Chapter 1. Antimicrobial resistance: A large and growing problem

Michele Cecchini and Driss Ait Ouakrim

Antimicrobial resistance (AMR) is a large and growing problem with the potential for enormous health and economic consequences, globally. As such, AMR has become a central issue at the top of the public health agenda of OECD countries and beyond. This chapter brings together the main messages of this publication and describes the key policy implications from new OECD analyses on the health and economic burden of AMR and on innovative actions to fight this top public health issue. The chapter presents AMR trends and projections in 52 OECD, Group of Twenty (G20) and European Union (EU) countries and makes a strong economic case to upscale investments in policies to promote prudent use of antibiotics in the human health sector and in policies to prevent the spread of infections. The chapter concludes by presenting the expected effectiveness, impact on healthcare expenditure and cost-effectiveness of such policies in 33 OECD and EU countries.

Key findings

- Despite being a natural phenomenon, antimicrobial resistance (AMR) became a prominent public health issue only in recent times, when an increasing share of infections proved to be resistant to available therapeutic options and the number of new antimicrobials reaching the market dropped significantly.
- AMR may develop and spread through exposure to antimicrobials in a number of settings including the human population in a community setting or in hospital, the animal sector or in the environment. The causes of the current growth in AMR rates are largely driven by human activity.
- In 2017, around 17% of bacterial infections in OECD countries were resistant to antibiotics; but in some countries, more than one-third of infections are resistant. In some Group of Twenty (G20) countries, more than 40% of infections are resistant to some antibiotics.
- If no effective public health actions are put in place, AMR rates are forecasted to grow further. The most worrying trend is that resistance to second and third-line antibiotics is forecast to grow the most, with AMR rates in 2030 projected to be 70% higher than in 2005.
- Around 2.4 million individuals could die in Europe, North America and Australia between 2015 and 2050 due to AMR; AMR would cost about USD PPP 3.5 billion per year to the healthcare services of this group of countries.
- Countries can put in place effective and cost-effective interventions to tackle AMR. Policies to promote hand washing, to enhance hygiene in healthcare facilities and stewardship programmes in healthcare facilities could avert between 34 931 and 37 836 deaths per year across the 33 countries included in the analysis. Other interventions such as mass media campaigns, delayed prescriptions and use of rapid diagnostic tests produce a positive, but more limited, health impact.
- Implementation costs for public health actions to tackle AMR vary between as little as USD PPP 0.3 per capita for mass media campaigns to a few hundred USD PPP per individual in the case of enhanced hygiene in healthcare services. Consistently across countries, all the assessed interventions show excellent cost-effectiveness ratios. Delayed prescriptions, improved hand hygiene and, often, stewardship programmes are cost saving.
- Based on their high effectiveness on population health, affordability to implement and excellent cost-effectiveness ratio, virtually all the assessed interventions can be defined as “best buys” to tackle AMR in the assessed countries.

1.1. Antimicrobial resistance: a growing threat to modern medicine

No innovation in the 20th century was more important to medicine than the discovery of antimicrobials. 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 and led to greatly improved survival and patient health outcomes.

However, today these health gains are at risk due to the development and spread of antimicrobial resistance (AMR). Pathogens which develop resistance may survive the effects of antimicrobials[1] making subsequent infections difficult or even impossible to treat and dramatically increasing the risk of developing complications and dying. The current rise of AMR and these very hard to treat infections threatens 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 fatal outcomes.

Further, once a bacterial strain develops resistance to an antimicrobial, this ability to resist antibiotics spreads rapidly. Fuelled by increasing mobility and globalisation, resistant infections can travel far and very quickly (Hawkey, 2008[1]). For instance, a carbapenem-resistant strain of *Klebsiella pneumoniae* (*K. pneumoniae*) needed only five years to spread globally from the United States, where it was first identified in 2003, to Israel in 2005 and to the United Kingdom, Italy and Colombia, in 2008 (McKenna, 2013[2]).

Despite being a process hundreds of times older than the humankind, AMR became a prominent public health issue only very recently. Overuse and inappropriate use of antimicrobials in humans (Cecchini and Lee, 2017[3]) and in the agricultural sector (FAO, 2016[4]) are key drivers underlying the growth of AMR. While, in the past, new antimicrobials were continuously made available to replace those becoming ineffective, now antimicrobials are progressively becoming more difficult to develop – only 1.5% of antibiotics in preclinical development reach the market (OECD et al., 2017[5]) – and the number of therapeutic options to treat common infections is significantly decreasing. Furthermore, clinical development of promising candidates is becoming more expensive and the business case and limited return on investment lead to declining private investment in AMR-relevant research and development (R&D) activities. This has led many pharmaceutical companies to abandon this business and, consequently, the number of new antimicrobials entering the market has decreased significantly (OECD et al., 2017[5]).

By using advanced statistical techniques, the OECD has analysed patterns and historical trends for eight key antibiotic-bacterium combinations and has projected historical trends up to 2030. Findings from these analyses are presented in the reminder of Section 1.1.

1.1.1. Almost one in five infections is caused by bacteria resistant to specific antibiotics in OECD and European Union (EU) countries and resistance proportions are expected to grow further if no effective action is put in place

The umbrella term AMR includes many different types of antimicrobial resistance. In principle, the list of antibiotic-bacterium combinations can be extremely 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)*, *Nontyphoidal Salmonella*, *Shigella*, *Neisseria gonorrhoeae*, *Mycobacterium tuberculosis* and *Plasmodium malariae* (WHO, 2014[6])[2]. More recently, WHO complemented this list of microorganisms with a list of 12 antibiotic-bacterium combinations for which there is an urgent need to produce new antimicrobials due to the high AMR rates and limited new therapeutic options in the R&D pipeline (WHO, 2017[7]).

Cross-country comparability of AMR data is difficult, due to the varying use of multiple drugs, standards, guidelines, methods and equipment in different parts of the world. However, the development of guidelines, as well as the establishment of international surveillance networks, such as EARS-Net (the European Antimicrobial Resistance

Surveillance Network), CEASAR (Central Asian and Eastern European Surveillance of Antimicrobial Resistance), GLASS (Global Antimicrobial Resistance Surveillance System) and ATLASS (Assessment Tool for Laboratory and Antimicrobial Surveillance Systems) have facilitated the collection and aggregation of international data on AMR.

The OECD used advanced statistical techniques to analyse and forecast data on AMR for eight high-priority antibiotic-bacterium combinations[3] for 52 countries. Results point to high resistance proportions across the globe:

- Between 2005 and 2015, estimated resistance proportions for eight high-priority antibiotic-bacterium combinations increased from 14% in 2005 to 17% in 2015 across OECD countries. The average resistance proportions in the countries with the highest resistance proportions (about 35% in Turkey, Korea and Greece) were five times higher than in countries with the lowest proportions (around 5% in Iceland, Netherlands and Norway). For some antibiotic-bacterium combinations, in certain OECD countries, only one in every four infections was caused by bacteria susceptible (i.e. not resistant) to drug treatment.
- Outside OECD countries, resistance proportions in 2015 were estimated at 29% across the same eight antibiotic-bacterium combinations, but could be in excess of 42% in India, the People's Republic of China and the Russian Federation. For some country-antibiotic-bacterium combinations, only 20% of infections were caused by bacteria susceptible to drug treatment.
- Within the EU, the average resistance proportion was 18% with countries in Eastern and Southern Europe generally showing higher resistance proportions, compared to countries in Northern and Western Europe.
- Members of the G20 averaged higher resistance proportions of 30%, while key partners of the OECD[4] had the highest estimated average resistance proportions, at 41%.

According to the OECD analyses, between 2005 and 2015, only seven countries were estimated to have achieved reductions in average resistance proportions. In Switzerland, the United Kingdom, Japan, Belgium, Germany, Iceland and Canada, resistance proportions went down by an average of 2.5 percentage points, across the eight antibiotic-bacterium combinations. However, not a single country, including those just mentioned, achieved reductions in all eight antibiotic-bacterium combinations. In contrast, in eight countries (Brazil, China, Peru, Argentina, Colombia, Saudi Arabia, Israel and the Russian Federation) resistance proportions are estimated to have increased for all eight antibiotic-bacterium pairs between 2005 and 2015. In Italy and the Slovak Republic, average resistance proportions went up by 13 percentage points.

A large majority of countries have seen both increases and reductions in drug resistance, depending on the microorganism and antimicrobial agent being considered. In France, for example, the proportion of *K. pneumoniae* resistant to third-generation cephalosporins increased by an estimated 27 percentage points (from 5% to 32%, a growth rate of 540%) while the proportion of *S. pneumoniae* resistant to penicillin went down by 13 percentage points over the same ten years (from 36% to 23%, a growth rate of -36%).

Taking resistance proportions in 2005 as the base value and averaging country-specific growth rates, resistance proportions for methicillin-resistant *S. aureus* (MRSA) went down by an estimated 17% across OECD countries, while the share of *E. coli* resistant to third-generation cephalosporins grew by an estimated 222%. On average across all eight antibiotic-bacterium combinations, growth rates varied between 140% (in Italy and the United States) and -10% (in Belgium). In non-OECD countries, the range was even bigger, indicating significant heterogeneity in the evolution of resistance proportions across countries, microorganisms and antimicrobial agents between 2005 and 2015.

1.1.2. AMR is projected to keep growing at least until 2030, with resistance to second and third-line antibiotics expected to grow the most

The projections produced with the OECD model suggest that, should antibiotic consumption, economic and population growth, and out-of-pocket health spending evolve along the trends observed in the past, and should no policy action be taken, resistance proportions for eight antibiotic-bacterium combinations are estimated to increase moderately from 17% in 2015 to 18% in 2030 across OECD countries. Despite reductions in average resistance proportions in some countries, no single country is projected to reduce resistance proportions for all eight antibiotic-bacterium combinations. On the other hand, in some countries, resistance proportions could increase in all eight antibiotic-bacterium combinations.

There will continue to be significant heterogeneity across not only countries and regions, but also antibiotic-bacterium pairs. For example, while growth in third-generation cephalosporin resistance in *K. pneumoniae* and *E. coli* will slow down significantly compared to the last decade, growth in vancomycin resistance among *Enterococci* is projected to accelerate in most OECD countries. MRSA could continue to decline in OECD countries overall while actually growing in EU countries. Growth in carbapenem-resistant *K. pneumoniae* proportions is projected for all regions but could be especially great in G20 countries.

While average growth rates seem to be slowing down, there are causes for concern. The OECD model suggests that resistance to second-line treatments, such as third-generation cephalosporins and fluoroquinolones, is expected to increase in a majority of countries, leading to greater consumption of carbapenems and potentially promoting carbapenem resistance. In some countries, resistance to the last line of treatment – polymyxins – is already emerging with potentially disastrous consequences. Growth in resistance proportions among difficult-to-treat microorganisms, like *Enterococci* and *P. aeruginosa*, is also worrisome. Overall, across OECD countries, resistance to second and third-line antibiotics is expected to be 70% higher in 2030, compared to AMR rates in 2005 for the same antibiotic-bacterium combinations. Similar trends are projected for G20 countries and for resistance to second-line treatments in EU countries. Should trends continue, resistance to the last line of treatment is expected to more than double in EU countries in the period 2005-30.

1.2. Factors underpinning the growth of AMR rates

The cause of the current exacerbation of growth in AMR rates is largely driven by human activity and is two-fold. On the pathogen level, AMR may develop and spread through exposure to antimicrobials in a number of settings including among humans in the community or healthcare setting, in the animal sector, or in the environment (e.g. waste treatment). 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. On the human level, a number of different factors may influence the probability of being infected, including hygiene and living conditions, vaccination, general health status of the population and access to healthcare services and medicines, among others. Other interactions also exist which can create a vicious circle, for example increased infection rates can lead to a higher use of antimicrobials, which in turn, may lead to more resistance.

1.2.1. Inappropriate use of antimicrobials: a leading cause of AMR

Inappropriate use of antimicrobials – including over-prescription, under-prescription, and the prescription and dispensing of unnecessary antimicrobial combinations – is widely considered as a principal factor underpinning AMR. This also includes the use of broad-spectrum antimicrobials when not needed, as well as incorrect dosage and or duration, and poor adherence to prescribed course. Overall, the proportions of inappropriate use may consist of up to 50% of all antimicrobials consumed in human health care. Primary and long-term care services are the areas of most concern, with consistently high levels of inappropriate use. Between 45% and 90% of antibiotic prescriptions in general practices do not meet guidelines (Cecchini and Lee, 2017[3]).

Inappropriate prescription of antimicrobials in humans, from the production and commercialisation of the antimicrobials to the final user, play a role in triggering inappropriate use (Paget et al., 2017[8]). While in many cases diagnostic uncertainty is reported to be the main reason for over-prescription, often inappropriate use of antimicrobials is the result of rational behaviour by one or more actors, driven by cognitive biases or some form of incentive, including economic incentives. In some cases, inappropriate antimicrobial use may be caused by illegal actions, (e.g. sale of counterfeit and poor quality products). Four main categories of actors are involved in ensuring prudent use of antimicrobials in the human sector: prescribers of antimicrobials, patients, health care organisations and producers and dispensers of antimicrobials. Different drivers may support inappropriate use of antimicrobials in each of these categories.

Too often, cognitive biases, perceived pressure and poor information may cause prescribers of antimicrobials not to follow best practices.

- While physicians usually identify the most appropriate antimicrobial therapy, they also often decide not to follow these guidelines to privilege local attitudes and usual business practices.
- The fear of a possible infection, especially in fragile patients, and even if there is no sign of an infection, has been identified as another strong factor promoting use of antimicrobials.
- Finally, physicians may decide to prescribe an antimicrobial, even if they feel it is not needed, to meet patients' expectations or requests, or to prescribe a second-line antibiotic if they feel that resistance to first-line antibiotics is high in the local environment. According to a survey among general practitioners in the United Kingdom, about 50% of practitioners admitted having prescribed antibiotics for a viral infection (Cole, 2014[9]).

Patients' inadequate knowledge of AMR and of the benefits of prudent use of antimicrobials also drives inappropriate use:

- In some OECD countries, use of self-prescribed antibiotics and self-medication with leftovers from previous therapies or with antibiotics provided by friends or pharmacies in the absence of a medical prescription occurs up to 40% of the occasions where antibiotics are used (Morgan et al., 2011[10]).

- When therapies are prescribed by a physician, patients may decide to stop the course earlier than prescribed, for example because they feel better (e.g. about 10% of patients in Spain and Sweden stop taking the medication before the end of its course (Axelsson, 2013[11]; Llor et al., 2014[12])). Patients may also decide to switch to another antibiotic or skip some doses (e.g. up to 44% of patients in the United States admit to skipping doses (Edgar, Boyd and Palamé, 2009[13])).
- Patients put some pressure on physicians to prescribe antibiotics even when they would not need one, for instance if they have a viral infection, or shop around physicians to obtain multiple prescriptions for the same diagnosis. Up to 7.5% of prescriptions in Japan were considered as duplicative prescriptions (i.e. prescription for the same condition from two or more health care providers in a month) (Takahashi et al., 2016[14]).

Ineffective organisational arrangements also lead to an imprudent use of antimicrobials.

- Antimicrobials can be used as a cheap and quick fix for lack of time or resources to carry out further diagnostic tests that could guide prescription. Lack of reimbursement from health care insurances for specific tests or diagnosis may also contribute to imprudent use.
- Poor implementation of guidelines or stewardship programmes in health care settings also supports inappropriate use of antimicrobials.
- Ineffective use of antimicrobials may also be the result of the unwanted effects of policies, such as a lack of separation between prescribing and dispensing which is still normal practice in a number of countries outside those of the OECD, particularly in Asia.
- Similarly, it was argued that different reimbursement systems for general practitioners may foster higher imprudent use of antimicrobials. For example, in systems based on a fixed budget, doctors may increase prescriptions because this practice would minimise the risk of a short-term re-examination of the patient (Kaier, Frank and Meyer, 2011[15]). Conversely, in different payment systems, patients may have incentives to shop around physicians until they find one prescribing the antimicrobial therapy they want.

Producers and vendors of antimicrobials also play a significant role in supporting prudent use.

- In the majority of European countries, sales of antibiotics without prescription were estimated to account for between 2% and 8% of total antibiotic sales (Safrany and Monnet, 2012[16]); this figure may become as high as 60% in some low and middle-income countries (Adeyi et al., 2017[17]).
- Sales of antimicrobials may be also supported by promotional efforts: in the past, antimicrobials have been among leading drug classes for promotional expenditure (Ma et al., 2003[18]).
- Finally, counterfeit antimicrobials, which are often of poor quality or have a reduced active principle, amount to about 5% of the global antimicrobial market (Delepierre, Gayot and Carpentier, 2012[19]). More than one in four counterfeit antimicrobials are sold in Europe or in the Americas (Kelesidis and Falagas, 2015[20]).

The extensive use of antimicrobials in livestock production makes agriculture a critical sector in the fight against AMR. In the United States, antimicrobial use in the livestock sector accounted for about 80% of the total annual antimicrobial sales (Spellberg et al., 2016[21]). At the global level, antimicrobial consumption in livestock production is 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[22]). These estimates do not take into account antimicrobial use in aquaculture where use is also high. Importantly, antimicrobials in the agriculture sector are also used for disease prevention and growth promotion, including use of low-level doses of antimicrobials in feed which presents a high risk for AMR development. Once a resistant bacterium develops, it could be passed on to humans via direct contact with animals. Also, animal faeces can spread antimicrobial-resistant bacteria to food crops and the environment.

The environment also plays a fundamental role in promoting AMR. Antimicrobials used in humans or agriculture as well as waste products from drug manufacturing can end up in the environment through sewage water. Once in the environment, the continued antimicrobial activity of these drugs affects local microbial communities and favours resistance development and spread. Poor environmental hygiene also underpins the spread of infections. The environment represents a reservoir of bacteria that can eventually contaminate individuals. The hospital environment represents a particularly important setting, given the high susceptibility of patients to infections. In the United States alone, 722 000 cases of health care-associated infections were documented in 2011 (Magill et al., 2014[23]).

AMR is a prominent "One Health" issue. Human health is interconnected with animals, agriculture and the environment. Addressing public health issues in a "One-Health" framework entails a close collaboration among different professionals including, for example, human and veterinary health experts.

1.2.2. Cross-country differences in AMR rates can be explained by key determinants but no single factor stands out for all the antibiotic-bacterium combinations

The OECD has assessed the relationship between AMR rates and some of the abovementioned dimensions that, on theoretical grounds, are believed to be key determinants of AMR. OECD analyses conclude that:

- Higher antibiotic consumption in humans is generally associated with higher resistance proportions, but this is not always the case. For example, resistance proportions in Belgium are lower than expected when considering antibiotic consumption in the human sector in the country, while the reverse is true in Mexico. While these associations could reflect the fact that the appropriateness of consumption also matters (Zilberberg et al., 2017[24]), they also suggest there are other factors at play.
- At the global level, the bulk of antimicrobials are consumed in the animal sector, mostly by food-producing animals, but there is evidence that resistance may spread to humans. For a subset of countries for which data are available, the OECD calculates that total antibiotic consumption (i.e. combined consumption in the human and animal sectors) is highly correlated with resistance in *E. coli*,

which can cause infections and sepsis in many organs (e.g. urinary tract, bloodstream, skin and soft tissues and gastro-enteric tract).

- Out-of-pocket health expenditure, which captures access to health care services including antimicrobial drugs, is positively associated with the share of *K. pneumoniae* infections that are resistant to third-generation cephalosporins.
- Per capita gross-domestic product (GDP), a proxy of the broader socio-economic environment of countries, is highly correlated with carbapenem-resistance among *P. aeruginosa*, which can cause infections and sepsis in many organs (e.g. urinary tract, respiratory tract, bloodstream, skin and soft tissues and gastro-enteric tract).
- The World Bank Worldwide Governance Indicators[5] scores, which capture governance and policy-related dimensions, are a very strong predictor for resistance proportions (Kaufmann, Kraay and Mastruzzi, 2011[25]): lower average scores, corresponding to poorer governance, are associated with higher resistance proportions.

Findings from the OECD analyses suggest that, while certain factors (e.g. governance, country income, out-of-pocket health expenditure, antimicrobial consumption in human and animal sectors) probably play a role in determining resistance proportions, particularly for specific antibiotic-bacterium combinations, there is no single major driver of drug resistance. The emergence and spread of AMR is a complex phenomenon with multiple interrelated causes and consequences and requires a multifaceted set of actions.

1.3. AMR is a significant burden on population health

Since their discovery, antimicrobials have become an essential instrument in medical therapies and surgical treatments. The introduction of antimicrobial therapies has markedly decreased the burden of infectious disease. In addition, by preventing hospital-acquired infections, antimicrobials have allowed the introduction of complex medical interventions such as organ transplantations, advanced surgery, chemotherapy and care of premature babies, just to cite a few. The number of clinical situations in which the use of an antimicrobial is essential is countless and covers the whole lifespan.

Even after accounting for methodological shortcomings, available evidence concludes that the burden of AMR in significant and infections could become a major cause of death in a "post-antibiotic" world. Previous analyses concluded that, at the current rates of resistance, about 23 000 and 25 000 deaths per year are directly attributable to AMR in the United States (CDC, 2013[26]) and Europe (ECDC and EMEA, 2009[27]), respectively.

By feeding its microsimulation model on AMR with cross-country comparable and updated evidence and by considering a more comprehensive set of infections susceptible of developing resistance, the OECD calculates that, under a business-as-usual scenario in which no new policy action is put in place:

- Around 2.4 million individuals could die in Europe, North America and Australia between 2015 and 2050. Italy, Greece and Portugal top the list with an annual mortality rate of, respectively 18.2, 14.8 and 11.3 deaths per 100 000 persons. In absolute terms, the United States has the highest number of AMR deaths with an average of almost 29 558 per year (9.0 deaths per 100 000); followed by Italy and France with around 10 778 and 5 620 deaths per year, respectively. Other populous European countries including Poland, Germany, the United Kingdom and Spain, despite substantially lower mortality rates (from 2.6 to 6.1 deaths per 100 000), would be affected by 1 800 to 2 300 AMR deaths per year.

- The impact on population health, measured in terms of quality of life, will be even larger than the impact on life expectancy. Accounting for the population size of the countries, Southern Europe (Italy, Portugal, France and Greece in particular) would be the most affected. For example, in Italy, up to one person in every 205 could lose one year of life in good health because of AMR.
- Children and the elderly are the two population groups whose health status is most affected by resistant infections, with probability of AMR several times higher in the age groups 0-1 and 70+, compared to the rest of the population. Men are more likely to develop resistant infections than women.

In the so-called "post-antibiotic" world, in which virtually no antibiotic would be effective, the burden caused by AMR could become significantly bigger as even small infections could lead to death. In OECD countries, every year, at least 47 million individuals develop an infection which has the potential to become resistant to antimicrobials[6] (IHME, 2017[28]) and many would die. In addition, in the absence of valid therapeutic alternatives or effective actions to prevent the spread of infections, the incidence rate for communicable diseases may grow further as people would be infected for a longer period and would have more opportunities to infect others.

In the same scenario, surgical operations for non-life threatening conditions, even if highly disabling, would be avoided or postponed, with a significant decrease in the quality of life of patients, as the risk of infection, and subsequently, death would be too high. For example, prophylactic use of antibiotics in hip replacement surgery reduces postoperative infection rates by up to 50% and death due to infection by 30% (Smith and Coast, 2013[29]).

In a scenario in which antibiotics would become almost completely ineffective for therapeutic and prophylactic use, the OECD calculates that the ten most common procedures carried out in hospitals in the European region in 2014, would have produced an additional 435 000 infections leading to an additional 30 000 deaths. A previous analysis, focused on the United States, concluded that the same scenario would produce an additional 400 000 infections and 21 000 deaths in 2010 (Teillant et al., 2015[30]). Such estimates roughly correspond to the yearly number of deaths due to motor vehicle accidents in the same regions.

Poor access to effective and high-quality antimicrobials is already causing a significant health burden in low and middle-income countries. In OECD countries, it is calculated that less than 450 000 individuals (i.e. about one person in every 3 000) die because of diseases such as lower respiratory infections, diarrhoea and neonatal sepsis which can be easily treated when good access to high-quality antibiotics is ensured. Conversely, more than 4.5 million people died in 2016 from this group of diseases in low and middle-income countries, accounting for about 12% of total mortality. Children would pay a particularly high toll as more than 25% of the 4.5 million deaths would be in the under-five age group (IHME, 2017[28]).

1.4. AMR is a significant source of welfare loss

AMR damages health, society and the economy of countries. Much of this is due to the incremental health care costs caused by resistant infections in the hospital setting. The additional costs caused by a resistant infection, compared to a susceptible infection, generally vary between USD 10 000 and USD 40 000 per case (Cecchini, Langer and Slawomirski, 2015[31]), depending on the type and body site of the infection, the country and the patient mix.

Such additional expenditure is caused by the use of more intensive health care procedures for the carrying out of surgical interventions or the treatment of complications. These include extra investigations or advanced laboratory tests to identify the most effective therapy; excess length of stay until the infection is eradicated; and, finally, the use of more aggressive antimicrobial therapies based on either second-line antimicrobials or combinations of different antimicrobials. More than half of the costs for all of these extra procedures are due to additional medical and nursing care while another 25% is for the payment of support services and diagnostics (Tumbarello et al., 2010[32]).

A number of previous country or region-specific studies evaluated the economic burden of AMR. Produced estimates are difficult to compare across countries as studies differ in terms of methodology, accounting approach, number of diseases included in the analyses and so on. Despite limited cross-country comparability, the impact of AMR on the budget of health care systems is estimated to be significant:

- In Europe, costs due to AMR were estimated at about EUR 940 million to treat the resistant strains of a limited set of the most common infective agents in 2007 (ECDC and EMEA, 2009[27]).
- In Canada, the total medical care costs associated with AMR are estimated at CAD 1 billion (PHAC, 2015[33]).
- In the United States, up to USD 20 billion could be spent on AMR (CDC, 2013[26]).

By using its microsimulation approach, with cross-country comparable data and an identical accounting system, the OECD calculates that, on average, every year between 2015 and 2050 up to USD PPP 3.5 billion are expected to be spent on AMR-related complications across the 33 OECD countries included in the analyses, corresponding to about USD PPP 2.4 per capita in those countries. In Italy, Malta and the United States this amount could be as high as USD PPP 6.2-6.6 per capita. In comparison, previous OECD analyses found that the average expenditure per capita for all infectious diseases in a group of 11 OECD countries was about USD PPP 20 (OECD, 2016[34]), meaning that AMR would be responsible for more than 10% of all healthcare costs caused by communicable diseases. The impact of AMR on health care expenditure (and on human health) would be even greater if, instead of considering as a comparator a scenario in which patients develop a susceptible infection (i.e. the closest alternative to a resistant infection), the analyses were based on a scenario assuming that no infection develops.

1.4.1. AMR has a greater impact on the economy of a country than its health care budget

Broader societal costs caused by AMR include time away from work, increased disability claims, loss of productivity and premature deaths. In addition, increased morbidity also affects the supply of labour if ill health requires the attention of a caregiver who would otherwise be economically productive. In the United States in the year 2000, the cost attributable to increased mortality and productivity losses due to AMR was about USD 38 000 per hospital patient, more than double the associated medical costs to treat the patients (Roberts et al., 2009[35]). Scaling up to the national level, in 2000 the

United States lost USD 35 billion (or about 0.35% of the national GDP) due to AMR. By using a different cost accounting technique and a different set of resistant infections, productivity losses due to absence from work caused by resistant infections in the European Union and the European Economic Area amounted to about EUR 600 million in 2007 (ECDC and EMEA, 2009[27]).

Societal costs caused by AMR are particularly high in low and middle-income countries. In such settings, high prevalence rates for key antibiotic-resistant infections combined with poor hygiene in health care services as well as limited protection against out-of-pocket expenditure and ineffective social safety nets significantly increases the probability that developing a resistant infection may lead to catastrophic expenditures. A non-trivial share of the 80 million individuals each year that experience impoverishment due to surgical care in low and middle-income countries (Meara et al., 2015[36]) could be already caused by AMR. Should resistance proportions keep increasing, an additional 19 million individuals in low and middle-income countries will fall into a situation of extreme poverty by 2030 due to negative repercussions on, for example, labour productivity and health care costs (Ahmed et al., 2017[37]).

Summing up the health and economic effects of AMR, the macroeconomic impact caused by resistant infections is considerable. The World Bank (Adeyi et al., 2017[17]) calculated that, at the global level, AMR could reduce GDP output by between 1.1% and 3.8%, depending on how severely the AMR epidemic develops up to 2050. Compared to a scenario without AMR, the total losses in the period 2015-50 in the worst-case scenario would add up to USD 85 trillion in GDP and USD 23 trillion in global trade. Low and middle-income countries would suffer the most, with an economic impact on GDP which would be up to 80% greater than for high-income countries. The detrimental effects caused by AMR on the labour force participation rate and productivity as well as on the size of the population would be the major drivers of this reduction in GDP. International trade and livestock production, in addition to the health care sector, would suffer the most due to reduced productivity and reduction in sales.

1.5. A strong economic rationale for taking action

Imprudent use of antimicrobials produces significant externalities imposing costs on others. The main externalities associated with imprudent use of antimicrobials include the additional costs borne by publicly-funded health care systems to treat resistant infections, the extra health burden and deaths attributed to the lack of available antimicrobial treatment borne by the population, as well as all the negative consequences on productivity and household income suffered by individuals developing a resistant infection.

Compared to other common causes of externality in public health, imprudent use of antimicrobials presents some specific characteristics. First, the consumption of an antimicrobial contributes to creating an environment supportive of AMR development, with effects deferred to a point after the direct consumption of a course of antimicrobials. The external costs associated to antibiotic consumption was calculated at about EUR 5 to EUR 12 for a single defined daily dose of common antibiotic therapies, or between EUR 101 to EUR 143 for a complete course of antibiotic therapy in hospitals (Kaier, 2012[38]). Second, both prudent and imprudent use of antimicrobials supports the development of AMR. When antimicrobials are used inappropriately, the benefits produced by the therapy tend to be zero as the antimicrobial does not produce any positive health effect, but the cost of the externalities associated with consumption increases. The deadweight loss to societal welfare attributed to inappropriate use of amoxicillin alone in the United States was estimated at USD 225 million in 1996 (Elbasha, 2003[39]).

Although outside the main focus of this report, a second strong economic rationale for governments to take action on AMR is the market failure affecting the R&D of new antimicrobials. Antimicrobials are inexpensive drugs but the cost of developing new molecules and bringing them to the market has increased over time. In addition, any newly developed product would likely be held in reserve, further discouraging private sector investments. In this context, a number of large pharmaceutical companies have decided to abandon the market and stop investments in antibiotic R&D, which has resulted in a failure in the supply of new antimicrobials that can substitute old therapies with reduced effectiveness (OECD et al., 2017[5]).

1.6. Governments need to put in place a comprehensive set of public health actions to tackle AMR

The rationale for government intervention to curb AMR is strong, with a wide range of policies potentially available. The ability of governments to design and implement wide-ranging prevention strategies, combining the strengths of different policy approaches is critical to success, including in the case of initiatives promoted in collaboration with the various stakeholders. This requires, however, drawing on objective and verified evidence. By taking as a starting point the Global Action plan on AMR, the OECD has reviewed the available evidence on the effectiveness of key public health policy options to tackle AMR and their level of implementation in OECD and G20 countries to evaluate the effectiveness and the cost-effectiveness of scaling up policy approaches at the national level. This work led to the identification of a first set of "best buys" of public health actions to tackle AMR in the human sector.

1.6.1. Global policy responses to tackle AMR is growing

Many countries have made substantial progress on policies to tackle AMR in the last few years. Following the approval of the WHO Global Action Plan on AMR in 2015 (WHO, 2015[40]), the World Health Assembly urged all Member States to develop and put in place, by 2017, national action plans on AMR. Half of the WHO Member States had a national action plan on antimicrobial resistance in place as of 2017, and another quarter had such a plan under development. According to the same survey, 84% of OECD, G20, and EU countries had developed a national action plan, with the remaining countries undertaking the development of a plan at the time of the survey (WHO, FAO and OIE, 2018[41]).

When designing action plans, countries have a broad arsenal of policy options from which to choose and the opportunity to tailor each of these policies to their unique needs. Effective policy implementation requires coordination of many different types of stakeholders, even at the local and regional levels, making antimicrobial policy making in a "One Health" (WHO, 2017[42]) perspective particularly challenging. In addition, strategies need to be tailored to specific cultures, existing practices and the resistance profile as the appropriateness of different interventions is shaped by factors such as the legal environment and how health care services are delivered in that country. Given the complex and cross-border nature of AMR, international coordination and cooperation is particularly important.

Traditional policy approaches to tackling AMR in the health care sector can be divided into two broad categories:

- interventions to promote rational use of antimicrobials which aim to prevent, or at least minimise, the emergence of new resistant microorganisms, and
- interventions to prevent the spread of existent infections by enhancing hygiene and minimising transmission.

In addition, by preventing the development of infections and by enhancing herd immunity, vaccination policies may also play a fundamental role in tackling AMR. Finally, policies in other areas, notably to promote prudent use of antimicrobials in agriculture and livestock production, also play a critical role in combatting AMR as part of a "One Health" approach.

Among the most widely deployed types of interventions in OECD countries, stewardship programmes involve the simultaneous implementation of regulations, guidelines, monitoring, education and campaigns to influence the prescribing of antimicrobials. These programmes help to determine whether a patient should be prescribed an antimicrobial, which antimicrobial should be prescribed, and for how long it should be taken. Provision of information to the public through mass media campaigns is another widely implemented intervention in OECD countries. This action aims to raise public awareness about the dangers associated with inappropriate antimicrobial prescription. Campaigns are usually delivered during the winter season as this is the period of the year during which antibiotics are more likely to be used for inappropriate purposes (e.g. to treat a cold).

Prescriber education entails a wide range of informative activities to enhance prescribers' knowledge of evidence-based medicine or to improve prescribers' communication skills as they relate to antimicrobial prescribing. While all OECD and G20 countries have in place some sort of education programme for physicians, only two countries, the United Kingdom and Norway, systematically incorporate courses on AMR in pre-service training curricula for all relevant health cadres. Use of new medical technologies, such as rapid diagnostic tests, is increasingly allowing clinicians to rapidly acquire information that can guide antimicrobial prescribing decisions.

Finally, selected countries are testing the use of delayed prescriptions, in which a patient receives a prescription that can only be filled after a certain period. For example, the National Institute for Health and Clinical Excellence, in the United Kingdom, recommends this intervention in patients with specific diseases. The use of financial incentives, usually in the form of pay-for-performance programmes, was also implemented in a few countries (e.g. in Sweden and in the United States), to tackle inappropriate prescription of antibiotics.

Interventions to enhance hygiene are formally in place in virtually every country in the world, but adherence to guidelines should be improved. Interventions such as hand hygiene and environmental hygiene in a health care setting are highly effective and, compared to interventions promoting the prudent use of antimicrobials, they produce an effect on both resistant and susceptible infections. Countries have experimented with policies to increase adherence to hand washing guidelines, which is still poor in many countries, and have tested more effective approaches to cleaning health care devices or facilities. In some countries, as for example in Hong Kong, health care services have implemented policies to systematically screen patients for infections at admittance with the objective of isolating or decontaminating infected individuals before they could spread the infection among the other patients.

Vaccination has been shown to be extremely effective in reducing the incidence of many clinical diseases, including those pathogens with high rates of resistance. For example, the introduction of the pneumococcal conjugate vaccine in children younger than two years reduced the incidence of infections (e.g. in the respiratory tract, meninges, ears, and bloodstream) by over 80% in countries at all levels of income (Kyaw et al., 2006[43]); (von Gottberg et al., 2014[44]). However, implementation of more widespread vaccination faces a number of issues, including ideological, logistical, and financial hurdles. In addition, further efforts should be invested into the R&D of new vaccines. Currently, there are no licensed vaccines for bacteria in the most critical categories of the WHO Priority Pathogens List (WHO, 2017[7]), and only 4% of R&D spending on products to prevent infections specifically related to AMR is spent on diagnostics, vaccines, or other technologies (OECD et al., 2017[5]).

1.6.2. Public health actions to tackle AMR have a positive impact on population health and are an excellent investment for OECD countries

Drawing on the available evidence, the OECD has assessed a set of policies aligned with the WHO global action plan on AMR. The OECD used its microsimulation model on AMR to examine stewardship programmes, media campaigns, actions to enhance hygiene in health care facilities, including promotion of hand-washing and enhanced environmental hygiene, delayed prescriptions and the use of diagnostic tests in 33 OECD and EU countries, and to identify “best buys” for tackling AMR.

Findings from the OECD microsimulation model on AMR show that substantial health gains may be achieved by scaling up to the national level many of the assessed policies. More specifically, results show that:

- Policies to promote hand washing and to enhance hygiene in health care facilities consistently rank as the most effective policies both in terms of reduction of mortality and burden of disease measured in disability-adjusted life years (DALYs). In the 33 countries included in the study, the implementation of these two policies could respectively avert about 37 836 and 34 931 deaths per year and increase the number of persons living in good health by about 21 000 and 17 000 per year. This means that, compared to a scenario in which no policy is in place, hand-washing promotion and hygiene enhancement would be expected to reduce the risk of death from AMR by more than half and to decrease its health burden, measured in DALYs, by about 40%. Compared to policies to promote rational use of antimicrobials, this group of policies tackle both susceptible and resistant bacteria. However, they do not tackle some of the key determinants of AMR associated with imprudent use of antimicrobials.
- Stewardship programmes are particularly effective, too, producing similar effects to hygiene-enhancing actions.
- Other interventions such as delayed prescriptions, use of rapid diagnostic tests and mass media campaigns produce more limited results, mainly because they are designed to tackle AMR in the community, which would have a more limited impact on the population health.

Implementation costs vary substantially across interventions and countries, but interventions are consistently shown to be an excellent investment, often resulting in cost savings. The cost of implementing the policy actions varies on a number of factors, including whether the intervention is targeted at the population level (e.g. mass media campaigns) or to individual patients (e.g. delayed prescriptions), with the latter generally being more costly. Other factors such as the purchasing of medical devices (e.g. rapid diagnostic tests) or the setting up of specific teams to support antibiotic prescriptions (e.g. in stewardship programmes) also have a higher implementation cost.

Interventions entailing a lower consumption of resources, including mass media campaigns, delayed prescriptions and improved hand hygiene cost from as little as USD PPP 0.3 up to USD PPP 2.7 per capita in many OECD countries. More resource-intense interventions can cost up to a few hundred USD PPP per hospitalised patient, as in the case of actions to enhance hospital environmental hygiene.

When both implementation costs and impact on health care expenditure are taken into account, the OECD model concludes that, consistently across interventions and geographical settings, all the considered policy actions are a cost-effective investment and, in a number of cases (e.g. delayed prescriptions, improved hand hygiene and, very often, stewardship programmes), the implementation cost of the intervention is lower than the corresponding savings on health care expenditure produced by the intervention. Thus, in other words, investing in public health actions to tackle AMR is a very good investment for the countries included in the analysis and the implementation cost of the public health actions completely pays for itself and produces some additional savings.

Based on the three quantitative criteria to identify the best policy options in public health (i.e. effectiveness on population health, affordability to implement the intervention, and cost-effectiveness ratio), virtually all the interventions considered in the analysis can be generally considered "best buys" to tackle AMR in the assessed countries. For some interventions, particularly those in the community (e.g. mass media campaigns and delayed prescriptions) the effectiveness is more limited but, due to their lower implementation cost, these interventions result in cost-effective investments. Extrapolation of these results beyond OECD countries is more difficult to assess as organisational arrangements and other factors may significantly influence the results of the analysis.

Combining AMR policies into a coherent prevention strategy that combines actions both to promote prudent use of antibiotics and to prevent the spread of infections in the health care sector and in the community, would help countries reach a critical mass having a greater impact on susceptible and resistant infections and their associated negative health and economic effects. The three package options considered: one for hospital measures, one for community actions and a mixed intervention package (based on a combination of selected hospital and community strategies) would each reduce the health burden of AMR by 85%, 23% and 73%, respectively. This corresponds to a total of approximately 1.3 million, 0.4 million and 1.1 million DALYs averted and 55, 15 and 47 life years saved across the 33 countries included in the study. In terms of health expenditure, the hospital-based intervention package would result into an annual average net saving (i.e. after accounting for the implementation cost of each intervention) of USD PPP 4.1 per capita (ranging from USD PPP 0.08 in Iceland to USD PPP 13.2 in Malta). The community-based intervention approach would also result in an average annual saving of around USD PPP 0.9 per capita across the 33 included countries. The mixed policy approach would result in an average net reduction in health expenditure of around USD PPP 3 per capita per year. In practical terms, this would mean that millions of people in these countries would avoid AMR-related complications and health problems, with major potential gains for themselves in terms of their health well-being, for society and economic outcomes.

Notes

[1] The term “antimicrobials” refers to a broad family of agents including any agent killing or inhibiting the growth of microbes. There are many classes of antimicrobials depending on the type of microbes targeted or the composition of the antimicrobial. Antibiotics (or antibacterials) are a sub-category of antimicrobials specifically targeting bacteria. “Antimicrobial” is used in this chapter to specifically describe those agents that exert a killing function against bacterial pathogens, or agents that work as treatment or prophylaxis against bacterial infections. In most contexts of this chapter, antimalarial, antifungal and antiviral medicines are not included under the term “antimicrobials”.

[2] Throughout this chapter, the name of the infectious microorganisms, rather than the name of the most common infections caused by such microorganisms, are used as virtually all the considered microorganisms can cause infections in many different organs. So, for example, *Neisseria gonorrhoeae* is used, rather than gonorrhea (which is commonly used to refer to the infections of the reproductive organs), as the same bacterium can also cause, among the others, infections of the musculoskeletal system (e.g. septic arthritis), of the gastrointestinal tract (e.g. pharynx and rectum), of the bloodstream, and other infections.

[3] The eight antibiotic-bacterium combinations included in the analysis are: third-generation cephalosporin-resistant *Escherichia coli*, fluoroquinolones-resistant *Escherichia coli*, penicillin-resistant *Streptococcus pneumoniae*, methicillin-resistant *Staphylococcus aureus*, carbapenem-resistant *Klebsiella pneumoniae*, third-generation cephalosporin-resistant *Klebsiella pneumoniae*, carbapenem-resistant *Pseudomonas aeruginosa*, and vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium*.

[4] OECD key partners include the following countries: Brazil, China, India, Indonesia and South Africa.

[5] The World Bank Worldwide Governance Indicators capture dimensions associated with traditions and institutions by which authority in a country is exercised, including the capacity of the government to effectively formulate and implement sound policies and the respect of citizens and the state for the governing institutions. More specifically, the indicators monitor the following six dimensions of governance: voice and accountability, political stability and absence of violence, government effectiveness, regulatory quality, rule of law, control of corruption.

[6] This number is calculated by summing up the number of cases of the following infections in OECD countries: gonococcal, chlamydial, lower respiratory, syphilis, tuberculosis, whooping cough, paratyphoid fever, typhoid fever, and meningitis. The list does not aim to be exhaustive of all the clinical conditions potentially caused by microorganisms with the ability to develop AMR.

References

Adeyi, O. et al. (2017), *Drug-resistant infections : a threat to our economic future (Vol. 2) : final report*, World Bank Group, Washington (DC), http://documents.worldbank.org/curated/en/323311493396993758/final-report (accessed on 09 May 2018). [17]

Ahmed, S. et al. (2017), "Assessing the Global Economic and Poverty Effects of Antimicrobial Resistance"*, Policy Research Working Paper*, No. 8133, World Bank, Washington (DC), http://documents.worldbank.org/curated/en/190151498872848485/pdf/WPS8133.pdf (accessed on 11 May 2018). [37]

Axelsson, M. (2013), "Report on personality and adherence to antibiotic therapy: a population-based study.", *BMC psychology*, Vol. 1/1, p. 24, http://dx.doi.org/10.1186/2050-7283-1-24. [11]

CDC (2013), *Antibiotic Resistance Threats in the United States, 2013*, Centers for Disease Control and Prevention, Atlanta (GA), https://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf (accessed on 11 May 2018). [26]

Cecchini, M., J. Langer and L. Slawomirski (2015), *ANTIMICROBIAL RESISTANCE IN G7 COUNTRIES AND BEYOND: Economic Issues, Policies and Options for Action*, OECD, Paris, http://www.oecd.org/els/health-systems/Antimicrobial-Resistance-in-G7-Countries-and-Beyond.pdf (accessed on 19 January 2018). [31]

Cecchini, M. and S. Lee (2017), "Low-value health care with high stakes: Promoting the rational use of antimicrobials", in *Tackling Wasteful Spending on Health*, OECD Publishing, Paris, http://dx.doi.org/10.1787/9789264266414-6-en. [3]

Cole, A. (2014), "GPs feel pressurised to prescribe unnecessary antibiotics, survey finds", *BMJ*, Vol. 349/aug19 15, pp. g5238-g5238, http://dx.doi.org/10.1136/bmj.g5238. [9]

Delepierre, A., A. Gayot and A. Carpentier (2012), "Update on counterfeit antibiotics worldwide; public health risks.", *Medecine et maladies infectieuses*, Vol. 42/6, pp. 247-55, http://dx.doi.org/10.1016/j.medmal.2012.04.007. [19]

ECDC and EMEA (2009), *The bacterial challenge: time to react*, ECDC and EMEA, Stockholm (SE), https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf (accessed on 10 October 2018). [27]

Edgar, T., S. Boyd and M. Palamé (2009), "Sustainability for behaviour change in the fight against antibiotic resistance: a social marketing framework.", *The Journal of antimicrobial chemotherapy*, Vol. 63/2, pp. 230-7, http://dx.doi.org/10.1093/jac/dkn508. [13]

Elbasha, E. (2003), "Deadweight loss of bacterial resistance due to overtreatment.", *Health economics*, Vol. 12/2, pp. 125-38, http://dx.doi.org/10.1002/hec.702. [39]

FAO (2016), *Drivers, Dynamics and Epidemiology of Antimicrobial Resistance in Animal Production*, FAO, Rome, http://www.fao.org/3/a-i6209e.pdf (accessed on 08 May 2018). [4]

Hawkey, P. (2008), "The growing burden of antimicrobial resistance.", *The Journal of antimicrobial chemotherapy*, Vol. 62 Suppl 1, pp. 1-9, http://dx.doi.org/10.1093/jac/dkn241. [1]

IHME (2017), *GBD Compare Data Visualization*, http://vizhub.healthdata.org/gbd-compare (accessed on 11 May 2018). [28]

Kaier, K. (2012), "Economic implications of the dynamic relationship between antibiotic use and hospital-acquired infections.", *Value in health*, Vol. 15/1, pp. 87-93, http://dx.doi.org/10.1016/j.jval.2011.09.005. [38]

Kaier, K., U. Frank and E. Meyer (2011), "Economic incentives for the (over-)prescription of broad-spectrum antimicrobials in German ambulatory care.", *The Journal of antimicrobial chemotherapy*, Vol. 66/7, pp. 1656-8, http://dx.doi.org/10.1093/jac/dkr134. [15]

Kaufmann, D., A. Kraay and M. Mastruzzi (2011), "The Worldwide Governance Indicators: Methodology and Analytical Issues", *Hague Journal on the Rule of Law*, Vol. 3/02, pp. 220-246, http://dx.doi.org/10.1017/S1876404511200046. [25]

Kelesidis, T. and M. Falagas (2015), "Substandard/counterfeit antimicrobial drugs.", *Clinical microbiology reviews*, Vol. 28/2, pp. 443-64, http://dx.doi.org/10.1128/CMR.00072-14. [20]

Kyaw, M. et al. (2006), "Effect of Introduction of the Pneumococcal Conjugate Vaccine on Drug-Resistant <i>Streptococcus pneumoniae</i>", *New England Journal of Medicine*, Vol. 354/14, pp. 1455-1463, http://dx.doi.org/10.1056/NEJMoa051642. [43]

Llor, C. et al. (2014), "Access to point-of-care tests reduces the prescription of antibiotics among antibiotic-requesting subjects with respiratory tract infections.", *Respiratory care*, Vol. 59/12, pp. 1918-23, http://dx.doi.org/10.4187/respcare.03275. [12]

Magill, S. et al. (2014), "Multistate Point-Prevalence Survey of Health Care–Associated Infections", *New England Journal of Medicine*, Vol. 370/13, pp. 1198-1208, http://dx.doi.org/10.1056/NEJMoa1306801. [23]

Ma, J. et al. (2003), "A statistical analysis of the magnitude and composition of drug promotion in the United States in 1998.", *Clinical therapeutics*, Vol. 25/5, pp. 1503-17, http://www.ncbi.nlm.nih.gov/pubmed/12867225 (accessed on 09 May 2018). [18]

McKenna, M. (2013), "Antibiotic resistance: The last resort", *Nature*, Vol. 499/7459, pp. 394-396, http://dx.doi.org/10.1038/499394a. [2]

Meara, J. et al. (2015), "Global Surgery 2030: evidence and solutions for achieving health, welfare, and economic development", *The Lancet*, Vol. 386/9993, pp. 569-624, http://dx.doi.org/10.1016/S0140-6736(15)60160-X. [36]

Morgan, D. et al. (2011), "Non-prescription antimicrobial use worldwide: a systematic review.", *The Lancet. Infectious diseases*, Vol. 11/9, pp. 692-701, http://dx.doi.org/10.1016/S1473-3099(11)70054-8. [10]

OECD (2016), *Expenditure by disease, age and gender*, OECD, Paris (FR), https://www.oecd.org/health/Expenditure-by-disease-age-and-gender-FOCUS-April2016.pdf (accessed on 18 May 2018). [34]

OECD et al. (2017), *Tackling Antimicrobial Resistance Ensuring Sustainable R&D*, http://www.oecd.org/els/health-systems/G20-AMR-Final-Paper-2017.pdf (accessed on 08 May 2018). [5]

Paget, J. et al. (2017), *Antimicrobial resistance and causes of non-prudent use of antibiotics in human medicine in the EU*, European Commission, Brussels, https://ec.europa.eu/health/amr/sites/amr/files/amr_arna_report_20170717_en.pdf (accessed on 27 September 2018). [8]

PHAC (2015), *Canadian Antimicrobial Resistance Surveillance System - Report 2015*, Public Health Agency of Canada, Ottawa (CA), http://publications.gc.ca/collections/collection_2015/aspc-phac/HP37-21-2015-eng.pdf (accessed on 11 May 2018). [33]

Roberts, R. et al. (2009), "Hospital and societal costs of antimicrobial-resistant infections in a Chicago teaching hospital: implications for antibiotic stewardship.", *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, Vol. 49/8, pp. 1175-84, http://dx.doi.org/10.1086/605630. [35]

Safrany, N. and D. Monnet (2012), "Antibiotics obtained without a prescription in Europe", *The Lancet Infectious Diseases*, Vol. 12/3, pp. 182-183, http://dx.doi.org/10.1016/S1473-3099(12)70017-8. [16]

Smith, R. and J. Coast (2013), "The true cost of antimicrobial resistance", *BMJ*, http://dx.doi.org/10.1136/bmj.f1493. [29]

Spellberg, B. et al. (2016), "Antibiotic Resistance in Humans and Animals", *Discussion paper*, National Academy of Medicine, Washington (DC), https://nam.edu/wp-content/uploads/2016/07/Antibiotic-Resistance-in-Humans-and-Animals.pdf (accessed on 09 May 2018). [21]

Takahashi, Y. et al. (2016), "Social network analysis of duplicative prescriptions: One-month analysis of medical facilities in Japan.", *Health policy (Amsterdam, Netherlands)*, Vol. 120/3, pp. 334-41, http://dx.doi.org/10.1016/j.healthpol.2016.01.020. [14]

Teillant, A. et al. (2015), "Potential burden of antibiotic resistance on surgery and cancer chemotherapy antibiotic prophylaxis in the USA: a literature review and modelling study.", *The Lancet. Infectious diseases*, Vol. 15/12, pp. 1429-37, http://dx.doi.org/10.1016/S1473-3099(15)00270-4. [30]

Tumbarello, M. et al. (2010), "Costs of Bloodstream Infections Caused by Escherichia coli and Influence of Extended-Spectrum- -Lactamase Production and Inadequate Initial Antibiotic Therapy", *Antimicrobial Agents and Chemotherapy*, Vol. 54/10, pp. 4085-4091, http://dx.doi.org/10.1128/AAC.00143-10. [32]

Van Boeckel, T. et al. (2015), "Global trends in antimicrobial use in food animals", *Proceedings of the National Academy of Sciences*, Vol. 112/18, pp. 5649-5654, http://dx.doi.org/10.1073/pnas.1503141112. [22]

von Gottberg, A. et al. (2014), "Effects of Vaccination on Invasive Pneumococcal Disease in South Africa", *New England Journal of Medicine*, Vol. 371/20, pp. 1889-1899, http://dx.doi.org/10.1056/NEJMoa1401914. [44]

WHO (2017), *Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics*, World Health Organization, http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf (accessed on 10 October 2010). [7]

WHO (2017), "One Health", http://www.who.int/features/qa/one-health/en/ (accessed on 10 October 2018). [42]

WHO (2015), *Global Action Plan on Antimicrobial Resistance*, World Health Organization, http://www.wpro.who.int/entity/drug_resistance/resources/global_action_plan_eng.pdf (accessed on 10 October 2018). [40]

WHO (2014), *Antimicrobial resistance: global report on surveillance 2014*, World Health Organization, Geneva, http://www.who.int/drugresistance/documents/surveillancereport/en/ (accessed on 10 October 2018). [6]

WHO, FAO and OIE (2018), *Global Database for AMRCSAT Country Self-Assessment Test*, https://extranet.who.int/sree/Reports?op=vs&path=%2FWHO_HQ_Reports/G45/PROD/EXT/amrcsat_AnswersForPublic (accessed on 18 May 2018). [41]

Zilberberg, M. et al. (2017), "Carbapenem resistance, inappropriate empiric treatment and outcomes among patients hospitalized with Enterobacteriaceae urinary tract infection, pneumonia and sepsis", *BMC Infectious Diseases*, Vol. 17/1, p. 279, http://dx.doi.org/10.1186/s12879-017-2383-z. [24]

From:

Stemming the Superbug Tide

Just A Few Dollars More

Access the complete publication at:

https://doi.org/10.1787/9789264307599-en

Please cite this chapter as:

OECD (2019), “Antimicrobial resistance: A large and growing problem”, in *Stemming the Superbug Tide: Just A Few Dollars More*, OECD Publishing, Paris.

DOI: https://doi.org/10.1787/9789264307599-4-en

OECD