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Chapter 2. Antimicrobial resistance: A frightening and complex public health challenge

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This chapter introduces the background and history of antimicrobial resistance (AMR) including its biological underpinnings. It offers a comprehensive look at the leading causes and consequences of AMR. It highlights the multi-sectorial aspects of resistance development and spread and describes antibiotic use and misuse across a range of sectors. The chapter then provides a framework for understanding how AMR develops and leads to infections and provides intervention targets aimed to disrupt this process. Finally, the chapter concludes by highlighting the need for multi-sectorial and multi-national solutions. This chapter provides the reader with the foundation for the following analytical chapters.

Key findings

- Antimicrobial resistance (AMR) is a large and growing problem with the potential for enormous health and economic consequences globally. Rising AMR threatens the achievement of several Sustainable Development Goals (SDGs) related to health and poverty reduction.
- The threat of AMR is heightened by the lack of new drugs. As resistance has grown in recent years, the antimicrobial research and development (R&D) pipeline has shrunk due to insufficient economic incentives.
- AMR arises principally through use of antimicrobials. As pathogens are exposed to drugs designed to treat them, they can develop defence mechanisms to resist their effects. High rates of inappropriate drug use may play a large role in drug exposure and AMR development.
- AMR is a multi-factorial and multi-sectorial problem necessitating multi-factorial solutions with the involvement of all the key stakeholders. The rise and spread of AMR occurs across human, animal, and environmental sectors, which must all be accounted for when developing prevention strategies.

2.1. Infectious disease in the 20th century: Rise of resistance

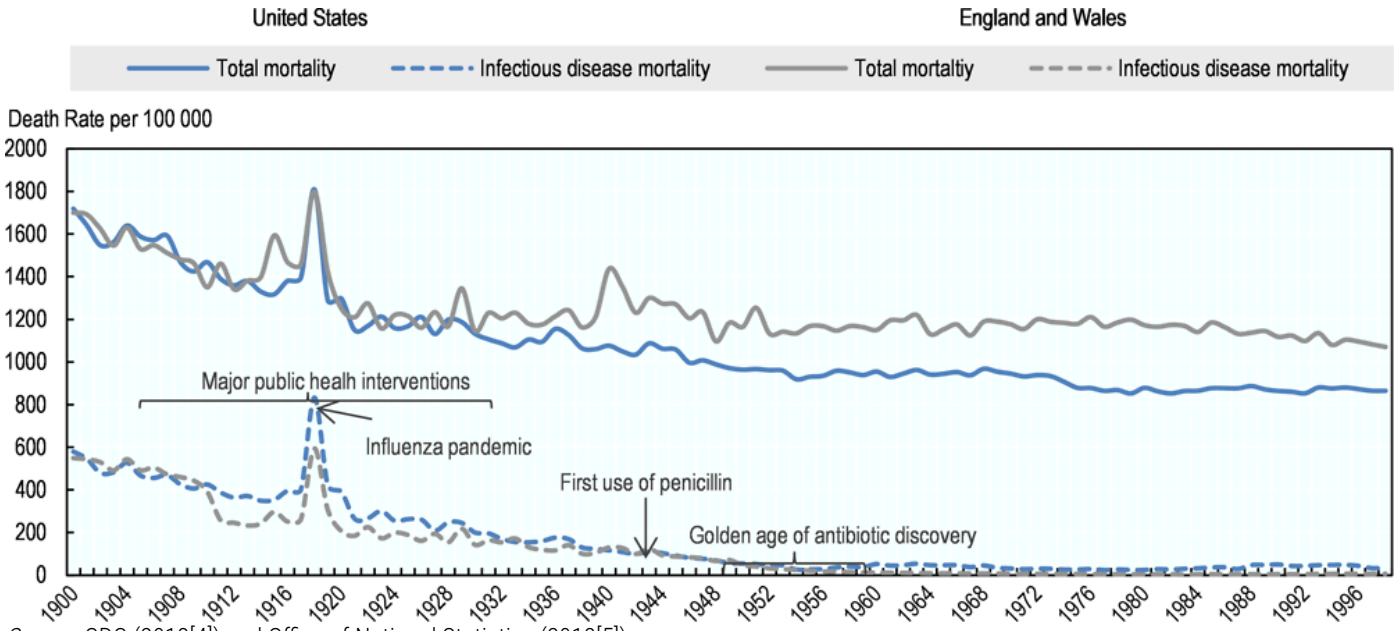
The 20th century was marked by tremendous improvements in life expectancy and health outcomes across Europe, North America and other developed countries. Driving these improvements were dramatic reductions in the burden of infectious disease. Contributing factors included public health advances such as water and waste management along with food regulation. This period also witnessed medical breakthroughs that lowered incidence rates and provided better treatment for infectious diseases such as tuberculosis and diarrhoea. Mortality due to infectious diseases in the United States fell from almost 600 deaths per 100 000 individuals per year in 1900 to 24 in 1980. In England and Wales deaths per 100 000 individuals dropped from approximately 550 to under 10 during the same period (see Figure 2.1).

Of all the medical discoveries in the 20th century, perhaps none was more important than that of antibiotics. These “miracle drugs” introduced as therapeutic agents in the 1940s allowed for effective management and treatment of long-feared diseases such as tuberculosis, bacterial pneumonia, and sepsis, leading to greatly improved survival and patient outcomes (Zaffiri, Gardner and Toledo-Pereyra, 2012[1]). With the help of penicillin, case fatality rates for bacterial pneumonia and bloodstream infections dropped from over 80% to under 20% between 1935 and 1952. Similar results were seen for other bacterial diseases (Austrian and Gold, 1964[2]).

The period following the Second World War was considered the golden age of antibiotic discovery and a number of important and widely used antibiotics were discovered (Davies and Davies, 2010[3]). The effectiveness of these drugs combined with their relatively few side effects and cheap costs quickly led to wide use and antibiotics became standard treatment for a number of common illnesses.

In recent years however, the potency of these drugs has started to wane with the development and spread of AMR. Pathogens that develop AMR may survive the effects of antimicrobials, including antibiotics, making subsequent infections difficult or even impossible to treat. The current rise of AMR and these hard to treat or untreatable infections threaten to turn back the clock on infectious disease gains and lead us toward a “post-antibiotic” world where minor infections can once again lead to death.

Figure 2.1. Total death rate vs. infectious disease death rate: United States, England and Wales



Source: CDC (2018[4]) and Office of National Statistics (2018[5]).

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2.2. What is antimicrobial resistance (AMR)?

AMR evolves naturally as a result of antimicrobial use and is an example of natural selection (see Section 2.4). Because of the selection pressure exerted by antimicrobials, pathogens may develop or acquire mechanisms allowing them to survive and reproduce in environments where antibiotics are present (see Box 2.3). Increasing pathogenic exposure to antimicrobials increases the chance that they become resistant. This means that the more antimicrobials are used, the less effective they become.

AMR is also a multi-sectoral or "one health" issue. The human, animal, and environmental health sectors influence the rates of AMR and resistant infections. This then necessitates a multi-sectorial response to AMR.

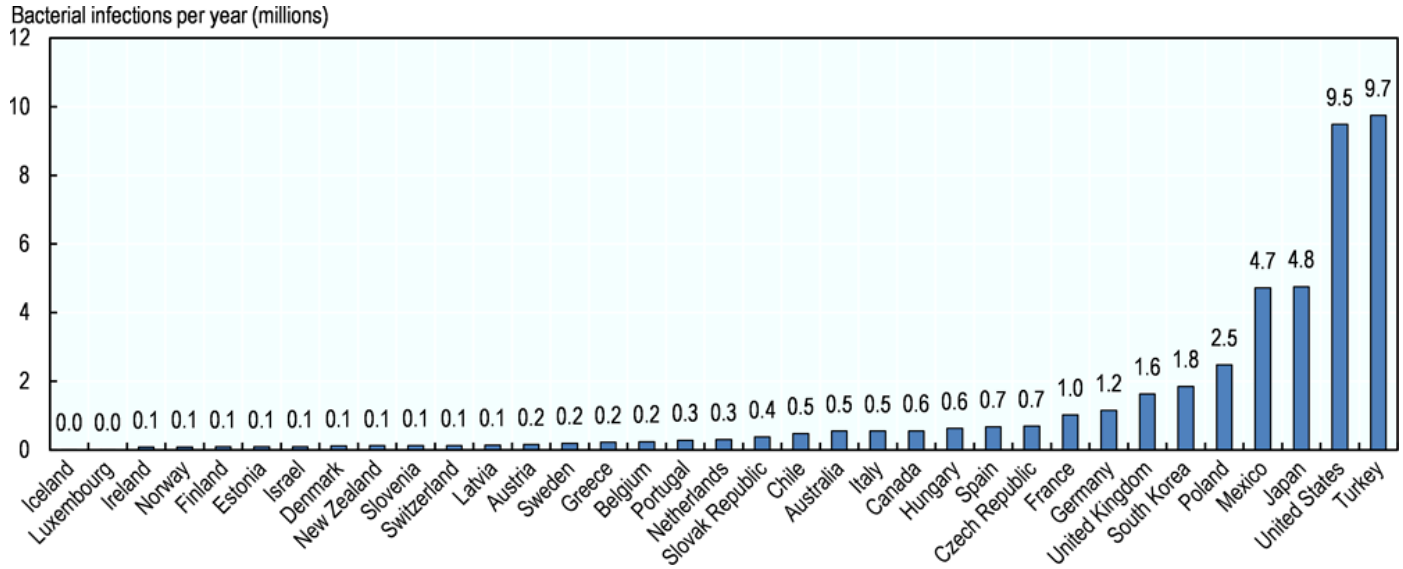
Finally, AMR is a "one world" issue. Resistant pathogens do not recognise national borders and can spread easily among populations, regions, and countries. Recent studies have shown that travel and tourism can lead to greater global spread of antibiotic resistance bacteria including powerful new forms of resistance (McNulty et al., 2018[6]) (Kumarasamy et al., 2010[7]). All countries, regardless of their economic situation or strength of their health system are vulnerable to rising resistance levels and risk devastating consequences in the absence of a global solution.

2.3. Why should we be worried about AMR?

AMR poses a particular threat to public health in OECD countries and globally due to four main causes.

First, bacterial infections are highly frequent. Figure 2.2 shows the number of yearly infections by country due to bacteria susceptible to becoming resistant to antibiotics. These numbers include a wide range of infection types and are a product of both the size of the population and the infection rate in each country. The total of these infections across all countries is just over 47 million per year with nearly 60% of these infections due to lower respiratory infections. Gonococcal infections (the cause of gonorrhoea) were another leading cause of bacterial infections making up over 20% of total infections.

Figure 2.2. Infections by microbes susceptible to the development of resistance in OECD countries



Note: The graph includes the following infections: gonococcal, chlamydial, lower respiratory, syphilis, tuberculosis, whooping cough, paratyphoid fever, typhoid fever, and meningitis.

Source: IHME (2018[8]).

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Second, resistant infections lead to considerable additional morbidity and mortality and previous estimates concluded that AMR may be responsible for 23 000 deaths in the United States and 25 000 deaths across Europe each year (CDC, 2018[9]) (European Commmission, 2018[10]). Recent data from Europe highlight growing rates of AMR including bacterial infections with resistance to carbapenems, an antibiotic used as a final treatment option for already highly resistant organisms (ECDC, 2017[11]). On a larger scale, rising AMR threatens progress toward global objectives such as the Sustainable Development Goals (SDGs), in particular those targeting child health, maternal health, and mortality (WHO, 2017[12]).

Third, the economic impact of AMR may also be devastating to local and global economies in coming years. Resistant infections are significantly more expensive for health systems, resulting in longer hospital stays, more intensive treatment and more expensive second line treatments.1 Second line treatment for tuberculosis for example may cost between 3 to 18 times more than first line treatments and on average a hospitalised patient infected with an antibiotic-resistant infection costs an additional USD 10 000 to USD 40 000 (Cecchini, Langer and Slawomirski, 2015[13]). AMR also results in lost productivity from death, longer periods of illness, and increased morbidity. In high-income countries productivity losses for resistant infections, including time away from work and informal care requirements are estimated at USD 38 000 per patient (Cecchini, Langer and Slawomirski, 2015[13]). In low and middle-income countries (LMICs) the cost of AMR may be even higher (See Box 2.1).

Box 2.1. The health and economic burden of AMR in LMICs

The burden of AMR may be much higher in LMICs than other countries given the high rates of infectious disease and the lack of access to quality medicines and care in some areas. (Gwatkin, Guillot and Heuveline, 1999[14]) (Newton et al., 2006[15]) Whereas in high-income countries the effects of resistance may include increased morbidity and economic costs, resistance in LMICs may translate directly into increased mortality (Okeke et al., 2005[16]). Mortality due to diseases such as lower respiratory infections, diarrhoea, and neonatal sepsis which could be easily managed through good health care and access to medicines accounted for an estimated 4.5 million deaths in LMICs in 2016 (IHME, 2018[8]).

LMICs are also particularly financially vulnerable to resistance. Rising resistance rates could lead to an additional 19 million individuals in LMICs falling into extreme poverty by 2030 due to the negative impacts on labour productivity and health care costs (Ahmed et al., 2017[17]). If solutions are not found, GDP losses in low-income countries due to the impacts of AMR may top 5% by 2050, 80% higher than the impact in high-income countries (World Bank, 2017[18]).

On a global scale, these costs, combined with AMR's impact on the agricultural sector and on international trade are projected to reduce the global economic output to between 1.1% and 3.8% by 2050. This will result in a large increase in extreme poverty worldwide and will threaten the achievement of the SDGs related to poverty, hunger, and inequality reduction (World Bank, 2017[18]).

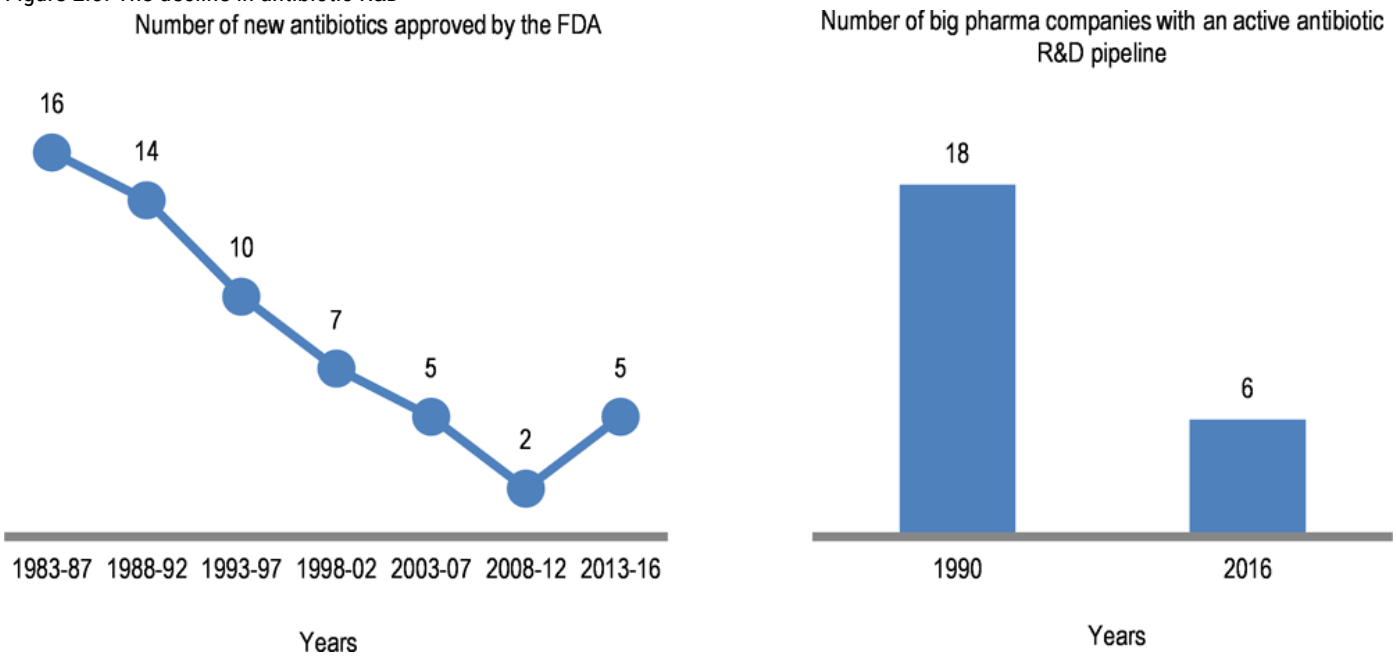
Finally, the impact of rising resistance levels on health outcomes has been exacerbated in recent years by the relative lack of new antibiotics available to treat these bacteria. In the past, development of resistance was quickly met with a steady stream of new anti-infective drugs. However, the antibiotic pipeline has dried up due to a lack of financial incentives to invest in antibiotic R&D (see Box 2.2).

Box 2.2. Lack of investment in antibiotic R&D

Unlike past eras where doctors could count on continued development of new antibiotics to combat bacterial resistance, scientific challenges and insufficient market incentives have slowed research and development in this area (see Figure 2.3). This issue was examined in depth in a 2017 paper authored by the OECD, WHO, FAO and OIE (2017[19]). The following is based on the results of this analysis.

New antibiotics have become increasingly difficult to discover and typically only 1.5% of antibiotics in preclinical development reach the market. Furthermore, clinical development of promising candidate molecules is expensive. This high cost of antibiotic R&D, the low chance of success, and low reimbursement prices on market entry have led to a number of actors in the pharmaceutical industry abandoning antibiotic research. Small and medium-sized enterprises where the majority of current antibiotic R&D now occurs typically lack the funds necessary to take early stage research through to clinical development. Some initiatives have been launched to stimulate R&D although current efforts are insufficient to guarantee a robust and sustainable pipeline. To respond to this need, in 2017, G20 leaders called for the creation of a global AMR R&D Hub, (G20, 2017[20]). Launched in 2018 and open to any interested countries or invited philanthropic foundations with a commitment to investing in AMR R&D, the Hub's purpose is to increase R&D investment through facilitating information exchange between existing funding streams, promoting alignment of funding to avoid overlaps, and mobilising additional resources for R&D investment. While solutions must be found to correct R&D market incentives in the short term, longer-term solutions (e.g. greater prevention of infectious diseases and the use of alternative treatments) may also be needed to ensure these antibiotics continue to work into the future.

Figure 2.3. The decline in antibiotic R&D



Source: OECD, WHO, FAO and OIE (2017[19]).

2.3.1. Antibiotics and the effects on the microbiota

Along with exerting selection pressure leading to resistance, antibiotics may have additional negative health consequences through the modification of the human microbiota (Langdon, Crook and Dantas, 2016[21]).

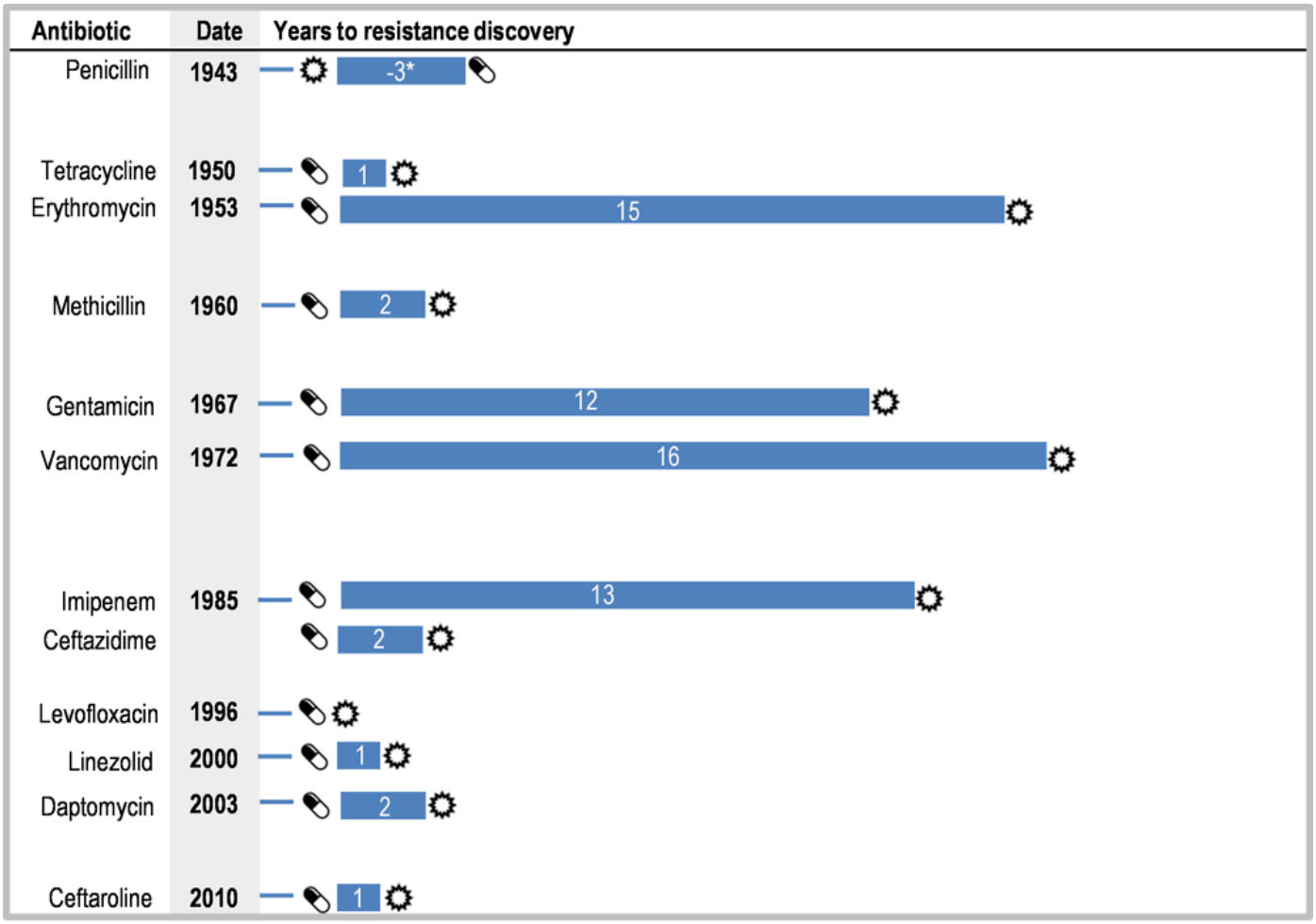
The human microbiota is the sum of all microorganisms that live in and on humans including importantly in the human gut. These naturally occurring microorganisms including bacteria are important for activities such as digestion, protection from pathogens and immune system development (Zhang et al., 2015[22]). Indeed, bacteria and humans have evolved together over centuries and humans cannot live or develop normally without the presence of bacteria (Young, 2017[23]).

Antibiotics taken regularly may disturb this delicate balance between man and bacteria. When oral antibiotics are taken to treat an infection they can disrupt naturally occurring bacterial populations and frequent use of antibiotics may lead to permanent changes in these bacterial populations (Francino, 2015[24]). Recent research has found that changes in the composition of the microbiota, particularly during young childhood, may increase the risk of development of a wide range of health problems including allergies, obesity, and even autism (Riiser, 2015[25]; Parekh, Balart and Johnson, 2015[26]; Strati et al., 2017[27]).

2.4. How did AMR originate?

Almost as soon as new antibiotics were discovered, bacteria capable of resisting their effects were identified (see Figure 2.4). Only one year after the discovery of tetracycline, a powerful broad-spectrum drug, resistant clinical isolates started to appear (Nelson and Levy, 2011[28]). Similarly, only two years after the discovery of methicillin, a drug designed to treat penicillin-resistant *Staphylococcus aureus*, were methicillin resistant strains discovered (Davies and Davies, 2010[3]). Famously, resistance to penicillin was discovered even before the introduction of this drug as a therapeutic agent (Davies and Davies, 2010[3]). The accumulation of these resistance mechanisms over the past 70 years has led to an increase in multi-drug resistant bacteria that are difficult to treat.

Figure 2.4. Timeline of antibiotic discovery and detection of antibiotic resistance



Source: Adapted from CDC (2013[29]), (Nelson and Levy, 2011[28]).

The rapid rise in resistance seen in recent years is not surprising given the fundamental and ancient role resistance plays in bacterial survival. Long before the discovery of antibiotics by humans, microorganisms have been using them to gain survival advantages over other competing organisms. Bacteria exposed to these antibiotics in nature have developed an extensive array of defense mechanisms including effective antibiotic resistance gene activation and exchange.

Bacterial antibiotic resistance is thus not a recent phenomenon and bacteria from as long ago as 30 000 years have been found to contain antibiotic resistant genes (D'Costa et al., 2011[30]) which helped them survive then as today.

Over time, this continuous struggle between microorganisms has resulted in a deep reservoir of antibiotic resistant genes known as the resistome that bacteria may access when necessary (Brown and Wright, 2016[31]).

Box 2.3. Antibiotic resistance: Acquisition and techniques

Bacteria can acquire antibiotic resistance through either spontaneous gene mutations or acquisition of resistance genes from other bacteria. This transfer of resistance genes is particularly effective in the dissemination of resistance and includes transfer of genes between different bacterial strains, species, or even genera. Mobile genetic elements shared between bacteria are capable of transmitting powerful multi-drug resistance genes such as extended spectrum beta-lactamases (ESBLs) or carbapenemases.

Antibiotic exposure increases the frequency of gene transfer increasing the likelihood of resistance spread. Even extremely low levels of antibiotics have been found to induce a stress response in bacteria provoking increased gene transfer (Andersson and Hughes, 2014[32]).

This selective pressure and gene transfer can occur in any situation where multiple bacteria are found in the presence of antibiotics. The human gut, home to an estimated 1 000 species of bacteria, is one such environment. Oral antibiotics, taken for one type of infection for example will affect all bacteria in the gut stimulating gene transfer and promoting resistance. Similar dynamics can be found in other types of environments such as water treatment plants, antibiotic contaminated soil, or any other area where large numbers of bacteria are exposed to antibiotics (Wachter, Joshi and Rimal, 1999[33]) (Xu and Gordon, 2003[34]). Limiting unnecessary exposure to antibiotics in these contexts is thus an important component in combatting rising resistance rates.

Resistance to antibiotics, whether acquired through gene mutation or gene transfer, is achieved through a number of diverse mechanisms. Some bacteria simply pump the antibiotic out of the cell wall before it reaches its target using efflux pumps. This technique can be effective against a range of antibiotics. Another resistance strategy involves modification of the antibiotic target. For example, some bacteria may alter

the proteins that penicillin target rendering this antibiotic ineffective. Common antibiotic targets and resistance mechanisms can be seen in Table 2.1.

Table 2.1. Antibiotic targets and resistance mechanisms

Resistance mechanism	Action	Effective against
Efflux pumps	Pumps antibiotic out of cell before it reaches target	Fluoroquinolones Aminoglycosides Tetracyclines Beta-lactams Macrolides
Immunity and Bypass	Antibiotics or antibiotic targets bound by proteins preventing antibiotic binding	Tetracyclines Trimethroprim Sulfonamides Vancomycin
Target modification	Antibiotic targets are modified to prevent antibiotic binding	Fluoroquinolones Rifamycins Vancomycin Penicillins Macrolides Aminoglycosides
Inactivating enzymes	Destroys antibiotic through catalysation	Beta-lactams Aminoglycosides Macrolides Rifamycins

Source: Adapted from Wright (2010[35]).

2.5. What are the priority pathogens?

The umbrella term AMR includes many different types of antimicrobial resistance. In principle, the list of antibiotic-bacterium combinations can be extensive, although the World Health Organization (WHO) recognises that the majority of the health burden is caused by a relatively limited number of organisms including: *Escherichia coli* (*E. coli*), *Klebsiella pneumoniae* (*K. pneumoniae*), *Staphylococcus aureus* (*S. aureus*), *Streptococcus pneumoniae (S. pneumoniae)*, *Salmonella, Shigella, Neisseria gonorrhoeae* (*N. gonorrhoeae*), *Mycobacterium tuberculosis* (*M. tuberculosis*) and *Plasmodium malariae* (*P. malariae*) (WHO, 2014[36]).

In 2017, WHO developed a list of priority pathogens in order to help focus efforts on reducing the impact of AMR at the global level (see Box 2.4). The WHO Pathogens Priority List Working Group and a group of experts used a multi-criteria decision analysis to categorise resistant bacteria into critical, high, and medium priority categories (Tacconelli et al., 2018[37]). These categories represent the relative threat level of each pathogen to human health. Efforts to reduce AMR should focus on the highest categories. Criteria for category inclusion included: mortality, health-care burden, community burden, prevalence of resistance, 10-year trend of resistance, transmissibility, preventability in the community setting, preventability in the health-care setting, treatability, and the treatment pipeline. Inclusion in each priority category was based on the total score from these variables with higher scores going into higher priority categories. *M. tuberculosis,* the bacteria responsible for tuberculosis and for which AMR is highly problematic was not included in the list of priority pathogens as WHO consider that this bacteria is already specifically targeted by other dedicated programmes.

The bacteria on the list of priority pathogens are responsible for a wide range of infections from skin to respiratory and bloodstream infections and include both those in hospital and outside. In order to avoid the worst effects of AMR, efforts to reduce resistance and to find new treatment solutions should focus on these priority pathogens.

Box 2.4. Priority pathogens

In 2017 WHO published a list of priority pathogens (Tacconelli et al., 2018[37]) for which urgent action is needed. This list divided pathogens into critical, high, and medium priority groups according to the threat level each poses to human health. Bacteria and specific antibiotic resistances, according to priority category, are:

Critical priority pathogens:

- *Acinetobacter baumannii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, carbapenem-resistant
- *Enterobacteriaceae*, carbapenem-resistant, third-generation cephalosporin-resistant

High priority pathogens:

- *Enterococcus faecium*, vancomycin-resistant
- *Staphylococcus aureus*, methicillin-resistant, vancomycin intermediate and resistant
- *Helicobacter pylori*, clarithromycin-resistant
- *Campylobacter spp.*, fluoroquinolone-resistant
- *Salmonella spp.*, fluoroquinolone-resistant
- *Neisseria gonorrhoeae*, third generation cephalosporin-resistant, fluoroquinolone-resistant

Medium priority pathogens:

- *Streptococcus pneumoniae*, penicillin-non-susceptible
- *Haemophilus influenzae*, ampicillin-resistant
- *Shigella spp.*, fluoroquinolone-resistant

The OECD analyses presented in the following chapters focus on a comprehensive set of bacteria, taking as starting point the two WHO lists mentioned above as well as other dimensions, including data availability. More specifically, the OECD analyses include:

- *Escherichia Coli*: a gram-negative commensal bacterium carried in the human gut and a common cause of infection including serious diarrhoea and urinary tract infections. *E. Coli* is also the leading cause of bloodstream infections in the community and the second leading cause of these infections in hospitals globally. Standard treatment for infection due to *E. Coli* includes third-generation cephalosporin antibiotics.
- *Klebsiella pneumoniae*, a common disease-causing pathogen also found in the human gut. *K. pneumoniae* can cause a wide range of infections from urinary tract and upper respiratory tract infections to sepsis and meningitis. It is also an important cause of hospital-acquired infections. Antibiotic treatment may depend on the infection site and local resistance profiles but can include third-generation cephalosporins, carbapenems, aminoglycosides, and quinolones.
- *Pseudomonas aeruginosa* (*P. aeruginosa*) can be found living in a wide variety of settings including natural environments such as on human skin or built environments including hospitals or on hospital equipment. This pathogen is naturally resistant to a number of antibiotics and is a major cause of nosocomial infections and infections among people with reduced immune function. Infections may include respiratory tract, urinary tract, or bloodstream infections. Treatment of infections with *P. aeruginosa* often relies on a combination of antibiotics including certain beta-lactams, aminoglycosides, carbapenems, and quinolone antibiotics.
- *Streptococcus pneumoniae* is often carried asymptomatically in the human respiratory tract or sinuses and is a leading cause of pneumonia and meningitis. Individuals with weakened immune systems including the elderly or young are particularly vulnerable to infection with *S. pneumoniae* which can also cause a range of localised and general invasive infections. Treatment guidelines may vary with infection site but beta-lactam antibiotics such as amoxicillin or cephalosporins are often recommended for treatment.
- *Staphylococcus Aureus* is commonly found on the skin or carried asymptomatically in the nares and is a frequent cause of skin, respiratory, and bloodstream infections. *S. Aureus* is also serious problem in hospitals including notably methicillin-resistance *S. Aureus* and is responsible for a large proportion of nosocomial infections. A number of treatment recommendations exist depending on local resistance profiles and may include penicillins, cephalosporins, or clindamycin.
- *Enterococcus faecium* (*E. faecium*) and *Enterococcus faecalis* (*E. faecalis*) are both commensal bacteria of the intestinal tract and important causes of nosocomial infections including sepsis and meningitis. Ampicillin or vancomycin is commonly used to treat enterococcal infections and rising vancomycin resistance among these bacteria make these infections hard to treat.

2.6. How do AMR bacteria spread and infect humans?

Human infection with resistant pathogens is the product of two separate but related phenomena: development of resistance and infection (see Figure 2.5).

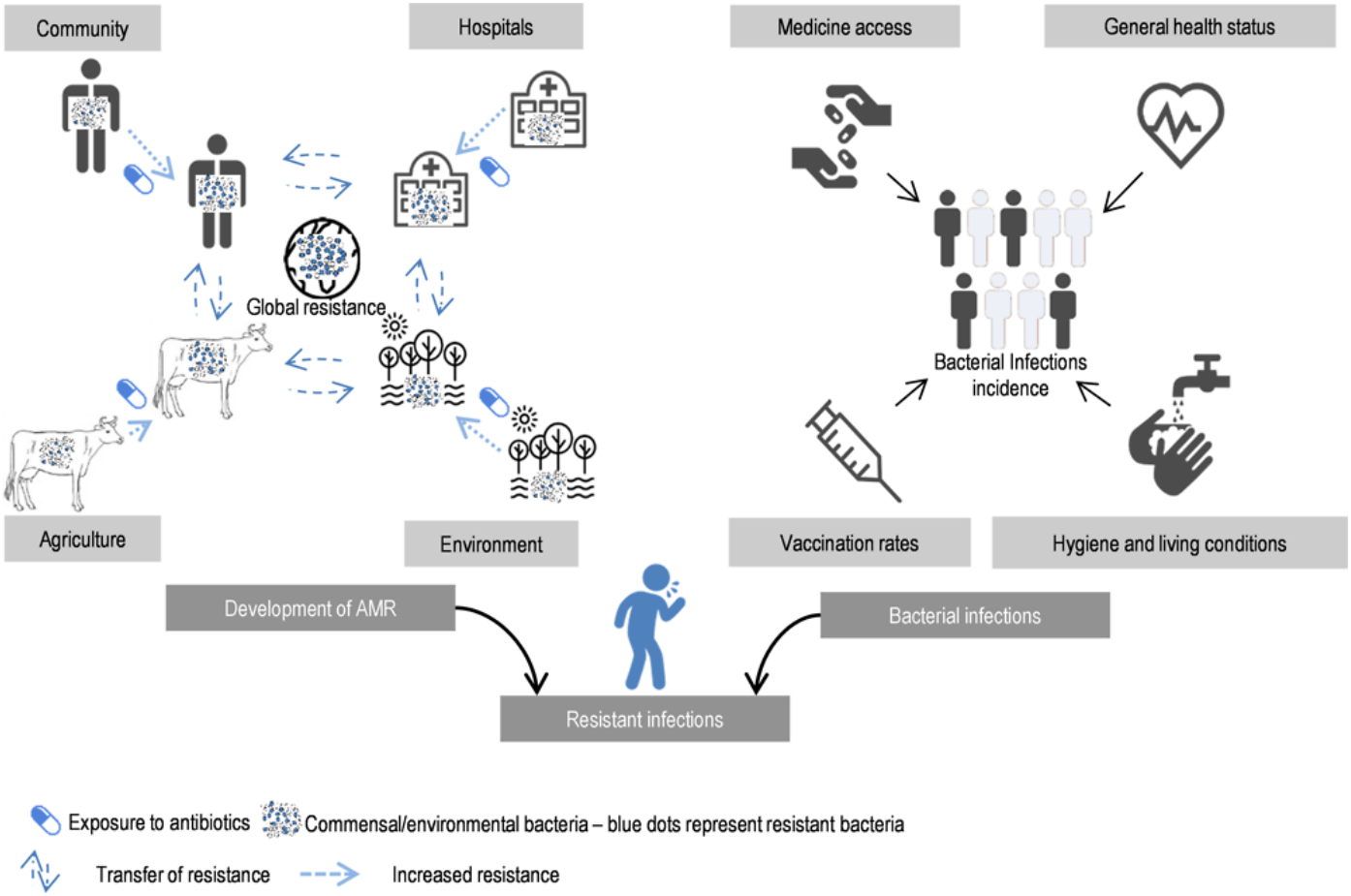
Antibiotic resistance among bacteria may develop and spread through exposure to antibiotics in a number of settings including among humans in the community or in hospital, in the animal sector, or in the natural environment. The combination of resistance across sectors creates a global population of resistant bacteria which may be transferred within and among sectors including to and from humans.

The second part of the resistance-infection equation is infection. Like resistance, a number of different factors influence infection including hygiene and living conditions, vaccination, the general health status of the population and access to medicines.

Interactions also exist between these two branches and the factors leading to resistance infections. Increased infection rates for example can lead to higher antibiotic use, which in turn may lead to more resistance and resistant infections. These resistant infections may also have variable effects on infection rates. Some studies have suggested that resistant and susceptible bacteria compete with each other and that resistant infections may replace susceptible infections (Popovich, Weinstein and Hota, 2008[38]). Others suggest that there is no competition between these bacteria and resistant infections simply add to the baseline number of susceptible infections (Mostofsky, Lipsitch and Regev-Yochay, 2011[39]).

The factors outlined in Figure 2.5 are further detailed below. Section 2.7 explains how each sector contributes to the development and spread of AMR, with a special emphasis on the misuse of antibiotics across sectors in Section 2.8. Section 2.9 discusses specific factors related to bacterial disease burden.

Figure 2.5. Factors influencing bacterial resistance, bacterial infections, and resistant infections



Source: Adapted from Chereau et al. (2017[40]).

2.7. How does each sector contribute to resistance development?

2.7.1. Animal sector

Use of antibiotics is particularly high among food animals and continues to grow worldwide. In the United States alone use in the animal sector represents an estimated 80% of all antibiotic use by weight (Spellberg et al., 2016[41]). Worldwide agricultural consumption is also predicted to increase by 70% by 2030 due to increases in demand for meat and changes in livestock production particularly in low and middle-income countries (Van Boeckel et al., 2015[42]). Furthermore, these estimates do not take into account antibiotic use in aquaculture where use may be high (Henriksson, Troell and Rico, 2015[43]).

Importantly, much of the antibiotic use in the agriculture sector is not for disease treatment but for disease prevention and growth promotion. This includes use of low-level doses of antibiotics in feed which presents a high risk for antibiotic resistance development (Van Boeckel et al., 2017[44]).

This high use has resulted in high rates of resistant bacteria detected in this sector including the emergence and spread of dangerous new forms of resistance such as colistin resistance or strains of methicillin-resistant *Staphylococcus aureus* (MRSA) (Price et al., 2012[45]).

2.7.2. Community

The largest source of antibiotic use and misuse in humans is in the outpatient or community sector (doctors, dentists, etc.). In the United States the majority (>60%) of antibiotic expenditure and consumption (80-90%) is associated with the outpatient setting (CDC, 2017[46]) with similar proportions reported in Europe (ECDC, 2017[11]). In 2014, there were nearly as many outpatient antibiotic prescriptions in the United States as people living in the country. In Europe, an average of 2.2 standard doses of antibiotics were consumed per 100 people per day in 2016 (ECDC, 2017[47]).

Certain sectors contribute heavily to high community antibiotic use such as long-term care where over half of nursing home residents use antibiotics each year (van Buul et al., 2012[48]). Dentistry is another important source of antibiotic consumption and can make up over 10% of community use in some countries (Marra et al., 2016[49]).

Like the animal sector, this heavy use of antibiotics in the community over recent years has led to a steady rise in the incidence of antibiotic resistance infections, including resistant tuberculosis as well as respiratory, skin, and sexually transmitted infections (CDC, 2013[29]).

2.7.3. Hospitals

Antibiotic resistance has historically been a hospital problem because these environments create a perfect storm for resistance development and infection by combining high antibiotic use with high infection rates. CDC data for 2016 showed that over half of US hospital inpatients received at least one antibiotic during their hospital stay (CDC, 2017[46]). Across Europe antibiotic use in hospitals made up nearly 10% of total human antibiotic use (ECDC, 2017[11]) despite the relatively small proportion of the population hospitalised.

Resistant infections are particularly common and problematic in hospitals due to the additional risk factors for infection among inpatients. Surgery patients or those using medical devices such as catheters, intravenous devices, or respirators are at heightened risk of infection as bacteria may infect surgical wounds or use medical devices as a vehicle for infection. Use of antibiotics is in itself a risk factor for resistant infection as it may increase the number of resistant bacteria in and around the patient while eliminating potentially protective susceptible bacteria.

Between 2008 and 2014, one in six central line-associated bloodstream infections in US hospitals were caused by dangerous resistant bacteria, as were one in seven surgical site infections. One in ten catheter-associated urinary tract infections were due to these bacteria during a similar period (CDC, 2016[50]).

2.7.4. Natural environment

While the role of human antibiotic use in resistance has been widely studied and described, the role played by the environment may be just as important. Antibiotics used in the community, hospitals, or the agricultural sector may end up in the environment through sewage water, farming activities including use of manures, or waste water from hospitals or antibiotic manufacturers (Amador et al., 2015[51]). Along with antibiotics used in terrestrial farming, those used in aquaculture may also pollute the environment and studies show a large proportion of these antibiotics end up in sediment (Henriksson, Troell and Rico, 2015[43]).

Once in the environment, the continued antimicrobial activity of these drugs may affect local microbial communities and favour resistance development and spread. Indeed, the majority of antibiotics consumed by humans or animals are excreted unmetabolised and some antibiotics such as fluoroquinolones may remain active for months in the environment (UNEP, 2017[52]).

Evidence of high rates of resistant bacteria in the environment due to antibiotic contamination has been reported and Li et al. (2015[53]) found up to three times as many antibiotic resistant genes among bacteria in natural environments affected by human activity versus those which were relatively unaffected.

2.7.5. Spread between sectors

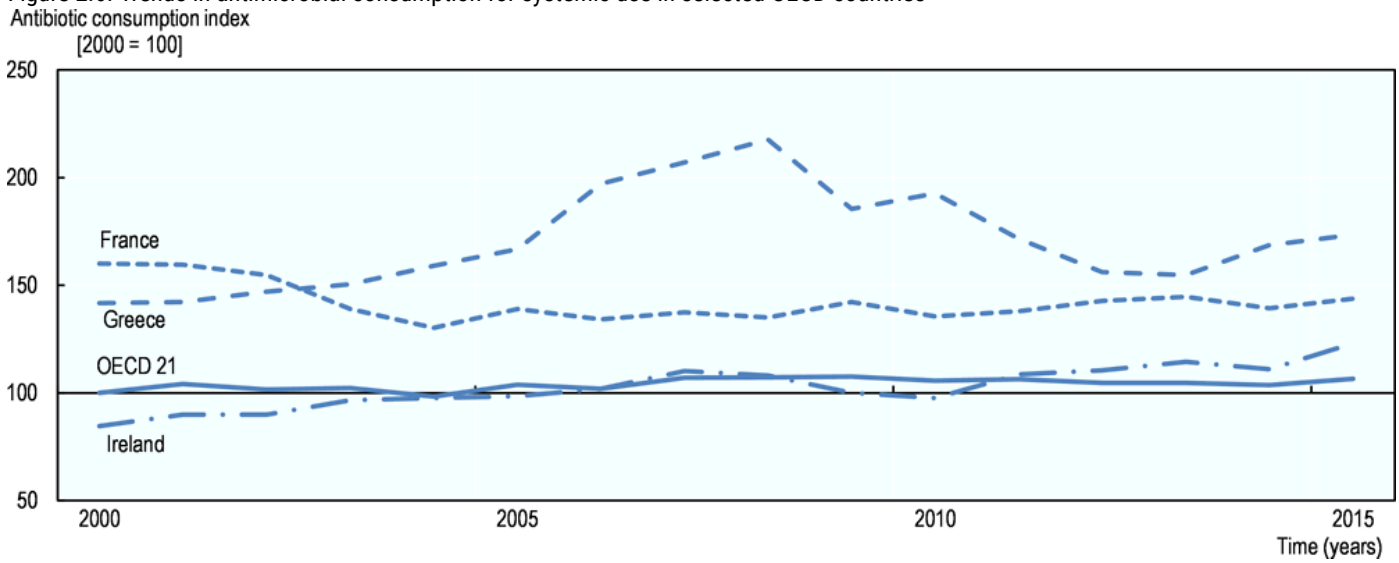
Resistance, once developed, can easily spread to other sectors. For example, MRSA, a dangerous resistant bacteria which first developed in the hospital sector, has spread outside of that environment in recent years and is now responsible for a rising proportion of community acquired infections (Salmenlinna, Lyytikäinen and Vuopio-Varkila, 2002[54]). The animal sector is also an important development and transmission point for resistance. High levels of antimicrobial use and resistance in animals has been linked to human disease both through natural environmental contamination and direct contact with animals or animal products such as meat or meat products (Nadimpalli et al., 2018[55]). A study by Fjalstat and colleagues found that the abundance of antibiotic resistance genes in the human gut is correlated with consumption of antibiotics in animals (Fjalstad et al., 2018[56]).

2.8. Use and misuse of antibiotics

2.8.1. High antibiotic use across OECD countries

The major factor contributing to increased resistance across sectors is antibiotic use. Across OECD countries, antibiotic use among humans has increased significantly since 1980. Most of this increase occurred from 1980 to 1995 with rates remaining relatively stable in the following years (OECD, WHO, FAO, OIE, 2017[19]). Figure 2.6 shows the trends in antibiotics for systemic use in OECD countries since 2000. On average 22.15 defined daily doses (DDD) were consumed per 1 000 inhabitants in 2015 across OECD countries. A number of countries such as France and Greece showed consistently higher consumption rates while others such as Ireland have seen growing rates over this period. Notably, consumption rates show no significant reduction during this period despite rising resistance and calls to action.

Figure 2.6. Trends in antimicrobial consumption for systemic use in selected OECD countries



Note: Data were normalised to average antimicrobial consumption in OECD 21 in 2000 (equal to 100). Data for missing years were estimated by linear interpolation. OECD 23 includes: Australia, Belgium, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Luxembourg, Netherlands, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, and the United Kingdom

Source: Analyses of OECD Health Statistics (2018), http://dx.doi.org/10.1787/health-data-en.

StatLink http://dx.doi.org/10.1787/888933854687

2.8.2. Antibiotic misuse

Along with high use of antibiotics, there is also significant overuse and misuse in OECD countries. An estimated 50% of antibiotics prescribed by general practitioners in OECD countries are used inappropriately including situations where antibiotics were not needed or the wrong antibiotic was prescribed (OECD, 2017[57]; Paget et al., 2017[58]).

In hospitals, roughly one-third of antibiotics used may be unnecessary (CDC, 2017[46]). Hospitals also use and misuse higher proportions of last-line antibiotics which can favour the development of powerful forms of resistance including to carbapenem and polymixin antibiotics.

2.8.3. Factors related to misuse

Many factors underpin the high levels of inappropriate use of antimicrobials in the human sector including those related to doctors, patients, health care organisations, and producers and vendors of antimicrobials.

Prescriber factors

Prescribers face various pressures leading to inappropriate prescription of antimicrobials including previous practice inertia, fear of treatment failure, perceived pressure from patients and a lack of time.

Many doctors prescribe antibiotics out of habit and studies show that doctors who prescribe the most antibiotics tend to be those longest out of university or those having spent the longest time in the same practice (Mainous III, Hueston and Love, 1998[59]) (Steinke et al., 2000[60]).

Doctors may also prescribe antibiotics out of fear of treatment failure and the possibility of a secondary bacterial infection. This may be particularly likely in patients with comorbidities such as old age and chronic disease (Vazquez-Lago et al., 2012[61]).

Some antibiotic misuse results from real or perceived patient expectations. A 2015 study showed that 55% of participating general practitioners in Britain felt pressure to prescribe antimicrobials and 45% admitted to prescribing an antimicrobial, even when they knew it would be ineffective, in response to patient pressure (Cole, 2014[62]).

Issues such as time limitations, patient health coverage, and organisation actions to control AMR are also drivers of inappropriate prescribing (Cabana et al., 1999[63]) (Teixeira Rodrigues et al., 2013[64]).

Patient factors

A number of patient factors may also lead to higher misuse of antibiotics including those related to an inadequate knowledge of AMR.

Many patients use antibiotics without a prescription, often leading to unnecessary and/or incorrect use. This usage represented between 3% and 44% of antibiotic use across a sample of OECD countries in a systematic review. (Morgan et al., 2011[65]). Countries in Southern and Eastern Europe as well as Mexico showed higher rates of non-prescription use. Sources of these non-prescription antibiotics include pharmacies, unfinished courses, or friends and family. This type of consumption is particularly frequent in LMICs (See Box 2.5).

Poor adherence to antimicrobial prescriptions by patients is another cause of inappropriate use if a patient does not follow guidelines on dose or duration. Up to 44% of patients in the United States may skip antibiotic doses (Edgar, Boyd and Palame, 2008[66]). Patients may also seek additional care including antimicrobial treatment if symptoms do not disappear immediately after beginning antimicrobial treatment. A study in Japan showed that 7.5% of antimicrobial prescriptions were given for a condition for which the patient had already received a prescription from another provider (Takahashi et al., 2016[67]).

Health care organisation factors

The organisation of health care also plays a role in inappropriate antimicrobial prescribing. For example, a prescription may be an easy solution for doctors when time or diagnostic resources are lacking. Insurance that does not reimburse diagnostic testing can affect the willingness to use these services and favour inappropriate prescribing.

Reimbursement systems also influence prescribing patterns by affecting the cost/benefit of a re-examination of the same patient. Doctors working with a fixed budget may be more likely to prescribe an antimicrobial to lower the risk of seeing the same patient again within a short time (Kaier, Frank and Meyer, 2011[68]). Under some payment systems, patients are incentivised to change physicians if one doctor does not provide the antimicrobial therapy they would like.

Policies regulating the separation of drug prescription and sales can also affect inappropriate prescribing. In some countries, and particularly in LMICs, doctors may be the ones selling drugs to patients giving them an economic incentive for overprescribing.

Industry factors

Lastly, the pharmaceutical industry can contribute to inappropriate antimicrobial use. Efforts to promote drug use including antimicrobials among both patients and doctors increase the likelihood that these drugs will be prescribed regardless of need (Wazana, 2000[69]).

Drug producers and vendors also play a role. Sales of antibiotics without a prescription make up an estimated 2% to 8% of total sales among European countries (Safrany and Monnet, 2012[70]) and counterfeit antimicrobials which are often of poor quality, make up 5% of the global market (Delepierre, Gayot and Carpentier, 2012[71]).

Box 2.5. Drivers of inappropriate antibiotic use in LMICs

Antibiotic misuse may be highly prevalent in LMICs due to the high infectious disease burden, the availability of non-prescription drugs, and lack of healthcare access in some regions. The topic of non-prescription antibiotic use is particularly important as it may represent up to 100% of antibiotic use among certain populations in LMICs as is correlated with a number of factors related to inappropriate use such as unnecessary consumption, inappropriate dosage and duration, and inappropriate molecule choice. (Morgan et al., 2011[65]).

Non-prescription antibiotic use is also associated with poor quality or counterfeit drugs which are common in LMICs and an estimated 60% of antimicrobials used in Africa and Asia contain little or no active ingredients (World Bank, 2017[18]).

2.9. Other public health factors that influence infection rates and AMR

A number of factors related to infection rates among humans include vaccination coverage, hygiene, access to medicines, and general health status.

2.9.1. Vaccination coverage

Vaccination coverage is one important factor in determining infection rates and may provide an important tool in reducing antibiotic resistance. (Rappuoli, Bloom and Black, 2017[72]). Vaccines target both bacterial and viral infections and have proven to be extremely successful in preventing or even eliminating infectious diseases such as smallpox, measles, and polio. Today vaccination is no less important in preventing the re-emergence of these diseases.

Across OECD countries, vaccines are used widely to effectively prevent bacterial diseases susceptible to the development of AMR including those from *Corynebacterium diphtheriae* (diphtheria), *Haemophilus influenzae* type B, *Neisseria meningitides*, *S. pneumoniae*, *Bordetella pertussis* (whooping cough), and *M. tuberculosis* (tuberculosis). Various vaccination strategies exist across OECD countries in terms of coverage and population. A number of countries ensure vaccination coverage through mandating vaccination for school attendance. Other countries such as Australia and Israel have tied family assistance payments or child tax credits to compliance with vaccination schedules to encourage coverage.

Because vaccination prevents rather than treats disease, it could automatically reduce the number of resistant infections by reducing overall infection numbers. This reduction would reduce the need for antibiotics to treat these infections having a positive effect on AMR. A review of the impact of the conjugate pneumococcal vaccine in 2008 showed not only reductions in overall disease burden but also in antibiotic use and resistant infections among vaccinated groups (Dagan and Klugman, 2008[73]). Unlike antibiotics, and despite the absence of any vaccine for priority pathogens, the vaccine pipeline continues to produce effective and important new products. Research is ongoing for development of vaccines for a number of important bacteria such as *E. coli, K. pneumoniae, S. aureus, Salmonella, P. aeruginosa*, and *A. baumannii* (Huttner et al., 2017[74]; Lee et al., 2015[75]; Giersing et al., 2016[76]; Erova et al., 2016[77]; Yang et al., 2017[78]; Ni et al., 2017[79]).

2.9.2. Hygiene

Hygiene is another major factor in the spread of infectious disease including those with AMR. In hospitals, hygiene includes infection prevention and control practices such as hand-washing practices, sterilisation of instruments and the cleaning of rooms, corridors, and other common spaces. Poor hygiene can result in greater rates of hospital-acquired infections (McLaws, 2015[80]). Poor hygiene also favours the spread of resistant pathogens from one patient to another within the hospital resulting in hospital outbreaks (Rampling et al., 2001[81]). Hygiene campaigns in hospitals have been shown to be effective in reducing infections and a study by Kirkland et al. (2012[82]) found that a hand hygiene initiative in a US hospital reduced infection rates by over 30%.

In the community, hygiene on an individual level should include good hand washing and food handling practices, avoiding putting individuals in contact with infectious (including resistant) pathogens (Landers et al., 2012[83]). On a population level poor hygiene can be linked to a lack of sufficient public health and sanitation infrastructure such as water treatment, urban planning, and food treatment and inspection, resulting in a much greater exposure of the population to infectious pathogens (WHO, 2001[84]).

2.9.3. Access to medicines

While many countries are working to restrict antimicrobial use to avoid resistance, insufficient access to medicines including antimicrobials may be a large driver of infectious disease burden in others. Restricted access to health care in some LMICs can lead to an increased burden of infectious disease. Normally treatable infections, including lower respiratory infections, diarrhoea and neonatal sepsis, account for an estimated 12% of deaths in LMICs (IHME, 2018[8]). Ensuring timely access to antibiotics would avert an estimated 445 000 pneumonia deaths alone in children living in low and middle-income countries (Laxminarayan et al., 2016[85]). In order to maximise the benefit of life-saving antimicrobials globally counties must not only work to reduce unnecessary use but also expand access when needed.

2.9.4. General health status

The general health status of a person or an entire population can influence the susceptibility to infectious diseases. Immunocompromised, elderly, or otherwise sick individuals run a much greater risk of contracting infectious diseases (Rubin, 1993[86]). As discussed in Section 2.7.3, many of these individuals also spend time in hospital and under antibiotic treatment thus increasing the chances of developing an antibiotic resistant infection (WHO, 2017[87]).

Factors such as malnourishment, a high burden of HIV, or malaria found in some populations in LMICs, put these populations at particular risk for infectious diseases (Katona and Katona-Apte, 2008[88]). Investing in measures for greater overall population level health such as increased health care access is an important strategy in lowering the infectious disease burden.

2.10. How can promoting prudent use of antimicrobials decrease AMR?

A number of existing strategies to reduce the burden of AMR focus on reducing the use of antimicrobials. These may include public health campaigns, doctor training, or the use of delayed prescriptions. These strategies rely on both a decrease in the “upward” selection pressure toward higher resistance, and an increase in the “downward” selection pressure toward less resistance through the relative bacterial fitness of resistant and susceptible bacteria to be effective.

2.10.1. Reducing “upward” resistance selection

AMR develops through a system of natural selection where bacteria or other organisms adapt to their environment through resistance development in response to the selection pressure exerted by the presence of antimicrobials (see Section 2.2). The presence of antibiotics pushes resistance rates “upward” by killing susceptible bacteria and providing an environment available only to resistant bacteria. Antibiotics also promote gene transfer including resistant genes to increase resistance rates (see Box 2.3). Continued presence of antibiotics in an environment will put continued pressure on bacteria pushing them toward greater and greater resistance levels (Baym et al., 2016[89]). Removal or reduction of antibiotics will thus remove or reduce this upward pressure and slow or stop increasing resistance.

2.10.2. Increase “downward” selection for susceptibility

While removing antibiotics may stop resistance rates from increasing, a second mechanism is needed for rates to decrease. Removing antibiotics may also allow for a “downward” pressure on resistance through the replacement of resistant bacteria by susceptible bacteria which may be better adapted to environments where antibiotics are not present (Andersson and Hughes, 2011[90]).

This downward pressure through replacement is created by differences in bacterial "fitness", which is the ability to replicate in a given environment. Bacteria with a greater fitness thus have a survival advantage over less fit bacteria. By acquiring resistance mechanisms, some bacteria may pay a "fitness cost" which can make them less able to replicate in environments without antibiotics (Melnyk, Wong and Kassen, 2015[91]). By removing antibiotics, these less fit resistant bacteria could theoretically be replaced with the more fit non-resistant bacteria over time reducing resistance levels.

This is an attractive idea and a key to strategies aiming to reduce antibiotic resistance through reduction in antibiotic use. Indeed, a number of interventions based on reduction of antibiotic use have reported lower resistance rates which may support the effectiveness of these interventions and the theory (Guillemot et al., 2005[92]) (Baur et al., 2017[93]). However, the reality of fitness is more complicated.

Along with the wide range of resistance mechanisms is a wide range of potential fitness costs. While some resistance mechanisms come with a clear fitness cost, others seem to incur no observable cost, meaning that these resistant bacteria are just as capable of reproducing in environments with no antibiotics as susceptible bacteria. For bacteria with "cost free" resistance, simply removing antibiotics will not reduce the underlying levels of resistance (Melnyk, Wong and Kassen, 2015[91]).

While fitness may not be able to reduce underlying resistance levels this does not mean that strategies to reduce antibiotic use should not be pursued. Regardless of the relative downward pressure induced by fitness costs, a reduction in antibiotic use will reduce the upward pressure for development of new resistance mechanisms, the transfer of resistance genes, and the growth of resistant bacteria in the absence of competing susceptible bacteria.

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Note

← 1. Lines of treatment correspond to the order of recommended treatment options for a given illness. First-line treatment is the first recommended treatment option. Second-line treatment is generally recommended only if a first-line treatment is insufficient.

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