respiratory syndrome (MERS) CoV outbreak in Saudi Arabia, the most common bacteria reported among infected patients were MRSA, among others such as carbapenem-resistant *Acinetobacter baumannii*, Vancomycin-Resistant Enterococci and *Streptococcus pneumoniae* [74]. Research suggests that about half of the deaths of patients hospitalized with COVID-19 are attributable to bacterial and fungal infections some of which are resistant to antibiotics and antifungals [68]. Antimicrobial-resistant infections including *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, extended-spectrum beta-lactamase, MDR *E. coli*, *Enterococcus Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and Acinetobacter have been reported in patients with COVID-I9 [75–78]. Antimicrobial-resistant infections usually happen in the healthcare-related environment, such as hospitals and nursing homes, where infections can spread rapidly between patients with compromised immune systems. Patients whose care requires devices like ventilators (breathing machines), urinary (bladder) catheters, or intravenous (vein) catheters, and patients who are taking long courses of certain antimicrobials are most at risk for Carbapenem-Resistant Enterobacteriaceae infections (CRE). These resistant infections are difficult to treat and could be fatal. In the United States, there are approximately 13,100 CRE cases in hospitalized patients, 1100 deaths, and 130 Million USD in attributable healthcare costs [8]. Hospital-acquired infections in intensive care units in developing countries are about three times more common than in the USA. Both the need for antimicrobials and the burden of resistance are expected to increase with the rate of hospital-acquired infections in Low and Middle-Income Countries [79]. The simultaneous occurrence of high antimicrobial use, seriously sick patients, and a constant invasion by disease-causing microbes within the healthcare environment enable the development of resistance and provide an ideal environment for the spread of resistant pathogens and horizontal transfer of resistance genes [47].

Discussion

Global actions are required to conquer AMR. Individual related AMR factors are linked to injudicious antimicrobials use because they are available over the counter, lack of awareness, misconceptions, and the cost of drugs prescribed in the public sector [19]. The community-level determinants comprising environmental hygiene and sanitation, overcrowding, inadequate infrastructure, and trained personnel, limited access to materials and equipment for infection control, and constraints in financial resources are fueling the rise of superbugs [80]. At the state/national level, there are lack of regulations or enforcement of policies on antimicro-

Fig. 1. The interrelationships and interdependency of determinants of antimicrobial resistance at all levels of society, past, current, and future pandemics.

bial use, especially in developing countries. In addition, there are challenges with climate change, healthcare financing, production and proliferation of counterfeit drugs that are often linked to other detrimental financial activities within and across countries such as organized crime, smuggling, tax avoidance, and racketeering [13]. Importantly, many COVID – 19 patients are treated with antibiotics, which may increase antibiotic resistance. About 50% of deceased COVID-19 patients had bacterial and fungal coinfections and some of the infections are antimicrobial-resistant. Deaths in past pandemics have been associated with antimicrobial-resistant infections. Fig. 1, depicts the complex, interrelated, and interdependent AMR determinants with past and future pandemics. The findings of this review support the suggestions by Laxminarayan, Duse, Wattal, Zaidi, Wertheim, Sumpradit, Vlieghe, Hara, Gould, Goossens, Greko, So, Bigdeli, Tomson, Woodhouse, Ombaka, Peralta, Qamar, Mir, Kariuki, Bhutta, Coates, Bergstrom, Wright, Brown and Cars [79] about the need for global solutions to deal with the challenges posed by antimicrobial resistance. To avoid overprescribing by healthcare providers, low-cost interventions such as audit and feedback, or the use of printed educational materials and educational outreach visits by trained personnel to facilitate change in prescribing behavior and consensus-driven guidelines to improve antimicrobial prescribing are needed [11]. Another option is to employ clinical decision support systems (CDSSs). Comprehensive multifaceted interventions appear to be the most effective mechanism for addressing AMR and inappropriate antimicrobial use [81,82]. Expanding universal health coverage across countries would improve measures to prevent and manage AMR, including the appropriate use of antibiotics [83]. A WHO report [84] indicates that among antimicrobials in development, none of them are expected to be effective against the most dangerous forms of AMR pathogens. Developing innovative antimicrobials, vaccines, access, and building AMR laboratory and surveillance systems capacity for countries to detect, track, and respond to antimicrobial resistance at all levels of society is an urgent priority. Data from these surveillance systems could be used to target intervention strategies as well as develop and promote antimicrobial stewardship programs [14,85,86]. There are emerging natural and nanoparticle-based antimicrobial therapies [87–89] but global partnerships are required for their development. Vaccines offer the potential to reduce demand for antimicrobials and slow the spread of AMR [40]. The importance of including AMR-susceptible serovar in recently developed vaccines is widely recognized [11]. However, the advent of the COVID-19 pandemic has adversely affected new antimicrobials and vaccines research and development for other infectious diseases.

Conclusion

This review outlines the crises in the public health sector at the individual, community, and national levels. The findings indicate complex and multifaceted interrelationships and interdependency of determinants of antimicrobial resistance and in past, current, and future pandemics. The immediate important parts of any mitigation strategy for AMR are strengthening investments in education and raising public awareness of AMR. There is an urgent need for more innovative interventions that promote and incentivize new antimicrobials and vaccine production for infectious agents, tackle climate change, better stewardship of antimicrobials for both humans and animals, and health systems integrated with surveillance systems for AMR, including intense collaboration with the pharmaceutical industries and security agencies worldwide to eradicate the production of counterfeit antimicrobials.

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