Mohsin and Amin
Bulletin of the National Research Centre (2023) 47:63
https://doi.org/10.1186/s42269-023-01036-7

Bulletin of the National Research Centre

REVIEW

Open Access

Superbugs: a constraint to achieving the sustainable development goals

Shahriar Mohsin[1*] and Mohammad Nurul Amin[2,3]

Abstract

Background Antimicrobial resistance has already emerged as a major concern not only for public health but also for global economy. It causes a multifaceted crisis in development and growth by increasing the number of infections and deaths. Sustainable Development Goals are in place to ensure that development and growth are continual, as well as to end poverty, protect the environment, and promote peace and prosperity. In this review we tried to highlight the reasons for the prevalence of superbugs as well as their multifaceted impact on healthcare, and demonstrate potential ways to combat them and incorporate them into international policymaking processes.

Main body of the abstract The literature review included articles from MEDLINE, EMBASE, Scopus, and PubMed published till the end of the year 2022 using keyword searches. Two hundred and forty-three research articles, review papers and studies written in English language evaluating the impact of Antimicrobial resistance (AMR) on patient, society and economy published until end of the year 2022 were included.

Short conclusion This review highlighted the significant impact of antimicrobial resistance (AMR) on the Sustainable Development Goals (SDGs) and was able to identify at least five SDGs that are linked to healthcare. The emergence of superbugs results in increased expenditure, which has serious consequences for the global economy, particularly in developing countries where infectious diseases are prevalent. The overuse and misuse of antibiotics, as well as poor infection control practices, are identified as primary drivers of superbug emergence. However, implementing strategies such as rational antibiotic use, effective infection control practices, and developing new antibiotics and alternative therapies can mitigate the adverse effects of AMR and contribute to achieving the SDGs. It is essential to integrate AMR strategies into national development plans and improve cross-sectoral collaboration among stakeholders to combat superbugs effectively.

Keywords SDGs, AMR, Superbugs, Antibiotic resistance, Antimicrobial resistance

Background

The discovery of antibiotics in the third decade of the twentieth century is regarded as one of the most significant triumphs of modern medicine. Since then, it has been playing a critical role in reducing the death toll caused by microbial infection. Prior to the discovery of antibiotics, case fatality rates caused by *Streptococcus pneumoniae* and *Staphylococcus aureus* were around 40% and 80%, respectively (Bartlett and Mundy 1995; Karchmer 1991). Amputation used to be the sole choice for treating wound infection and the advent of antibiotics transformed the situation drastically (Hirsch 2008; Friedman et al. 2016). Complex surgeries, transplantations, and chemotherapies were greatly benefited by this discovery as well. Despite their great contribution, the biological and medical sciences have faced several new and novel challenges since then. Emergence of antimicrobial

*Correspondence:
Shahriar Mohsin
mohsin.pharm@gmail.com
[1] Center of Molecular Biotechnology, University of Bonn, 53115 Bonn, Germany
[2] School of Basic Pharmaceutical and Toxicological Sciences, College of Pharmacy, University of Louisiana at Monroe, Monroe, LA 71201, USA
[3] Pratyasha Health Biomedical Research Center, Dhaka 1230, Bangladesh

resistance is one of them which is making antimicrobial treatment more difficult day by day. Many organizations, including the Centers for Disease Control and Prevention (CDC), the Infectious Diseases Society of America, the World Economic Forum, and the World Health Organization (WHO), have already recognized it as a worldwide public health risk (Frieden 2013; World Health Organization 2014; Dellit 2007; Global Risks 2013; Michael et al. 2014; Spellberg et al. 2016). When a new antibacterial agent is developed and widely administered, a small number of bacteria develop the ability to counteract the drug's effects by multiple resistance mechanisms such as limiting uptake, modification of drug target, inactivation, and active efflux of a drug (Reygaert 2018; Dever and Dermody 1991). This bacteria type is the most adaptable. They acquire genomic mutations or resistance genes by resisting that effect. The antibiotic-resistant bacteria are then reproduced by the genetically modified bacteria. Resistant bacteria that have just been grown can transfer their resistance gene to another species of bacteria. This process is known as conjugation, and it involves the development of new bacteria strains that can protect against the effects of existing antibiotics. Such lethal and contagious organisms are often referred as multidrug-resistant (MDR) bacteria or superbugs. Superbugs lead to emergence of resistant pathogens into human, animal and environment simply because they exist in those interlinked niche (Reygaert 2018; Dever and Dermody 1991). Because the therapeutic options against superbugs are limited, morbidity and mortality rates are also increased, as well as treatment costs (Aslam et al. 2018; Spellberg and Gilbert 2014; Rossolini et al. 2014; Sengupta et al. 2013; Resistant "Superbugs" Create Need for Novel Antibiotics 2021). Antibiotic resistant bacteria are increasing mortality rates and putting a strain on the global economy. Antimicrobial resistance causes approximately 700,000 fatalities per year worldwide, with the figure expected to reach 10 million by 2050, resulting in a $100 trillion economic loss (O'Neill 2016), see Fig. 1.

In recent years, the rate of antimicrobial resistance has skyrocketed. What is more, the number of new antibiotics being produced to combat resistant bacteria is not sufficient (O'Neill 2014; Luepke 2017; Spellberg et al. 2004). The Centers for Disease Control and Prevention (CDC) published a report on antimicrobial resistance in the USA in 2019 that listed 18 germs and classified them as urgent, serious, or concerning. They also added a few germs to their watch list. These germs have the potential to spread and infect people in other countries (Table 1) (Centers for Disease Control U 2019).

Antibiotics are manufactured, prescribed, consumed, and released into the environment in an irrational manner nowadays. Such practices have posed a serious threat to global health and the environment's long-term viability. A global responsibility is required to limit such practices and make the planet more livable. To address 2015such liabilities and many others, the Sustainable Development Goals (SDGs), or Global Goals, were established by 193 UN members in 2015 (United Nations General Assembly Sustainable Development Goals 2015).

Proposal of The Sustainable Development Goals (SDGs) was a universal call to action to end poverty, protect the environment, and ensure peace and prosperity for all people on the planet by 2030. The United Nations has recognized 17 goals for both developed and developing countries and they are part of the United Nations resolution known as the 2030 Agenda or Agenda 2030. These SDGs are divided into five categories: People,

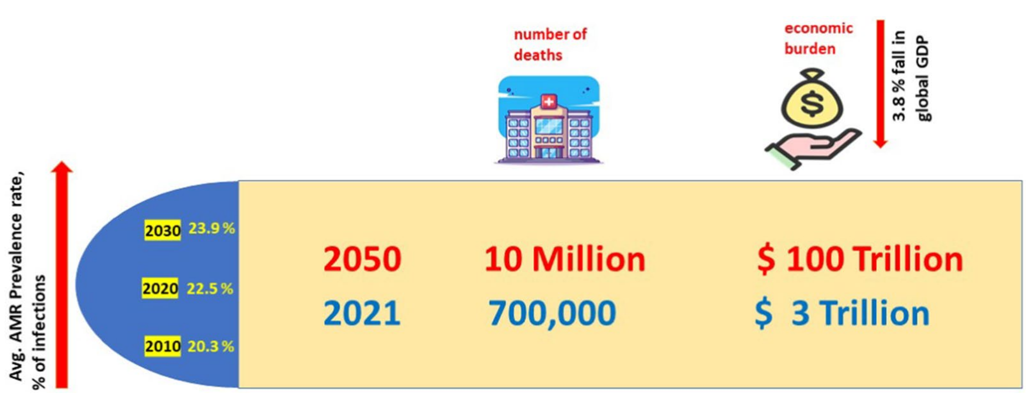

Fig. 1 Projected impact of antimicrobial resistance on healthcare and economy by 2050. Upward trend of AMR prevalence rate has been shown from the year of 2010 with a projection for 2030. % Infection has been shown for all countries (Resistance and - "Stemming the Superbug Tide"|Compare your country). Comparison of number of deaths and economic burden has been illustrated between current situation and the year of 2050. Costs have been calculated for both healthcare and societal loss (O'Neill 2016; Drug-resistant infections: a threat to our economic future 2017; Naylor et al. 2018; Kraker et al. 2016)

Table 1 Categorization of germs according to their severity, reported by CDC

Urgent	Serious	Concerning	Watch list
Carbapenem-resistant *Acinetobacter* *Candida auris* Clostridioides difficile Carbapenem-resistant Enterobacteriaceae Drug-resistant *Neisseria gonorrhoeae*	Drug-resistant *Campylobacter* Drug-resistant *Candida* Extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae Vancomycin-resistant *Enterococci* Multidrug-resistant *Pseudomonas aeruginosa* Drug-resistant nontyphoidal *Salmonella* Drug-resistant *Salmonella* serotype Typhi Drug-resistant *Shigella* Methicillin-resistant *Staphylococcus aureus* Drug-resistant *Streptococcus pneumoniae* Drug-resistant Tuberculosis (TB)	Erythromycin-resistant group A *Streptococcus* Clindamycin-resistant group B *Streptococcus*	Azole-resistant *Aspergillus fumigatus* Drug-resistant *Mycoplasma genitalium* Drug-resistant *Bordetella pertussis*

Planet, Prosperity, Peace, and Partnership, and have their vision finding environment-friendly solutions for economic and social development. In order to protect the environment, these goals also include avoiding overuse of natural resources. Out of 17 proposed SDGs, health receives adequate attention, see Fig. 2 (United Nations General Assembly Sustainable Development Goals 2015).

What is unfortunate is that antimicrobial resistance caused by superbugs has already emerged as one of the most difficult barriers to achieving the SDGs (Akinsemolu 2018a; Costanza et al. 2016; The Sustainable Development Goals Report 2016). To pinpoint the causes of AMR development, many articles and reports have been published already. The same is true for achieving the

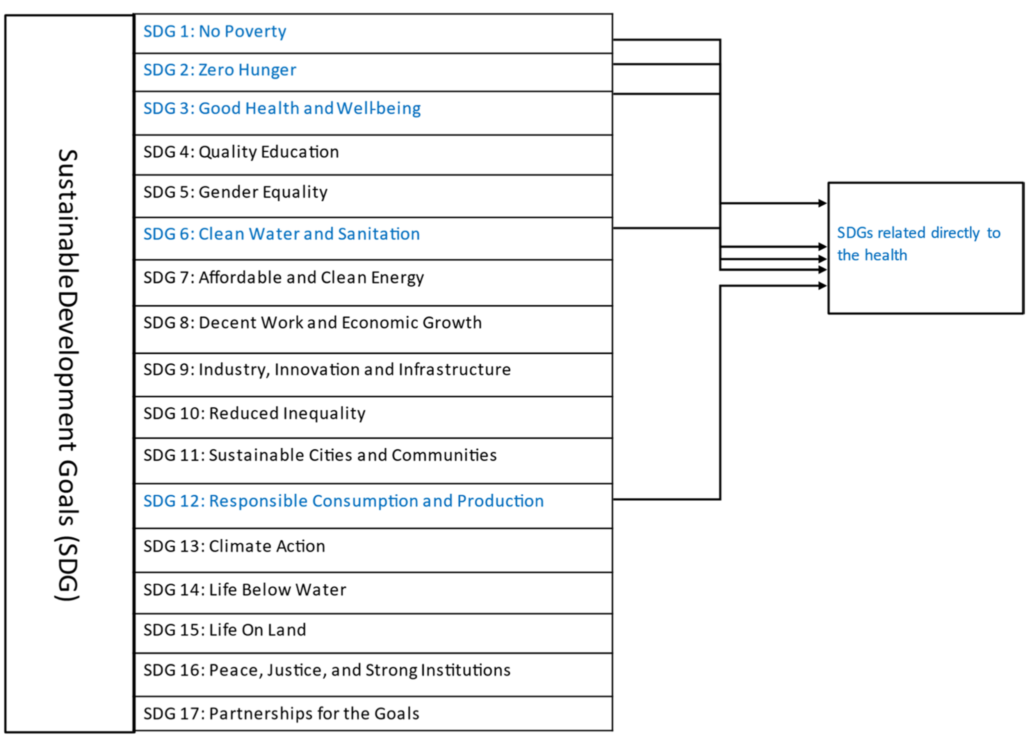

Fig. 2 Sustainable Development Goals and healthcare. Seventeen goals have been set by 193 UN member countries in 2015, and at least five of them are related to healthcare and are interlinked to each other

SDGs, but the number of articles focusing on the impact of AMR on health-related SDGs is still limited. In this review, we tried to find the link between SDGs and AMR based on the following objectives:

1. Investigate reasons behind emergence of superbugs among humans
2. Explore prevalence of deadly superbugs in different parts of the world and its impact on healthcare as well as environmental, social, and economic goals of the SDG
3. Identify strategies to combat superbugs and facilitate ways to achieve the SDGs

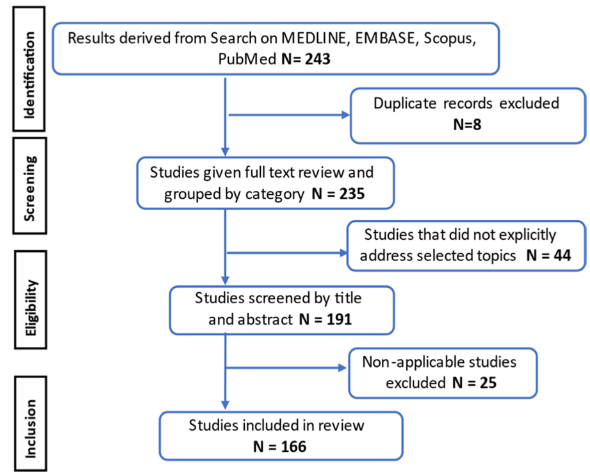

Fig. 3 Search strategy and study inclusion protocol

Main text

Methods

To conduct this review, the WHO and World Bank reports, along with four electronic databases (MEDLINE, EMBASE, Scopus, and PubMed), were searched using keywords such as SDGs, AMR, Superbugs, antibiotic resistance, and antimicrobial resistance, covering the period up to December 31, 2022. Two hundred and forty-three research articles, review papers and studies written in English language evaluating the impact of AMR (from any microbe) on patient, society and economy published until end of the year 2022 were included. Independent screening of title/abstracts followed by full texts was performed using pre-specified criteria and not-applicable studies were excluded. Extracted study data were used to compare prevalence of superbugs and economic and health burden. Monetary costs were calculated into USD. No reference protocol was used, however, for search strategy and study inclusion, the protocol diagram of PRISMA guideline has been used, see Fig. 3 (Moher et al. 2009).

Discussions

Antimicrobial resistance is a true multifaceted global crisis

Because infectious organisms are constantly evolving and gaining antimicrobial resistance, it is critical to investigate the key socioeconomic and political factors that contribute to the emergence of superbugs in both developed and developing countries. In poor countries, the following variables are thought to cause antimicrobial resistance: (1) insufficient surveillance of resistance development, (2) lack of control over current antibiotics, (3) clinical antibiotic overuse, and (4) ease of availability. In wealthy countries, however, the reasons are (1) weak hospital regulation and (2) excessive antibiotic usage in farmed animals. Not to mention the fact that a lack of research on novel antibiotics has impacted both developed and underdeveloped countries (Water, sanitation and hygiene: an essential ally in a superbug age 2021; Ramay et al. 2020; Chokshi et al. 2019).

Inappropriate and unnecessary intake When antibiotics were originally discovered in the 1940s, Sir Alexander Fleming expressed his concern about its overuse due to the possibility of widespread demand and misuse (Aminov 2010; Sb et al. 2017; Ventola 2015). Nowadays the most common form of antibiotic misuse is taking antibiotics without consulting physicians. This occurs primarily in underdeveloped and least developed countries due to a lack of regulatory oversight of both prescribed and non-prescribed antibiotics (Chokshi et al. 2019; Sb et al. 2017; Ventola 2015; Global action plan on antimicrobial resistance 2015; Van et al. 2013; Muhie 2019). Physicians often struggle there to follow guidelines for prescribing antibiotics especially when patients' urge for antibiotics is strong (Pp et al. 2014).

Inappropriate prescription Antibiotics given incorrectly contribute to the development of bacterial resistance (US Department of Health and Human Services 2019). Evidence indicates that in 30–50% of instances, treatment indication, medication selection, and antibiotic treatment duration are incorrect. According to one study in the USA, a pathogen was detected in only 7.6% of 17,435 patients brought to the hospital with community acquired pneumonia (CAP), and almost 30–60% of total antibiotics provided were unnecessary (Centers for Disease Control U 2019; Rhodes et al. 2000; Luyt et al. 2014; Bartlett et al. 2013). A similar scenario has been reported by a study conducted in a Chinese university hospital. Only 39 cases out of 1025 were microbiologically examined to determine the source of the infection. The same study reported that 77.8% of infected people receive one or more antibiotics

(Hu et al. 2003). In Jakarta, Indonesia, nearly 94% of children were given antibiotics for diarrhea, despite the fact that doctors assumed the diarrhea was caused by a viral infection (Gani et al. 1991). That is the reason why antimicrobial resistance is becoming more likely as a result of incorrect diagnosis.

Ease of availability and poor quality In developing countries, there is a lack of regulatory policy and law enforcement when it comes to pharmaceutical retail. Antibiotics are prescribed by about 81 percent of pharmacists for common colds in Minya, Egypt, according to a study on antibiotic use (Dooling et al. 2014). A study with 2000 participants conducted in Bangladesh's rural areas reported that 95% of medications are purchased from local pharmacies, while only 8% are prescribed by physicians (Okeke et al. 1999). Besides, lack of adequate quality assurance systems to ensure the quality of antibiotics supplied leads to poor quality of available antibiotics. Based on a 2006 Nigerian study, substandard formulation was used for 25–40% of ampicillin/cloxacillin production. It has also been reported that using outdated pediatric antibiotics increases the risk of resistance compared to using active (unexpired) antibiotics. When expired medications are used instead of new ones, the resistance rate increases by almost 2–6 times (Chokshi et al. 2019; Okeke et al. 1999; Obodozie et al. 2006; Ogunshe and Adinmonyema 2014).

Hospital-acquired infections One of the causes of antibiotic-resistant infection in developed countries is hospital-acquired infections (nosocomial infections). Antibiotics are used more frequently to prevent infection caused by bacteria as well as to reduce the risk of infection during surgeries. Antibiotic overuse, combined with close interactions between patients and the hospital's hygiene and sanitation system, play a key role in the development and spread of antibiotic-resistant bacteria (Chokshi et al. 2019; Weinstein 2001).

Overwhelming use in livestock and fish farming Incorrect antimicrobial use in livestock, fish farming, and agriculture leads to the development of resistant bacteria, which causes major health risks. Those bacteria, coupled with antibiotic resistant genes, are eventually transferred to the human body (O'Neill 2015). The number of antimicrobial agents used in cattle feed was revealed in a report published by the FDA in 2019. According to that report, domestic sales and distribution of medically important antimicrobials approved for use in food producing animals increased by 3% between 2018 and 2019 (US Food and Drug Administration 2019; Landers et al. 2012). Global food fish consumption, on the other hand, has increased at an annual rate of 3.1% between 1961 and 2017. This is nearly twice the rate of annual world population growth (1.6%) (FAO 2020). This tremendous expansion of fish farming resulted in increased usage of antimicrobial agents. Antimicrobials and chemical disinfectants are currently being used to prevent bacterial infection and control disease outbreaks in fish. Because no antibiotics have been approved for use in aquaculture, veterinary drugs from other branches are used. Such improper and excessive use of aquaculture medicine is extremely harmful to the species, as it weakens the fish immune system's ability to resist infection and bacterial colonization (Chee-Sanford et al. 2013; Cabello 2006, 2004).

Tedious approval procedure of NDA Pharmaceutical companies have found it increasingly difficult to obtain regulatory approval for newly discovered antibiotics in recent decades. Between 1983 and 2007, the rate of approval of newly discovered antibiotics dropped dramatically. This is primarily due to the implementation of new and stricter drug regulations, such as differences in the requirements for conducting clinical trials between countries, modifications to existing license restrictions, and so on (Ventola 2015; Gould and Bal 2013). Lack of clarity and a poor communication system are considerable factors as well. The FDA recently changed the guidelines and regulations for conducting clinical trials, making conducting antibiotic clinical trials much more difficult than before. Because placebo-controlled clinical trials for antibiotics are prohibited, trials are designed to show that new medications are not inferior to older ones. This requires a large number of population samples, raising overall costs and making antibiotic development unprofitable (Piddock 2012; Wright 2014; Shlaes et al. 2013).

Unhygienic conditions Most South-East Asian health-care institutions, according to the World Health Organization, lack proper sanitation and hygiene systems, leading to hospital-acquired infections and bacterial mutations. In low- and middle-income countries, poor sanitation and hygiene are found in 38% of health-care facilities, contributing to the spread of a variety of toxic bacteria. It is no surprise that some of the most dangerous superbugs, such as NDM1 and MRSA, have been discovered in medical facilities. Untreated waste water also contributes to the spread of drug residues and antibiotic-resistant bacteria in the environment, contaminating drinking water and the food chain. Contaminated wastewater from households, hospitals, pharmaceutical plants, nursing homes, and livestock farms is contaminating natural water sources across the region. This paradigm is hastening the spread of antibiotic-resistant bacteria and increasing human antibiotic consumption (Water, sanitation and hygiene: an essential ally in a superbug age 2021; Ramay et al. 2020).

Superbugs are severe and ubiquitous

Antimicrobial resistance caused by superbugs has become a major concern for almost all countries, regardless of their location, population, or economic status. According to a WHO report published in 2018, antimicrobial resistance was detected in 500,000 people in 22 countries. The most common types were *Escherichia coli, Klebsiella pneumoniae, S. aureus, and S. pneumoniae,* followed by *Salmonella spp*. It is of no surprise that the situation in LDCs and developing countries is far worse than that in developed ones (WHO 2017a) (Fig. 4).

In the USA and Europe alone, methicillin-resistant *S. aureus* (MRSA) kills 50,000 people each year (O'Neill 2014). Drugs that target penicillin-like beta-lactamases have become resistant to this superbug. Unfortunately, only a few antibiotics, such as glycopeptide, linezolid, tigecycline, and daptomycin, and some fifth-generation beta-lactam antibiotics like ceftaroline and ceftobiprole are effective against MRSA. Vancomycin-resistant enterococci are another dangerous superbug (VRE). In hospitals and other health-care settings, enterococci infect patients, spreading to the bloodstream, surgical sites, and the urinary tract (Wamel et al. 2007). *Enterococcus faecium* and *Enterococcus faecalis* are the most common bacteria found in reported cases. Even though VRE has a lower prevalence and epidemiologic impact than MRSA, there are still 54,500 "hospital acquired" enterococci infections reported annually in the USA. The infection rates between different species of enterococci vary, but Vancomycin resistance accounts for 30% of all health-care-associated enterococcal infections in the USA each year (Centers for Disease Control U 2019). Bacterial pneumoniae, meningitis, and bloodstream, ear, and sinus infections are all fatal infections caused by drug-resistant *S. pneumoniae*. Infections caused by resistant *S. pneumoniae* limit treatment options, resulting in 1.2 million new cases and 7000 deaths each year. This is especially prevalent in patients over the age of 50. In at least 30% of cases, this bacterium has been found to be completely resistant to multiple antibiotics used to treat severe *S. pneumoniae* infections. According to the World Health Organization, drug-resistant Mycobacterium tuberculosis infection killed 170,000 people worldwide in 2012 (Sengupta et al. 2013; Centers for Disease Control U 2019; Ventola 2015; Gross 2013). Because of the airborne nature of the infection, the lungs are the most common site of infection, but other body parts can also be infected. In 2011, 10,528 new tuberculosis (TB) cases were reported in the USA, with 9.9% of those cases being resistant to antibiotics. Over the next few years, the situation appeared to remain unchanged. First-line drugs like isoniazid or rifampicin are used to treat tuberculosis infection, but *M. tuberculosis* is already resistant to multiple first-line drugs (Frieden 2013). Patients are at risk due to extensively drug-resistant tuberculosis (XDR-TB), which has developed resistance to most TB medications. Even though harmonizing strict preventative measures and management programs can reduce the occurrence of drug-resistant TB and XDR-TB infections, the situation in most countries remains out of control (Frieden 2013). Carbapenem-resistant Enterobacteriaceae (CRE) is a deadly superbug that is resistant to almost all antibiotics, including carbapenem, which is meant to be the last line

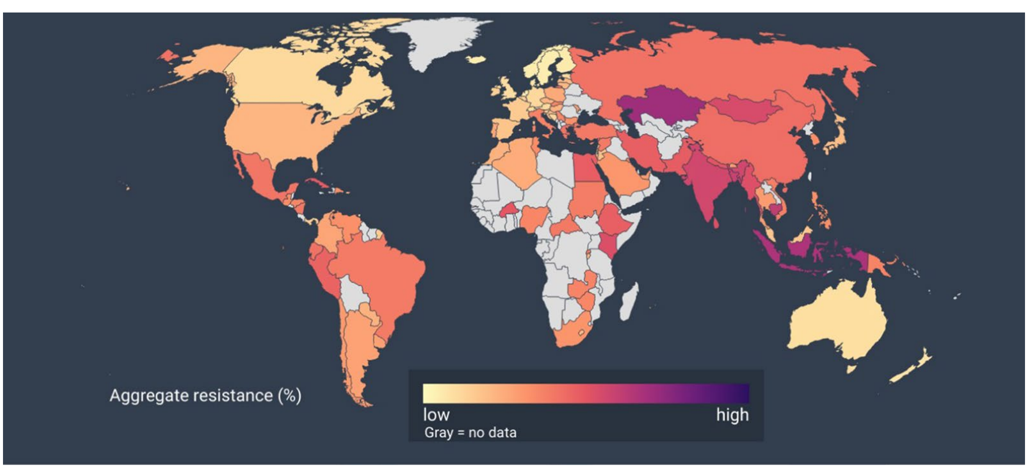

Fig. 4 Global prevalence of antibiotic resistance (%). Global prevalence has been shown with low to high severity across the regions. Aggregate resistance rate has been defined as average resistance prevalence of *E. coli*, *Klebsiella spp.* and *Staphylococcus aureus*. Regions with gray represents no data availability (Collignon et al. 2018)

of defense against drug-resistant bacteria. Many gram-negative bacteria, including *E. coli* and *K. pneumoniae*, produce the enzyme New Delhi metallo-beta-lactamase (NDM-1), which renders bacteria resistant to all beta-lactam antibiotics and carbapenem (Frieden 2013; Sengupta et al. 2013; Gross 2013).

Superbug-caused diseases, such as tuberculosis (TB), are particularly devastating in less developed countries. In 2013, there were 480,000 cases of multidrug-resistant tuberculosis (MDR-TB) and 210,000 deaths due to the disease, with the poorest people being most of the victims (Global Tuberculosis Report 2014).

Will the SDGs be far reaching due to antimicrobial resistance?

SDG-1: no poverty The first SDG aims to eradicate poverty, and AMR is a major impediment to achieving that goal. Antimicrobial resistance treatment is a time-consuming and costly process. Antimicrobial resistance, as well as superbugs, are rapidly spreading in developing and least developed countries due to the lack of a universal healthcare system. People struggle to meet their basic needs there, and the cost of healthcare is an additional burden for them. This situation exacerbates the "vicious cycle of poverty," which results in lower earning capacity, productivity, and living standards. If AMR spreads unchecked, the World Bank estimates that more than 24 million people will face severe poverty by 2030 (Drug-resistant infections : a threat to our economic future 2017; Akinsemolu 2018b).

SDG-2: zero hunger Poverty and hunger are inextricably linked, and if one is not addressed, the other will inevitably follow. According to the Food and Agriculture Organization of the United Nations (FAO), 793 million people go hungry every day, with 791 million of them living in developing and least developed countries. Global food production is expected to double in order to meet rising demand due to the exponential growth of the global population. This will eventually result in an increase in antimicrobial use, with global antimicrobial use in livestock animals expected to increase by 70% by 2030 (Akinsemolu 2018b; The State of Food Insecurity in the World 2015).

SDG-3: good health and well being The third SDG will be tedious to achieve due to the scarcity of effective anti-AMR drugs. AMR kills 25,000 people every year in the European Union alone (Authors 2009). Every year, 30,000 women and 200,000 newborn children die from infections that are not treatable with currently available drugs, according to the World Health Organization. This occurrence has a disproportionately negative impact on developing countries (O'Neill 2016; WHO 2016b). Antibiotic efficacy reduction will inevitably result in an increase in mortality (Liu et al. 2016; Newman et al. 2015). Drug resistance has been reported in cases of communicable diseases like HIV, tuberculosis, and malaria, posing yet another barrier to the achievement of the third SDG. Physicians and healthcare providers run out of options on a daily basis, resulting in costly treatments with long-term side effects (Littmann et al. 2016; WHO 2017b). According to the WHO, 650,000 (5.4%) of the world's 12 million TB cases were MDR-TB, with 9.7% of MDR-TB patients having XDR-TB (Global Tuberculosis Report 2017). Same is true for sexually transmitted infections (STIs) where 357 million cases were reported worldwide, with many of them becoming drug-resistant. This type of infection can lead to long-term disability, infertility, and even death. Because some gonorrheal infections are resistant to antibiotics, gonorrhea has gotten a lot of attention (Newman et al. 2015; Laxminarayan et al. 2013). Antimicrobial resistance has a significant impact on the treatment of many noncommunicable diseases. Medical procedures, organ transplants, and cancer treatment could all be jeopardized (Laxminarayan et al. 2013). In the USA, more than half of the microbes that cause surgical site infection are resistant to standard prophylactic antibiotics. An infection affects one out of every four cancer patients, and the bacteria that causes it is resistant to antibiotics (Teillant et al. 2015). Immunocompromised patients who went through chemotherapy or diagnosed with AIDS have a weakened immune system and are more susceptible to infection (Gudiol and Carratalà 2014; Nuorti et al. 2000). As a result, achieving several SDGs aimed at reducing noncommunicable diseases requires access to effective antibiotics. In order to combat antimicrobial resistance, it is critical to improve the performance of the healthcare system while moving toward universal health coverage. Without effective antibiotics, the healthcare system is doomed. This can be justified simply by looking at the cost of treatment and proper care for a patient with extensively drug-resistant tuberculosis, which is $430,000 (White House Administration 2015; Marks et al. 2014). As a result, antimicrobial resistance has emerged as a serious threat to the global health system's long-term viability.

SDG-6: clean water and sanitation Despite the lack of direct evidence that pharmaceutical and microbial hazards from the health-care system are causing widespread illness in people around the world, poorly managed health-care waste has the potential to contaminate groundwater, drinking water, soil, food crops, and sediments, as well as endangering the environment by introducing toxicants to wildlife and leading to the development of antibiotic-resistant bacteria (WHO 2017c, 2012; Küster and Adler 2014; Chartier et al. 2014). According to a recent report, a wastewater treatment plant receives waste from around

90 pharmaceutical companies, and 45 kg of commonly used antibiotics are released into a nearby river every day (Littmann et al. 2016). What is more shocking is that the antibiotic concentration in the river was higher than in the patients who received antibiotics (Larsson et al. 2007). Antibiotic residues in water, sediments, and soil combine to form antibiotics of varying concentrations, and extremely resistant bacteria can grow selectively against low antibiotic concentrations (WHO 2017b; Gullberg et al. 2011). Surprisingly, a lack of clean water and sanitation hastens the spread of bacterial diseases in children, increasing morbidity and mortality (WHO 2017b).

SDG-12: responsible consumption and production Antimicrobial resistance kills 700,000 people each year, with the number expected to rise to ten million by 2050, at a cost of $100 trillion (O'Neill 2014). Antibiotic efficacy loss raises a country's health-care spending, lowering productivity, household income, tax revenues, and GDP (Smith et al. 2005) Antimicrobial resistance is a major roadblock to global development because such large expenditures may jeopardize efforts for long-term economic development (O'Neill 2014; WHO 2017b; Smith et al. 2005).

What are our weapons?

The challenge of antimicrobial resistance has been exacerbated by pharmaceutical companies' indifference. They believe that conducting research for new antimicrobial drugs will yield limited profit because of high research expenditure. The average cost to develop an antibiotic could be as high as $1.5 billion (Towse et al. 2017), while the average revenue generated from an antibiotic's sale is near about $46 million only per year (Plackett 2020; Brandenburg and Schürholz 2015). Additionally, some experts doubt that bacteria will develop resistance to the newly developed antibiotics. They prefer to focus on drugs that treat chronic diseases (such as diabetes and hypertension) as well as drugs that improve overall quality of life (e.g., Cialis, Viagra, etc.) (Brandenburg and Schürholz 2015; Peña et al. 2021). Given these facts, appropriate steps for a long-term solution to this problem should be taken, with a focus on methods to prevent resistance and the spread of superbugs.

Vaccination Acute microbial infections are thought to be treated only with antibiotics. Vaccination, on the other hand, is the most effective way to prevent the spread of infectious diseases and combat antimicrobial resistance. Vaccines, such as the pneumococcal vaccine, work by preventing the spread of antibiotic-resistant bacteria (Rappuoli et al. 2017). Other vaccines, such as the influenza vaccine, prevent fevers indirectly, reducing the number of antibiotic doses prescribed on a regular basis (Hinman and Orenstein 2007). Vaccination reduces disease severity, protects against infection, and even increases the number of microbes needed to initiate infection (Iglehart 1983; Robinson and Bart 1993). Vaccines have helped to eradicate diseases like smallpox, measles, mumps, rubella, diphtheria, hepatitis A, pertussis, and polio in many parts of the world (Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease—United States 2005; Thanks to Vaccines).

Alternative therapies Alternatives to antibiotics will be the focus of future medical therapeutics and research, and these therapies may have a significant impact on the severity of microbial growth and infection. There have been few alternatives to combat AMR and the spread of superbugs until now.

1. A number of experts have suggested bacteriophage as a potential treatment for bacteria-induced infections. Bacteriophage is a virus capable of infecting bacterial cells and causing them to lyse. The use of bacteriophage is becoming more popular as a result of the need for quick substitutes and the pharmaceutical industry's aversion to investing in new antibiotics (Lin et al. 2017; Sabino et al. 2020; Moghadam et al. 2020).
2. Bacterial Quorum Sensing has been identified as a promising target for the treatment of bacterial infections in a number of studies. The communication mechanism is turned off or blocked without destroying the bacteria's cells. The selective pressure and the rate of AMR during treatment are both reduced as a result of this technique (Bhardwaj et al. 2013; Hentzer and Givskov 2003). Antibiotics kill or slow the growth of bacteria, whereas quorum sensing inhibitors or quorum quenchers reduce bacterial virulence. *Pseudomonas aeruginosa, S. aureus, Vibrio fischeri, Vibrio harveyi, E. coli,* and *Vibrio cholerae* have all been used in extensive research on Quorum Sensing.
3. Probiotics, also known as fecal transplant therapy (FTT), have been used for over a decade, despite conflicting results. Pathogen-free healthy donors' feces are used to repopulate a recipient's microbiota in this case. By producing antimicrobial compounds such as bacteriocins and organic acids, probiotics are thought to be able to eliminate microbes. This will improve the gastrointestinal microbial environment by attaching to the intestinal mucosa. As a result, pathogen adhesion is stymied. Probiotics such as *Bacillus*, *Lactobacillus*, *Lactococcus*, *Streptococcus*,

and others are frequently used (Holleran et al. 2018; McEwen and Fedorka-Cray 2002; Gargiullo et al. 2019).

Drug repositioning Drug repositioning relies on FDA-approved drug candidates, either for therapeutic use or for molecules with clinical data. When combined with screening methods, this innovation has the potential to play a significant role in the long-awaited discovery of antimicrobial drugs (Konreddy et al. 2019; Domínguez et al. 2020; Issa et al. 2013; Farha and Brown 2019; Bessoff et al. 2013). A common approach in drug repositioning strategy is systemic screening of non-antimicrobial drugs approved by the FDA with antimicrobial property in a cell-based model. This empirical phenotypic-based screening is focused on compounds that can inhibit the growth of microbes, and it differs from general repurposing, which requires prior knowledge of the disease, binding characteristics, and the mechanism of action (MOA) (Konreddy et al. 2019; Farha and Brown 2019; Swinney and Lee 2020). Cell-based high-throughput screening (HTS) has been used in many studies to demonstrate the findings of non-antimicrobial approved drugs. Because of advancements in HTS, empirical screening has become a popular and simple rapid screening technique that employs the most cutting-edge methods in bioassay, robotics, computation, and data management (Debnath et al. 2012; Chockalingam et al. 2010; Lucumi et al. 2010; Dyall et al. 2014; Krysan et al. 2013; Krysan and Didone 2008; Jacobs et al. 2013; Khodaverdian et al. 2013). Another useful and widely used screening method is in-silico screening, also known as computational screening. Due to the abundance of information available for approved drugs, in-silico drug repurposing has become more advantageous. There are two types of in-silico screening: ligand-based and network-based (Astolfi et al. 2017).

Probably the most common computational technique for computer-aided drug discovery is molecular docking, which reveals the binding affinity between a drug and a target molecule to the target's active site. A higher binding affinity is indicated by a higher negative binding energy. Molecular docking provides information on the key residues of the target molecule interacting with the drug molecule in addition to the binding affinity (Astolfi et al. 2017). Entacapone, for instance, was used to treat Parkinson's disease, this computational method identified it as a novel antibacterial drug against multiple drug-resistant Mycobacterium tuberculosis (Carlson-Banning et al. 2013; Deng et al. 2009).

Initiatives taken by regulatory bodies In 2014, WHO published a report on superbugs for the first time, obtaining the most recent information on resistance surveillance and data for a selected set of nine bacteria–antibacterial drug combinations of public health importance from 129 Member States. 114 of them provided data for at least one of the nine combinations (22 countries provided data on all nine combinations) (World Health Organization 2014). WHO also approved a global antimicrobial resistance (AMR) strategy in May 2015 (Global action plan on antimicrobial resistance 2015). The 'National Strategy for Combating Antibiotic-Resistant Bacteria' was published by the US government in September 2014 (U.S. 2014). It listed a number of objectives and plans for leading nations in the fight against AMR. In 2013, the United Kingdom announced the "UK Five Year Antimicrobial Resistance Strategy (2013–2018)," which aimed to provide a roadmap for dealing with AMR issues (2013). A Federal Action Plan to Combat Antimicrobial Resistance was released by the Canadian government in 2015 (Federal action plan on antimicrobial resistance and use in Canada: building on the federal framework for action 2015). The European Antibiotic Resistance Surveillance Network (EARS-Net) has been providing updated country-specific records of antibiotic consumption and resistance for more than a decade already (EARS-Net). In developing and least developed countries, particularly in Africa, such a scheme does not exist. However, many African countries are members of the Global Antibiotic Resistance Partnership (GARP), which was founded in 2009 to provide a platform for low- and middle-income countries to focus on antimicrobial resistance (2009). The African Society for Laboratory Medicine (ASLM) has recently been involved in research, debate, and solution-finding to ensure a strong African laboratory infrastructure in order to combat global health issues such as AMR, HIV/AIDS, and other diseases (Home - African Society for Laboratory Medicine). The World Organization for Animal Health (OIE) has developed international standards and guidelines for the responsible use of antimicrobials in animals, including measures to promote good animal husbandry and hygiene practices, reduce the need for antibiotics, and monitor antimicrobial use in animals (Standards and Guidelines and resolutions on antimicrobial resistance and the use of antimicrobial agent).

According to a WHO report based on a survey, enough initiatives are planned and governments around the world are committed to ending the AMR problem, but strategies to prevent inappropriate antibiotic use and reduce the spectrum of AMR differ significantly across six WHO regions. The monitoring framework for the SDG added a new AMR indicator in 2019. This indicator tracks the number of bloodstream infections caused by two drug-resistant bacteria: methicillin-resistant *S. aureus* (MRSA) and *E. coli* resistant to third-generation cephalosporins (3GC) (WHO 2016a).

Conclusions

This review aimed to explore the link between the Sustainable Development Goals (SDGs) and Antimicrobial Resistance (AMR), specifically focusing on the emergence of superbugs among humans, prevalence of deadly superbugs in different parts of the world, and strategies to combat superbugs while facilitating the achievement of the SDGs.

Our investigation found that the overuse and misuse of antibiotics, in addition to poor infection control practices, are key drivers of superbug emergence. Moreover, our review revealed the prevalence of deadly superbugs worldwide and their impact on healthcare, environment, social and economic goals of the SDGs. The increasing resistance of bacteria to antibiotics has significant implications for the achievement of the SDGs, particularly in developing countries where infectious diseases are prevalent, and the impact on health systems can be overwhelming.

By identifying approaches to combat superbugs, such as the rational use of antibiotics, implementing effective infection control practices, and developing new antibiotics and alternative therapies, including vaccination, we can mitigate the adverse effects of AMR and make progress toward accomplishing the SDGs. Furthermore, integrating AMR strategies into national development plans and improving cross-sectoral collaboration among stakeholders can facilitate ways to achieve the SDGs while reducing the spread of superbugs.

Abbreviations

ABR	Antibiotic resistance
AHLs	N-acyl lhomoserine lactones
AIDS	Acquired immunodeficiency syndrome
AMR	Antimicrobial resistance
AMRB	Aquatic antimicrobial-resistant bacteria
ASLM	The African Society for Laboratory Medicine
CAP	Community acquired pneumonia
CDC	Center for Disease Control and Prevention
CRE	Carbapenem-resistant Enterobacteriaceae
EARS-Net	European Antibiotic Resistance Surveillance Network
FDA	Food and Drug Administration
FTT	Fecal transplant therapy
GARP	Global Antibiotic Resistance Partnership
GDP	Gross domestic product
HGT	Horizontal Gene Transfer
HIV	Human immunodeficiency viruses
HSL	Homoserine lactone (HSL)
HTS	High-throughput screening
LDC	Least Developed Countries
MDRTB	Multi-drug resistant tuberculosis
MRSA	Methicillin-resistant *Staphylococcus Aureus*
NDM-1	New Delhi metallo-beta-lactamase
OIE	The World Organization for Animal Health
SDGs	Sustainable Development Goals
STI	Sexually transmitted infections
UN	United Nations
VRE	Vancomycin-resistant enterococci
WEF	World Economic Forum
WHO	World Health Organization
XDR-TB	Extensively drug resistant tuberculosis

Acknowledgements

The authors are grateful to Mrs. Tanjina Yousuf, graduate pharmacy student from Noakhali Science and Technology University, Bangladesh in reviewing the search strategy and providing resources.

Author contributions

The first author, SM wrote the manuscript, identified the suitable keywords for search strategy, designed the search protocol and created the illustrations (figures). The second author, MNA reviewed the whole manuscript and checked the references. All authors have read and approved the manuscript.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Availability of data and materials

All the data and material will be provided upon request and as per requirements of the journal.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declared no potential competing interests with respect to the research, authorship, and/or publication of this article.

Received: 27 March 2023 Accepted: 30 April 2023
Published online: 05 May 2023

References

14 diseases you almost forgot about (Thanks to Vaccines)|CDC. https://www.cdc.gov/vaccines/parents/diseases/forgot-14-diseases.html. Accessed 5 Sep 2021

Akinsemolu AA (2018a) The role of microorganisms in achieving the sustainable development goals. J Clean Prod. https://doi.org/10.1016/j.jclepro.2018.02.081

Akinsemolu AA (2018b) The role of microorganisms in achieving the sustainable development goals. J Clean Prod 182:139–155. https://doi.org/10.1016/j.jclepro.2018.02.081

Aminov RI (2010) A brief history of the antibiotic era: lessons learned and challenges for the future. Front Microbiol. https://doi.org/10.3389/FMICB.2010.00134

Antimicrobial Resistance - "Stemming the Superbug Tide"|Compare your country. https://www1.compareyourcountry.org/antimicrobial-resistance/en/1/808/default/all/ALL. Accessed 6 Sep 2021

Aslam B, Wang W, Arshad MI et al (2018) Antibiotic resistance: a rundown of a global crisis. Infect Drug Resist 11:1645. https://doi.org/10.2147/IDR.S173867

Astolfi A, Felicetti T, Iraci N et al (2017) Pharmacophore-based repositioning of approved drugs as novel *Staphylococcus aureus* NorA Efflux pump inhibitors. J Med Chem 60:1598–1604. https://doi.org/10.1021/ACS.JMEDCHEM.6B01439

Author (2014) Global tuberculosis report
Authors (2009) The bacterial challenge: time to react
Bartlett JG, Mundy LM (1995) Community-acquired pneumonia. N Engl J Med 333:1618–1624. https://doi.org/10.1056/NEJM199512143332408
Bartlett JG, Gilbert DN, Spellberg B (2013) Seven ways to preserve the miracle of antibiotics. Clin Infect Dis off Publ Infect Dis Soc Am 56:1445–1450. https://doi.org/10.1093/CID/CIT070
Bessoff K, Sateriale A, Lee KK, Huston CD (2013) Drug repurposing screen reveals FDA-approved inhibitors of human HMG-CoA reductase and isoprenoid synthesis that block Cryptosporidium parvum growth. Antimicrob Agents Chemother 57:1804–1814. https://doi.org/10.1128/AAC.02460-12
Bhardwaj AK, Vinothkumar K, Rajpara N (2013) Bacterial quorum sensing inhibitors: attractive alternatives for control of infectious pathogens showing multiple drug resistance. Recent Pat Anti-Infect Drug Discovery 8:68–83. https://doi.org/10.2174/1574891X11308010012
Brandenburg K, Schürholz T (2015) Lack of new antiinfective agents: passing into the pre-antibiotic age? World J Biol Chem 6:71. https://doi.org/10.4331/WJBC.V6.I3.71
Cabello FC (2004) Antibióticos y acuicultura en Chile: consecuencias para la salud humana y animal. Rev Méd Chile 132:1001–1006. https://doi.org/10.4067/S0034-98872004000800014
Cabello FC (2006) Heavy use of prophylactic antibiotics in aquaculture: a growing problem for human and animal health and for the environment. Environ Microbiol 8:1137–1144. https://doi.org/10.1111/J.1462-2920.2006.01054.X
Carlson-Banning KM, Chou A, Liu Z et al (2013) Toward repurposing ciclopirox as an antibiotic against drug-resistant *Acinetobacter baumannii*, *Escherichia coli*, and *Klebsiella pneumoniae*. PLoS ONE 8:e69646. https://doi.org/10.1371/JOURNAL.PONE.0069646
Centers for Disease Control U (2019) Antibiotic resistance threats in the United States. https://doi.org/10.15620/cdc:82532
Chartier Y, Emmanuel J, Pieper U et al (2014) Safe management of wastes from health-care activities Second edition
Chee-Sanford JC, Aminov RI, Krapac IJ et al (2013) Antimicrobial use in aquaculture re-examined: its relevance to antimicrobial resistance and to animal and human health. Environ Microbiol 15:1917–1942. https://doi.org/10.1111/1462-2920.12134
Chockalingam K, Simeon RL, Rice CM, Chen Z (2010) A cell protection screen reveals potent inhibitors of multiple stages of the hepatitis C virus life cycle. Proc Natl Acad of Sci 107:3764–3769. https://doi.org/10.1073/PNAS.0915117107
Chokshi A, Sifri Z, Cennimo D, Horng H (2019) Global contributors to antibiotic resistance. J Glob Infect Dis 11:36–42. https://doi.org/10.4103/JGID.JGID_110_18
Collignon P, Beggs JJ, Walsh TR et al (2018) Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis. Lancet Planet Health 2:e398–e405. https://doi.org/10.1016/S2542-5196(18)30186-4
Costanza R, Fioramonti L, Kubiszewski I (2016) The UN sustainable development goals and the dynamics of well-being. Front Ecol Environ 14:59–59. https://doi.org/10.1002/FEE.1231
de Kraker MEA, Stewardson AJ, Harbarth S (2016) Will 10 million people die a year due to antimicrobial resistance by 2050? PLOS Med 13:1002184. https://doi.org/10.1371/JOURNAL.PMED.1002184
Debnath A, Parsonage D, Andrade RM et al (2012) A high-throughput drug screen for Entamoeba histolytica identifies a new lead and target. Nat Med 18:956–960. https://doi.org/10.1038/NM.2758
Dellit TH (2007) Infectious diseases society of america and the society for healthcare epidemiology of america guidelines for developing an institutional program to enhance antimicrobial stewardship. Infect Dis Clin Pract 15:263–264. https://doi.org/10.1097/IPC.0b013e318068b1c0
Deng L, Sundriyal S, Rubio V et al (2009) Coordination chemistry based approach to lipophilic inhibitors of 1-deoxy-D-xylulose-5-phosphate reductoisomerase. J Med Chem 52:6539–6542. https://doi.org/10.1021/JM9012592
Department of Health (2013) UK five year antimicrobial resistance strategy 2013 to 2018
Dever LA, Dermody TS (1991) Mechanisms of bacterial resistance to antibiotics. Arch Intern Med 151:886–895. https://doi.org/10.1001/archinte.1991.00400050040010
Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease—United States, 1998–2003. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5436a1.htm. Accessed 30 Aug 2021
Domínguez AV, Mejías MEJ, Smani Y (2020) Drugs repurposing for multidrug resistant bacterial infections. Drug Repurposing Hypothesis Mol Aspects Ther Appl. https://doi.org/10.5772/INTECHOPEN.93635
Dooling KL, Kandeel A, Hicks LA et al (2014) Understanding antibiotic use in Minya District, Egypt: physician and pharmacist prescribing and the factors influencing their practices. Antibiotics 3:233–243. https://doi.org/10.3390/ANTIBIOTICS3020233
Drug-resistant infections: a threat to our economic future (Vol. 2): final report (English) (2017). https://documents.worldbank.org/en/publication/documents-reports/documentdetail/323311493396993758/final-report. Accessed 30 Aug 2021
Dyall J, Coleman CM, Hart BJ et al (2014) Repurposing of clinically developed drugs for treatment of middle east respiratory syndrome coronavirus infection. Antimicrob Agents Chemother 58:4885. https://doi.org/10.1128/AAC.03036-14
European Antimicrobial Resistance Surveillance Network (EARS-Net). https://www.ecdc.europa.eu/en/about-us/partnerships-and-networks/disease-and-laboratory-networks/ears-net. Accessed 28 Aug 2021
FAO (2020) FAO. 2018. The state of world fisheries and aquaculture 2018 - meeting the sustainable development goals, Rome
Farha MA, Brown ED (2019) Drug repurposing for antimicrobial discovery. Nat Microbiol 4:565–577. https://doi.org/10.1038/s41564-019-0357-1
Federal action plan on antimicrobial resistance and use in Canada: building on the federal framework for action - Canada.ca (2015). https://www.canada.ca/en/health-canada/services/publications/drugs-health-products/federal-action-plan-antimicrobial-resistance-canada.html. Accessed 30 Aug 2021
Frieden T (2013) Antibiotic resistance threats in the United States. Centers Dis Control Prev, 114
Friedman ND, Temkin E, Carmeli Y (2016) The negative impact of antibiotic resistance. Clin Microbiol Infect 22:416–422
Gani L, Arif H, Widjaja SK et al (1991) Physicians' prescribing practice for treatment of acute diarrhoea in young children in Jakarta. J Diarrhoeal Dis Res 9:194–199. https://doi.org/10.1186/S12889-021-11254-1
Gargiullo L, Del Chierico F, D'Argenio P, Putignani L (2019) Gut microbiota modulation for multidrug-resistant organism decolonization: present and future perspectives. Front Microbiol. https://doi.org/10.3389/FMICB.2019.01704
Global Antibiotic Resistance Partnership (GARP) - Center for Disease Dynamics, Economics & Policy (CDDEP). https://cddep.org/projects/global-antibiotic-resistance-partnership/. Accessed 20 Aug 2021
Global Risks (2013) Global Risks 2013 Eighth Edition an initiative of the risk response network insight report
Global Tuberculosis Report (2017) Global tuberculosis report 2015
Gould IM, Bal AM (2013) New antibiotic agents in the pipeline and how they can help overcome microbial resistance. Virulence 4:185. https://doi.org/10.4161/VIRU.22507
Gross M (2013) Antibiotics in crisis. Current biology : CB 23. https://doi.org/10.1016/J.CUB.2013.11.057
Gudiol C, Carratalà J (2014) Antibiotic resistance in cancer patients. Exp Rev Anti-Infect Ther 12:1003–1016. https://doi.org/10.1586/14787210.2014.920253
Gullberg E, Cao S, Berg OG et al (2011) Selection of resistant bacteria at very low antibiotic concentrations. PLOS Pathog 7:e1002158. https://doi.org/10.1371/JOURNAL.PPAT.1002158
Hentzer M, Givskov M (2003) Pharmacological inhibition of quorum sensing for the treatment of chronic bacterial infections. J Clin Investig 112:1300–1307. https://doi.org/10.1172/JCI20074
Hinman AR, Orenstein WA (2007) Adult immunization: what can we learn from the childhood immunization program? Clin Infect Dis off Publ Infect Dis Soc Am 44:1532–1535. https://doi.org/10.1086/519543
Hirsch EF (2008) "The treatment of infected wounds", Alexis Carrel's contribution to the care of wounded soldiers during World War I. J Trauma Injury Infect Crit Care. https://doi.org/10.1097/TA.0b013e31816b307d
Holleran G, Scaldaferri F, Ianiro G et al (2018) Fecal microbiota transplantation for the treatment of patients with ulcerative colitis and other gastrointestinal conditions beyond Clostridium difficile infection: an update.

Drugs Today (barcelona, Spain : 1998) 54:123–136. https://doi.org/10.1358/DOT.2018.54.2.2760765
Home - African Society for Laboratory Medicine. https://aslm.org/. Accessed 25 Aug 2021
Hu S, Liu X, Peng Y (2003) Assessment of antibiotic prescription in hospitalised patients at a Chinese university hospital. J Infect 46:161–163. https://doi.org/10.1053/JINF.2002.1078
Iglehart JK (1983) Health policy report. The Reagan record on health care. New Engl J Med 308:232–236. https://doi.org/10.1056/NEJM198301273080434
Issa NT, Kruger J, Byers SW, Dakshanamurthy S (2013) Drug repurposing a reality: from computers to the clinic. Expert Rev Clin Pharmacol 6:95–97. https://doi.org/10.1586/ECP.12.79
Jacobs AC, DiDone L, Jobson J et al (2013) Adenylate kinase release as a high-throughput-screening-compatible reporter of bacterial lysis for identification of antibacterial agents. Antimicrob Agents Chemother 57:26–36. https://doi.org/10.1128/AAC.01640-12
Karchmer AW (1991) *Staphylococcus aureus* and vancomycin: the sequel. Ann Intern Med 115:739–741. https://doi.org/10.7326/0003-4819-115-9-739
Khodaverdian V, Pesho M, Truitt B et al (2013) Discovery of antivirulence agents against methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother 57:3645–3652. https://doi.org/10.1128/AAC.00269-13
Konreddy AK, Rani GU, Lee K, Choi Y (2019) Recent drug-repurposing-driven advances in the discovery of novel antibiotics. Curr Med Chem 26:5363–5388. https://doi.org/10.2174/0929867325666180706101404
Krysan DJ, Didone L (2008) A high-throughput screening assay for small molecules that disrupt yeast cell integrity. J Biomol Screen 13:657–664. https://doi.org/10.1177/1087057108320713
Krysan DJ, Baxter YC, Wellington M et al (2013) A repurposing approach identifies off-patent drugs with fungicidal cryptococcal activity, a common structural chemotype, and pharmacological properties relevant to the treatment of cryptococcosis. Eukaryot Cell 12:278–287. https://doi.org/10.1128/EC.00314-12
Küster A, Adler N (2014) Pharmaceuticals in the environment: scientific evidence of risks and its regulation. Philos Trans R Soc B Biol Sci. https://doi.org/10.1098/RSTB.2013.0587
Landers TF, Cohen B, Wittum TE, Larson EL (2012) A review of antibiotic use in food animals: perspective, policy, and potential. Public Health Rep 127:4–22. https://doi.org/10.1177/003335491212700103
Larsson DJ, de Pedro C, Paxeus N (2007) Effluent from drug manufactures contains extremely high levels of pharmaceuticals. J Hazard Mater 148:751–755. https://doi.org/10.1016/J.JHAZMAT.2007.07.008
Laxminarayan R, Duse A, Wattal C et al (2013) Antibiotic resistance—the need for global solutions. Lancet Infect Dis 13:1057–1098. https://doi.org/10.1016/S1473-3099(13)70318-9
Lin DM, Koskella B, Lin HC (2017) Phage therapy: an alternative to antibiotics in the age of multi-drug resistance. World J Gastrointest Pharmacol Thera. https://doi.org/10.4292/WJGPT.V8.I3.162
Littmann J, Zorzet A, Cars O (2016) Antimicrobial resistance-a threat to the world's sustainable development. Upsala J Med Sci 121:159–164. https://doi.org/10.1080/03009734.2016.1195900
Liu L, Oza S, Hogan D et al (2016) Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the Sustainable Development Goals. Lancet 388:3027–3035. https://doi.org/10.1016/S0140-6736(16)31593-8
Lucumi E, Darling C, Jo H et al (2010) Discovery of potent small-molecule inhibitors of multidrug-resistant plasmodium falciparum using a novel miniaturized high-throughput luciferase-based assay. Antimicrob Agents Chemother 54:3597. https://doi.org/10.1128/AAC.00431-10
Luepke KH (2017) III JFM the antibiotic pipeline: reviving research and development and speeding drugs to Market. Expert Rev Anti-Infec Ther 15:425–433. https://doi.org/10.1080/14787210.2017.1308251
Luyt CE, Bréchot N, Trouillet JL, Chastre J (2014) Antibiotic stewardship in the intensive care unit. Crit Care. https://doi.org/10.1186/S13054-014-0480-6
Marks SM, Flood J, Seaworth B et al (2014) Treatment practices, outcomes, and costs of multidrug-resistant and extensively drug-resistant tuberculosis, United States, 2005–2007. Emerg Infect Dis 20:812. https://doi.org/10.3201/EID2005.131037
McEwen SA, Fedorka-Cray PJ (2002) Antimicrobial use and resistance in animals. Clin Infect Dis off Publ Infect Dis Soc Am 34(Suppl 3):S93–S106. https://doi.org/10.1086/340246
Michael CA, Dominey-Howes D, Labbate M (2014) The antimicrobial resistance crisis: causes, consequences, and management. Front Public Health. https://doi.org/10.3389/fpubh.2014.00145
Moghadam MT, Khoshbayan A, Chegini Z et al (2020) Bacteriophages, a new therapeutic solution for inhibiting multidrug-resistant bacteria causing wound infection: lesson from animal models and clinical trials. Drug Des Dev Ther 14:1867–1883. https://doi.org/10.2147/DDDT.S251171
Moher D, Liberati A, Tetzlaff J et al (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 151:264–269
Muhie OA (2019) Antibiotic use and resistance pattern in Ethiopia: systematic review and meta-analysis. Int J Microbiol. https://doi.org/10.1155/2019/2489063
Naylor NR, Atun R, Zhu N et al (2018) Estimating the burden of antimicrobial resistance: a systematic literature review. Antimicrob Resist Infect Control 7:58. https://doi.org/10.1186/S13756-018-0336-Y
Newman L, Rowley J, Vander HS et al (2015) Global estimates of the prevalence and incidence of four curable sexually transmitted infections in 2012 based on systematic review and global reporting. PLoS ONE. https://doi.org/10.1371/JOURNAL.PONE.0143304
Nuorti JP, Butler JC, Gelling L et al (2000) Epidemiologic relation between HIV and invasive pneumococcal disease in San Francisco County, California. Ann Intern Med 132:182–190. https://doi.org/10.7326/0003-4819-132-3-200002010-00003
O'Neill J (2014) Antimicrobial resistance: tackling a crisis for the health and wealth of nations
O'Neill J (2015) Antimicrobials in agriculture and the environment: reducing unnecessary use and waste
O'Neill J (2016) Tackling drug-resistant infections globally: final report and recommendations the review on antimicrobial resistance
Obodozie O, Mustapha K, Ebeshi B, Inyang U (2006) A comparative study on the prevalence of substandard ampicillin/cloxacillin preparations in the Nigerian market: mid 1990's and present. J Phytomedicine Ther 11:1–8. https://doi.org/10.4314/jopat.v11i1.48619
Ogunshe A, Adinmonyema P (2014) Evaluation of bacteriostatic potency of expired oral paediatric antibiotics and implications on infant health. Pan Afr Med J. https://doi.org/10.11604/PAMJ.2014.19.378.2156
OIE Standards, Guidelines and resolutions on antimicrobial resistance and the use of antimicrobial agent
Okeke IN, Lamikanra A, Edelman R (1999) Socioeconomic and behavioral factors leading to acquired bacterial resistance to antibiotics in developing countries. Emerg Infect Dis 5:18. https://doi.org/10.3201/EID0501.990103
Peña OIG, Zavala MÁL, Ruelas HC (2021) Pharmaceuticals market, consumption trends and disease incidence are not driving the pharmaceutical research on water and wastewater. Int J Environ Res Public Health 18:1–37. https://doi.org/10.3390/IJERPH18052532
Piddock LJ (2012) The crisis of no new antibiotics—what is the way forward? Lancet Infect Dis 12:249–253. https://doi.org/10.1016/S1473-3099(11)70316-4
Plackett B (2020) Why big pharma has abandoned antibiotics. Nature 586:S50–S52. https://doi.org/10.1038/D41586-020-02884-3
Pp D, Ac B, Le W et al (2014) Primary care clinicians' perceptions about antibiotic prescribing for acute bronchitis: a qualitative study. BMC Fam Pract. https://doi.org/10.1186/S12875-014-0194-5
Ramay BM, Caudell MA, Cordón-Rosales C et al (2020) Antibiotic use and hygiene interact to influence the distribution of antimicrobial-resistant bacteria in low-income communities in Guatemala. Sci Reports 10:1–10. https://doi.org/10.1038/s41598-020-70741-4
Rappuoli R, Bloom DE, Black S (2017) Deploy vaccines to fight superbugs. Nature 552:165–167. https://doi.org/10.1038/D41586-017-08323-0
Resistant "Superbugs" Create Need for Novel Antibiotics. https://www.medscape.com/viewarticle/554935. Accessed 30 Aug 2021
Reygaert WC (2018) An overview of the antimicrobial resistance mechanisms of bacteria. AIMS Microbiol 4:482–501. https://doi.org/10.3934/MICROBIOL.2018.3.482
Rhodes G, Huys G, Swings J et al (2000) Distribution of oxytetracycline resistance plasmids between aeromonads in hospital and aquaculture

environments: implication of *Tn1721* in dissemination of the tetracycline resistance determinant Tet A. Appl Environ Microbiol 66:3883–3890. https://doi.org/10.1128/AEM.66.9.3883-3890.2000
Robinson CA, Bart KJ (1993) Disease prevention through immunization: the beginning of health care reform. Public Health Rep 108:417
Rossolini GM, Arena F, Pecile P, Pollini S (2014) Update on the antibiotic resistance crisis. Curr Opin Pharmacol 18:56–60. https://doi.org/10.1016/J.COPH.2014.09.006
Sabino J, Hirten RP, Colombel J-F (2020) Review article: bacteriophages in gastroenterology—from biology to clinical applications. Aliment Pharmacol Ther 51:53–63. https://doi.org/10.1111/APT.15557
Sengupta S, Chattopadhyay MK, Grossart HP (2013) The multifaceted roles of antibiotics and antibiotic resistance in nature. Front Microbiol. https://doi.org/10.3389/FMICB.2013.00047
Shlaes DM, Sahm D, Opiela C, Spellberg B (2013) The FDA reboot of antibiotic development. Antimicrob Agents Chemother 57:4605–4607. https://doi.org/10.1128/AAC.01277-13
Smith RD, Yago M, Millar M, Coast J (2005) Assessing the macroeconomic impact of a healthcare problem: the application of computable general equilibrium analysis to antimicrobial resistance. J Health Econ 24:1055–1075. https://doi.org/10.1016/J.JHEALECO.2005.02.003
Spellberg B, Gilbert DN (2014) The future of antibiotics and resistance: a tribute to a career of leadership by John Bartlett. Clin Infect Dis 59:S71. https://doi.org/10.1093/CID/CIU392
Spellberg B, Powers JH, Brass EP et al (2004) Trends in antimicrobial drug development: implications for the future. Clin Infect Dis off Publ Infect Dis Soc Am 38:1279–1286. https://doi.org/10.1086/420937
Spellberg B, Srinivasan A, Chambers HF (2016) New societal approaches to empowering antibiotic stewardship. JAMA J Am Med Assoc 315:1229–1230
Swinney DC, Lee JA (2020) Recent advances in phenotypic drug discovery. F1000Research 9:1–9. https://doi.org/10.12688/f1000research.25813.1
Teillant A, Gandra S, Barter D et al (2015) Potential burden of antibiotic resistance on surgery and cancer chemotherapy antibiotic prophylaxis in the USA: a literature review and modelling study. Lancet Infect Dis 15:1429–1437. https://doi.org/10.1016/S1473-3099(15)00270-4
The State of Food Insecurity in the World (2015). Meeting the 2015 international hunger targets: taking stock of uneven progress|Policy Support and Governance|Food and Agriculture Organization of the United Nations. http://www.fao.org/policy-support/tools-and-publications/resources-details/en/c/469455/. Accessed 30 Aug 2021
The Sustainable Development Goals Report (2016). https://unstats.un.org/sdgs/report/2016/. Accessed 31 Aug 2021
Towse A, Hoyle CK, Goodall J et al (2017) Time for a change in how new antibiotics are reimbursed: development of an insurance framework for funding new antibiotics based on a policy of risk mitigation. Health Policy 121:1025–1030. https://doi.org/10.1016/J.HEALTHPOL.2017.07.011
U.S. National Strategy for Combating Antibiotic-Resistant Bacteria (National Strategy)|Antibiotic/Antimicrobial Resistance|CDC (2014). https://www.cdc.gov/drugresistance/us-activities/national-strategy.html. Accessed 5 Sep 2021
United Nations General Assembly (2015) Sustainable Development Goals. https://sdgs.un.org/
US Department of Health and Human Services, CDC (2019) Antibiotic resistance threats in the United States
US Food and Drug Administration (2019) 2019 Summary report on antimicrobials sold or distributed for use in food-producing animals
Van Wamel WJB, Hendrickx APA, Bonten MJM et al (2007) Growth condition-dependent Esp expression by *Enterococcus faecium* affects initial adherence and biofilm formation. Infect Immun 75:924. https://doi.org/10.1128/IAI.00941-06
Van NK, Thi Do NT, Chandna A et al (2013) Antibiotic use and resistance in emerging economies: a situation analysis for Viet Nam. BMC Public Health 13:1–10. https://doi.org/10.1186/1471-2458-13-1158
Ventola CL (2015) The antibiotic resistance crisis: part 1: causes and threats. Pharm Ther 40:277
Water, sanitation and hygiene: an essential ally in a superbug age. https://www.who.int/southeastasia/news/opinion-editorials/detail/water-sanitation-and-hygiene-an-essential-ally-in-a-superbug-age. Accessed 30 Aug 2021
Weinstein RA (2001) Controlling antimicrobial resistance in hospitals: infection control and use of antibiotics. Emerg Infect Dis 7:188. https://doi.org/10.3201/EID0702.010206
White House Administration (2015) National action plan for combating antibiotic-resistant bacteria
WHO (2016a) WHO|WHO report finds systems to combat antibiotic resistance lacking. WHO
WHO (2016b) WHO. 2016. Fight Antimicrobial Resistance: protect mothers and newborns. https://www.who.int/drugresistance/activities/Women-Deliver-AMR-side-event-Handout-May2016.pdf?ua=1. Accessed 30 Aug 2021
WHO (2017a) GLASS|Global antimicrobial resistance surveillance system (GLASS) report 2016-17. World Health Organization
WHO (2017b) Antimicrobial resistance fact sheets on sustainable development goals: health targets
WHO (2017c) Fact sheets on sustainable development goals: health targets
World Health Organization (2012) Pharmaceuticals in drinking-water
World Health Organization (2014) Antimicrobial resistance: global report on surveillance. http://www.who.int/drugresistance/documents/surveillancereport/en/
World Health Organization (2015) Global action plan on antimicrobial resistance
Wright GD (2014) Something old, something new: revisiting natural products in antibiotic drug discovery. Can J Microbiol 60:147–154. https://doi.org/10.1139/CJM-2014-0063
Zaman SB, Hussain MA, Nye R et al (2017) A review on antibiotic resistance: alarm bells are ringing. Cureus. https://doi.org/10.7759/CUREUS.1403

Publisher's Note