Chapter 4. Health and economic burden of antimicrobial resistance

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Antimicrobial resistance (AMR) is a major public health concern worldwide. The OECD has developed a micro-simulations model to produce comparable cross-country estimates of the health and economic impact of AMR, for a comprehensive set of infections susceptible to develop resistance. Individual analyses were performed for 33 OECD and European Union/European Economic Area (EU/EEA) member countries. The model estimates for the included countries show that the current burden of AMR is substantial but, at this point, still limited in comparison to the impact of other conditions. This chapter provides an overview of current economic studies on AMR, describes the findings of the main analyses, along with the major knowledge gaps in the current economic literature on AMR. The characteristics and results of the OECD AMR microsimulation model are then presented, followed by the results of a second analysis conducted by the OECD, focusing specifically on the potential health burden of AMR in the context of antimicrobial prophylaxis treatments. The final section of this chapter summarises the main findings and discusses their policy implications.

Note by Turkey:

The information in this document with reference to "Cyprus" relates to the southern part of the Island. There is no single authority representing both Turkish and Greek Cypriot people on the Island. Turkey recognises the Turkish Republic of Northern Cyprus (TRNC). Until a lasting and equitable solution is found within the context of the United Nations, Turkey shall preserve its position concerning the "Cyprus issue".

Note by all the European Union Member States of the OECD and the European Union:

The Republic of Cyprus is recognised by all members of the United Nations with the exception of Turkey. The information in this document relates to the area under the effective control of the Government of the Republic of Cyprus.

Key findings

- Large variations exist between countries. Across the 33 countries included, the model estimates that on average antimicrobial resistance (AMR) causes around 60 000 deaths per year. Of these, around 33 000 occur in the European Union (EU) and European Economic Area (EEA) countries, while 29 500 occur in the United States.
- Between 2015 and 2050, AMR will have caused around 2.4 million deaths in the included countries and 1.3 million in the EU/EEA region. With one million deaths over the 35 year period, the United States will experience the highest number of cumulative AMR deaths for an individual country.
- There are large differences between countries. In relative terms, southern European countries carry the heaviest burden of AMR. The situation of some of those countries is of particular concern. In Italy, for example, between 2015 and 2050, the model estimates that 500 000 people will die due to AMR. Over the same period, the model predicts that around 92 000 AMR deaths will occur in Germany.
- Each year, AMR results in around 1.75 million disability-adjusted life years (DALYs) lost across the modelled countries with 1 million DALYs lost in EU/EEA countries. In absolute terms, the largest countries experience the highest health burden of AMR. The United States comes first with 724 000 DALYs per year, followed by Italy, France, the United Kingdom, Germany and Spain with estimates ranging from 67 000 to 311 000 DALYs.
- Annually, AMR results in over 700 million extra hospital days (EHDs) across all the included countries and 568 million in the EU/EEA area. The country-specific estimates follow a pattern similar to the other outcomes. The highest number occurs in Italy with almost 2 300 EHDs per 100 000 persons due to AMR, followed by Portugal and France with around 1 250 EHDs per 100 000 persons.
- The effects of AMR cost the health systems of the countries included in the analysis around USD purchasing power parity (PPP) 3.5 billion per year. For EU/EEA countries, that estimate amounts to USD PPP 1.5 billion, per year, which means that in less than 10 years, the impact of AMR on health care expenditure has increased by 60%.
- Over the periode 2015-2050, AMR will have cost the health systems of EU/EEA countries a total of USD PPP 60 billion, while in the United States, Canada and Australia, this amount will reach a combined total of approximatly of USD PPP 74 billion.
- Around 439 000 additional postoperative infections and 307 000 post-intervention deaths would occur each year in the EU if no effective antimicrobial treatment was available for the eleven most common surgical and blood cancer chemotherapy interventions in the EU, which require prophylactic antibiotic treatment.
- Across the modelled countries, a scenario of absence of effective antimicrobial treatments would result in approximately 288 000 deaths per year and cost the different health systems a total of USD PPP 16.3 billion, annually. In the EU/EEA area, this scenario would result in 142 000 deaths per year for a cost of USD PPP 6.4 billion.

4.1. Quantifying the burden of AMR

Antimicrobials are an essential instrument in modern medicine. Their diffusion and widespread use in clinical care throughout the second half of the twentieth century markedly decreased the burden of infectious diseases, and lead to the development of many complex medical interventions such as organ transplantations, advanced surgery, chemotherapy and care for premature babies. AMR represents a direct threat to all these advances. Its rise and dissemination, if left unchecked, will inflict considerable damage to population health, and place a heavy burden on economies and society as a whole.

To address such a threat, it is important for policy makers to have accurate estimates of the health and economic burden of AMR, to inform the design of policies and regulations able to mitigate its current and long-term consequences.

The OECD developed a micro-simulations model to produce comparable cross-country estimates of the health and economic impact of AMR, for a comprehensive set of infections susceptible to develop resistance. Individual analyses were performed for 33 OECD and EU member countries. Three main areas were examined:

- the current health burden caused by AMR and its impact on expenditure and hospital cost
- the potential impact of the decreasing effectiveness of prophylactic antimicrobial therapies on common surgical and chemotherapeutic procedures in Europe
- the potential health and economic consequences of the so-called 'post-antibiotic' world, in which virtually no antibiotic would be effective. It should be noted that there is relative consensus that such an extreme scenario is unlikely to materialise (De Kraker, Stewardson and Harbarth, 2016[1]). Modelling its potential consequences is therefore mainly useful from a conceptual and theoretical point of view – in line with previous AMR models – to inform a benchmark for advocacy.

AMR is currently one of the world's leading public health concerns. It is a significant global threat that is particularly complex to apprehend from an analytical and economic perspective (see Box 4.1). Over the last decade, many studies have provided estimates of the potential economic impact of AMR. This chapter provides an overview of current economic studies. Their main findings are described, along with the major knowledge gaps in the current economic literature on AMR. The characteristics and results of the OECD AMR microsimulation model are presented. The results of a second model focusing specifically on the potential health burden of AMR in the context of antimicrobial prophylaxis treatments, and under different scenarios of treatment effectiveness, are presented. The final section of this chapter summarises the main findings and discusses their policy implications.

4.2. What does the current evidence tell us?

Quantifying the health and economic burden of antimicrobial resistance is challenging both because of the paucity of the data and the multi-dimensionality of the issue (Laxminarayan et al., 2016[2]). Many studies have investigated the burden of antimicrobial resistance, using a variety of approaches (Cohen et al., 2010[3]) (Sipahi, 2008[4]) (Tansarli et al., 2013[5]). Two of the first prominent analyses of the effects of AMR have been produced by the United States Centre for Disease Control and

Prevention (CDC, 2013[6]) and by a joint effort of the European Centre for Disease Prevention and Control (ECDC) and the European Medicines Agency (ECDC-EMEA, 2009[7]):

- The ECDC and EMEA estimated the burden of five resistant bacteria[1] in EU countries, Norway and Iceland. The report concludes that in 2007, over 386 000 people developed one of the included resistant infections in the bloodstream, respiratory tract, urinary tract or skin/soft tissue, which resulted in over 25 000 extra deaths and 2.5 million EHDs. The attributable health care costs and productivity losses associated with resistance were estimated at EUR 1.5 billion per year (ECDC-EMEA, 2009[7]).
- In 2013, the CDC concluded that each year, at least 2 million illnesses and 23 000 deaths are caused by AMR infections[2] in the United States. These estimates have a direct cost to the US health system of more than 20 billion dollars per year (CDC, 2013[6])

In the last five years, several other studies have attempted to provide global estimates of the health and economic burden of resistance. In high-income countries, with low prevalence of infectious diseases such as tuberculosis or malaria, healthcare-associated infections are a major concern. Health systems are heavily dependent on antimicrobials for many aspects of secondary health care such as cancer treatment or the prevention of iatrogenic infections during surgery. Studies in this category have therefore predominantly focused on assessing the health and economic burden of AMR from the hospital perspective. Some of the most prominent studies in this category include:

- A large retrospective cohort study estimated that patients with methicillin-resistant *Staphylococcus aureus* (MRSA) and cephalosporin-resistant *Enterobacteriaceae* bloodstream infections are, respectively, 2.4 and 1.8 times more likely to die after admission to hospital and have an excess length of stay in hospitals of 13.3 and 9.3 days compared to non-infected patients. The cost of each infection was estimated, respectively, at EUR 11 000 and 7 300 (Stewardson et al., 2016[8]).
- A study investigating the potential health consequences of increases in antibiotic resistance on the ten most common surgical procedures and immunosuppressing cancer chemotherapies that rely on antibiotic prophylaxis in the United States. The results showed that a 30% reduction in the efficacy of antibiotic prophylaxis for the included procedures would result on average, each year, in 120 000 additional post-treatment infections (ranging from 40 000 for a 10% reduction in efficacy to 280 000 for a 70% reduction in efficacy), and 6 300 infection-related deaths (ranging from 2 100 for a 10% reduction in efficacy, to 15 000 for a 70% reduction). A scenario of 100% reduction in efficacy would result in around 390 000 additional infections and 21 600 additional deaths per year, for the included procedures (Teillant et al., 2015[9]).

Box 4.1. AMR as a negative externality

In economic terms, AMR represents an externality (i.e. an activity causing an effect on third parties) resulting from the use of antimicrobials to treat infections. This means that the effect of antimicrobial use, in terms of selection pressure and subsequent drug resistance, may not initially be felt directly by the patient or the prescribing clinician but will ultimately have an impact on the overall welfare of other patients in the community and have adverse social and economic effects (Coast, Smith and Millar, 1996[10]). Determining the cost of resistance is a complex task due to lack of evidence and good quality data, and high parameter uncertainty related to the complex nature of the problem of resistance. Some of the challenges include the following:

- Cost of externalities are difficult to measure. In the case of antimicrobials neither the immediate consumer, nor the supplier or prescriber, has to bear the full cost of inappropriate usage, i.e. AMR.
- Precise cost estimates should take into account the specificity of each microorganism in terms of single or combined resistance, treatment procedures, and associated costs.
- AMR can undermine the safety of hospitals and that of many medical interventions, whose success relies on the existence of effective antimicrobial prophylaxis treatments. This in turn can push people not to undergo recommended procedures due the higher risk of infection and potential death, which can lead to increased morbidity and health care expenditure (Smith and Coast, 2013[11]).
- The effect of AMR goes beyond public health and has potential detrimental impacts on a number of social and economic sectors (e.g. the labour market, livestock industries, tourism industry). Assessing the economic burden of AMR implies that its associated costs, across various sectors of the economy, should be clearly identified and measured.

A second group of studies focus on the impact of AMR on the broader economy, usually reporting results in terms of impact on gross domestic product (GDP). The two main drivers used in these analyses to assess the impact on GDP are changes in population size and in the supply of labour force that might result from increased levels of AMR. Some of the most prominent studies in this category include:

- A study published by KPMG in 2014, estimated that by 2050, under a 100% resistance scenario, 700 million deaths would occur annually as a direct result of AMR[3], which would inflict a reduction of USD 1.4 trillion on the world economy (KPMG, 2014[12]).
- In a report commissioned in 2014 by the UK Independent Review on Antimicrobial Resistance (O'Neill, 2016[13]). Rand Europe estimated[4] that by 2050, under a 100% resistance scenario, the cumulative loss of people in productive age would range from 11 million to 444 million, which would correspond to a cumulative GDP loss to the global economy between USD 5.8 trillion and USD 49.4 trillion (Jirka et al., 2014[14]).

- Finally, the Word Bank (World Bank, 2016[15]) provided estimates based on two potential scenarios low and high prevalence of AMR. The analysis projects that by 2050, annual global GDP would likely fall by 1.1%, relative to a base-case scenario with no AMR effects; the GDP shortfall would exceed USD 1 trillion annually after 2030. In the high AMR-impact scenario, the world will lose 3.8% of its annual GDP by 2050, with an annual shortfall of USD 3.4 trillion by 2030.

Overall, the findings from most published burden of disease studies and health economic analyses, consistently suggest that AMR is a major and global public health issue and a critical challenge faced by health systems worldwide. These studies are based on a variety of methodologies, accounting systems, diseases included, and often reach very different estimates (see Annex 4.A), which cannot be directly compared. Despite this heterogeneity, however, they systematically highlight the urgent need for policies to contain resistance.

A common limitation of most existing evaluations is their focus on usually small sets of resistant infections and an analytical approach that does not take into account the broader potential effects of AMR on other conditions and the health care system in general. To a large extent, this is due to the complex nature of the problem of resistance. A second issue concerns the fact that most economic studies on AMR – including the one described above – tend to consider the costs and health outcomes due to resistance without comparison. They provide valuable and detailed descriptive information in terms of cost and health consequences of resistance. This kind of descriptive work is very important but does not provide a complete picture of the problem of AMR in terms of either costs or effects (see Chapter 6).

4.3. The OECD Strategic Public Health Planning for AMR (SPHeP-AMR) model

The OECD developed a health economic model to evaluate the burden of AMR and provide estimates of the current and long-term effects on the population health and health system finances of a selected number of OECD and EU/EEA countries (see Box 4.2). The main aim of the SPHeP-AMR model is to address some of the knowledge gaps and limitations of the current health economic literature described above. The model has two complementary objectives:

1. design a base case model to estimate the current health and economic effects of AMR and to calculate the projections of those effects into the future
2. develop a cost-effectiveness model to assess the impact of selected AMR prevention policies by comparing the potential effects of their implementation to the base case scenario.

The rest of this chapter describes the findings and implications of the first objective. The methodology and findings of the second objective are discussed in Chapter 6.

Box 4.2. The OECD Strategic Public Health Planning for AMR (SPHeP-AMR) model

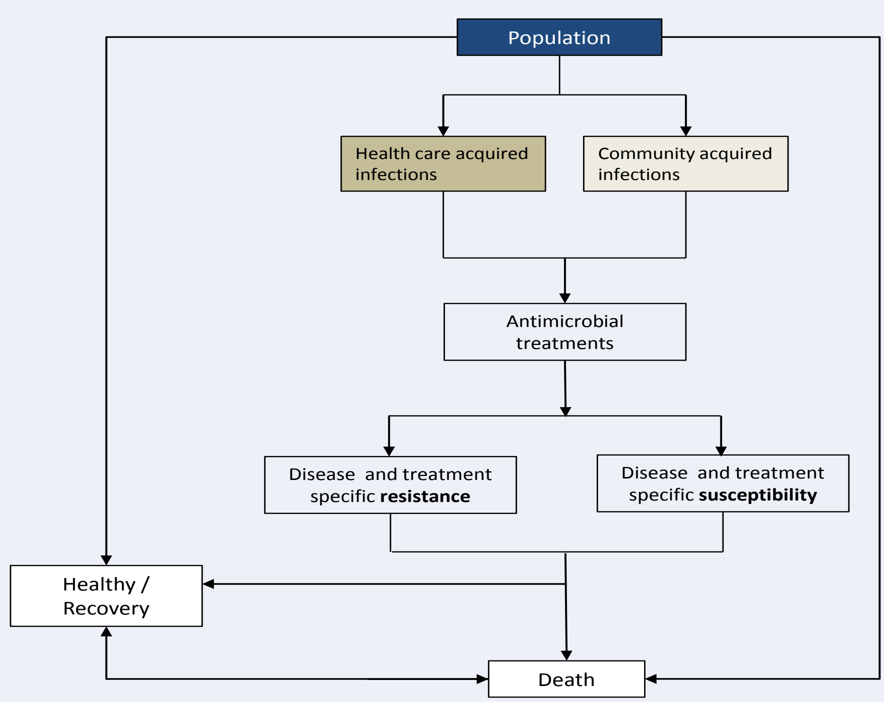
The OECD SPHeP-AMR model is designed as a first order Monte Carlo Markov microsimulation. Based on a dynamic population, it simulates the natural history of AMR and the evolution of its impact on health and economic outcomes between 2015 and 2050 (Figure 4.1). The model includes ten possible and mutually exclusive states. Transition probabilities (derived from current estimates of prevalence and incidence of included pathogens, rates of resistance or non-resistance, mortality and other parameters) allow movement between the health states during yearly cycles. Costs and health outcomes are assigned to each state and transition.

The model projects the population, number of deaths, disability-adjusted life years (DALYs), health expenditure and extra hospital days (EHDs) associated with each pathogen into the future under the following assumptions:

- No co-infections: subjects cannot develop multiple infections at the same time.
- The evolution of AMR incidence was based on estimates from the model described in Chapter 3.
- Transmission from infected to healthy subjects is exogenous to the model and relies on estimates from the model described in Chapter 3.
- Subjects with a history of AMR have the same risk of an AMR infection as those with no previous diagnosis.
- All other resistant infections other that the antibiotic-bacterium combinations included in the model are considered as susceptible.

Individual models were run separately for 33 countries: the 28 members of the European Union (EU28), along with Norway, Iceland, Australia, Canada and the United States, taking into account national characteristics, including functioning of the health care system (e.g. probability of admittance to a hospital, average length of stay, etc.), demography and prevalence of hospital and community infections. All analyses were conducted from the health care system perspective.

Figure 4.1. Structure of the AMR model



The model accounts for 8 bacteria and a total of 17 antibiotic-bacterium combinations and simulates resistant and susceptible infections occurring in five body sites: bloodstream, respiratory system, urinary tract, surgical site, and other. The selection of the infective agents included in the analysis was based on ECDC experts' advice following three main criteria: i) significance of the burden of disease in OECD countries and the EU, both in the health care sector and the community; ii) policy priority for OECD and EU countries; and iii) data availability. Table 4.1 shows the full list of antibiotic-bacterium combinations included in the microsimulation.

Table 4.1. Pathogens included in the model

Species	Strain-characteristics	Setting	
		Health care	Community
Acinetobacter spp.	*Acinetobacter spp* excluding those with resistance to carbapenem and/or fluoroquinolones and/or colistin	X	
	Acinetobacter spp with resistance to carbapenem	X	
	Acinetobacter spp with resistance to fluoroquinolones	X	
	Acinetobacter spp with resistance to colistin	X	
Streptococcus pneumoniae (*S. p pneumoniae*)	*S. pneumoniae* excluding single penicillin resistance and combined resistance to penicillins and macrolides		X
	penicillin-resistant *S. pneumoniae* (excluding macrolide resistant isolates)		X
	S. pneumoniae with combined penicillin and macrolide resistance		X
Staphylococcus aureus (*S. aureus*)	*S. aureus* excluding MRSA-positive isolates	X	X
	Methicillin-resistant *S. aureus*	X	X
Escherichia coli (*E. coli*)	*E. coli* excluding those with resistance to third-generation cephalosporins and/or carbapenem and/or colistin.	X	X
	E. coli with resistance to third-generation cephalosporins excluding carbapenem and colistin	X	X
Klebsiella pneumoniae (*K. pneumoniae*)	*K. pneumoniae* excluding isolates with resistance to third-generation cephalosporins and/or carbapenems and/or colistin.	X	X
	K. pneumoniae with resistance to third-generation cephalosporins excluding carbapenem and colistin resistance.	X	X

	K. pneumoniae with carbapenem resistance excluding colistin resistance	X	
	K. pneumoniae with colistin resistance.	X	
Pseudomonas aeruginosa (*P. aeruginosa*)	*P. aeruginosa* excluding carbapenem resistance and/or colistin resistance and/or resistance to three or more of piperacillin ±tazobactam, fluoroquinolone, ceftazidime and aminoglycosides	X	
	P. aeruginosa with carbapenem resistance (not resistant to colistin)	X	
	P. aeruginosa with multidrug resistance (i.e. three or more of piperacillin ±tazobactam, fluoroquinolone, ceftazidime and aminoglycosides) excluding carbapenem and colistin.	X	
	P. aeruginosa with colistin resistance.	X	
Enterococcus faecalis (*E. faecalis*) & *Enterococcus faecium* (*E. faecium*)	*E. faecalis* and *E. faecium* excluding vancomycin-resistant isolates	X	
	Vancomycin-resistant *E. faecalis* and *E. faecium*	X	

Data to model the epidemiology of infections in EU and EEA countries, by 5-year age categories was made available by the ECDC. A detailed description of the methodology used by the ECDC to derive the AMR incidence estimates used in the SPHeP-AMR model for different countries and body sites is provided elsewhere (Cassini et al., 2018[16]).

Estimates of the number of incident cases for Australia, Canada and the United States were provided by the projection model described in Chapter 3. Other input data to model the health impact of infections (e.g. the increased risk of death for resistant infections) and their impact on use of health care services, including case fatality, length of stay associated with the development of an infection were extracted from extensive reviews of the literature conducted by the ECDC (Cassini et al., 2018[16]).

The economic data and approach is largely based on the WHO-CHOICE methodology (WHO, 2003[17]). The hospital costs are calculated as the product of the average cost for a hospital day in a given country (as provided by WHO (Johns, Baltussen and Hutubessy, 2003[18])) multiplied by the average length of stay for each pathogen as found in the literature. The advantages and limitations of this approach have been described elsewhere (Graves et al., 2010[19]). All cost estimates are expressed in 2017 USD PPP.

Health outcomes are expressed in terms of DALYs. These were calculated following the standard WHO approach for cost-effectiveness analysis described in previous OECD publications (Cecchini, Devaux and Sassi, 2015[20]). Disability weights – specific to the pathogens and body sites considered in this study – were provided by the ECDC (Cassini et al., 2018[16]).

The uncertainty around the key model parameters was assessed with a probabilistic sensitivity analysis approach, where all parameters are varied simultaneously, with multiple sets of parameter values being sampled from a priori-defined probability distribution (Briggs, Claxon and Sclulpher, 2006[21]). This approach was also used to derive 95% uncertainty intervals for each model outcome estimate.

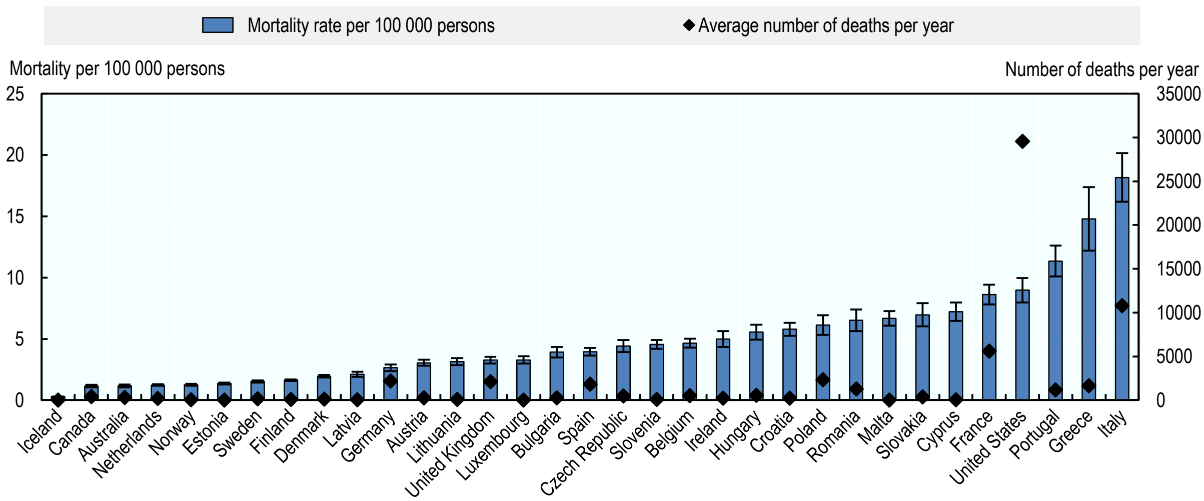
4.4. The heavy burden of AMR on population health

4.4.1. Mortality

Figure 4.2 presents the OECD model estimates of mortality due AMR infections for the countries included in the simulation. Large variations exist between countries. Across all 33 countries in the model, the model estimates that on average AMR causes around 60 000 deaths per year. Of these, around 33 000 occur in the EU/EEA counties, while 29 500 occur in the United States. With an average of 18.1 deaths per 100 000 persons due to AMR each year, Italy has the highest mortality rate among the included countries, followed by Greece, Portugal, the United States and France with 14.8, 11.3, 8.9 and 8.6 AMR deaths per 100 000 persons, respectively. For the rest of the countries the estimated rates range from around 7 deaths for Cyprus to 0.3 for Iceland, per 100 000 persons. Figure 4.3 shows the cumulative number of AMR deaths over the 35 years of the simulation. The model estimates that by 2050, AMR will have caused around 2.4 million deaths in the included countries and 1.3 million in the EU/EEA region. The United States will experience the highest number of cumulative AMR deaths for an individual country. Estimates for Europe show large differences between countries. With almost 500 000 AMR deaths over the simulation period Italy is in stark contrast to the rest of Europe, as the estimate for France – the second country with the highest projected cumulative mortality – is around 238 000 deaths.

These estimates are substantially lower than results reported by some of the recently published analyses described above. The RAND model, for example, estimated that by 2050, with an assumption of stable resistance rates, AMR would cause around 2.1 million deaths per year for the working age population in the OECD-EU-EEA region. It is, however, difficult, if not impossible to compare this finding to the OECD model estimates due to major differences in methodology and analytical scope. For example, the RAND model has a strong focus on low and middle-income countries (LMICs) and therefore included AMR in the context of HIV, tuberculosis and malaria, given the high burden of these diseases in LMICs. The OECD model, on the other hand, deals primarily with health-care associated resistant infections, which are the current priority of high-income countries. Other differences can be identifies with the RAND model and all of the studies mentioned earlier. These methodological differences are similarly reflected in model outputs.

Figure 4.2. Average annual number of deaths due to AMR – 2015-2050



Note: For EU/EEA countries, AMR incidence and fatality parameters used in the model were provided by the ECDC (Cassini et al., 2018[16]).
Source: OECD analysis based on the OECD SPHeP-AMR model.

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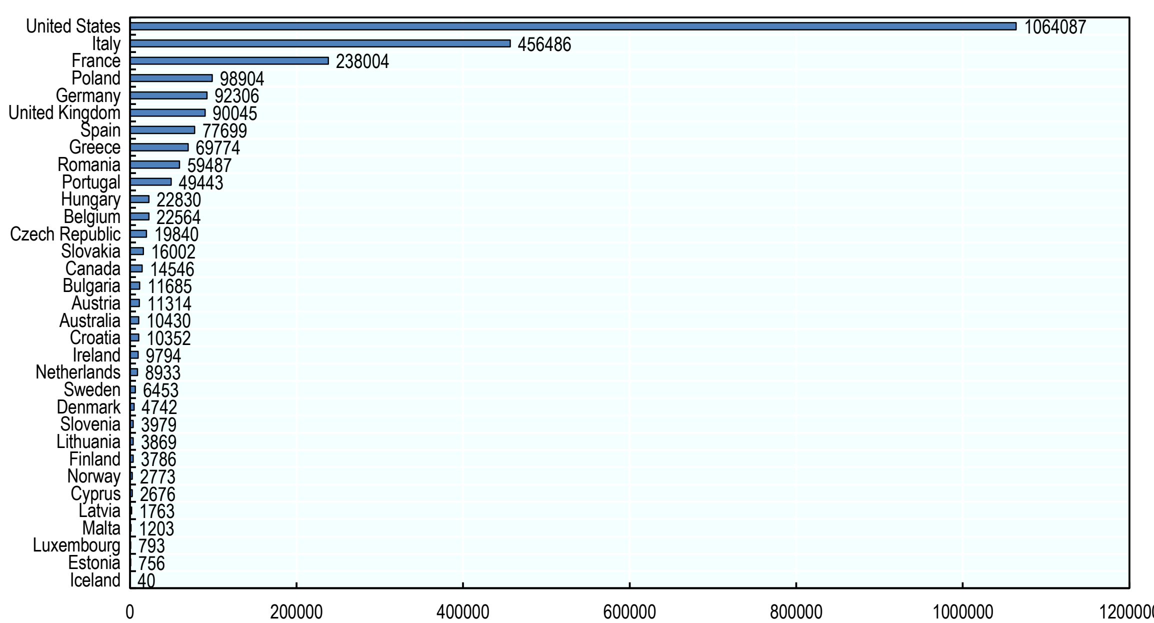
Figure 4.3. Cumulative number of AMR deaths – 2015-2050



Note: For EU/EEA countries, AMR incidence and fatality parameters used in the model were provided by the ECDC (Cassini et al., 2018[16]).
Source: OECD analysis based on the OECD SPHeP-AMR model.

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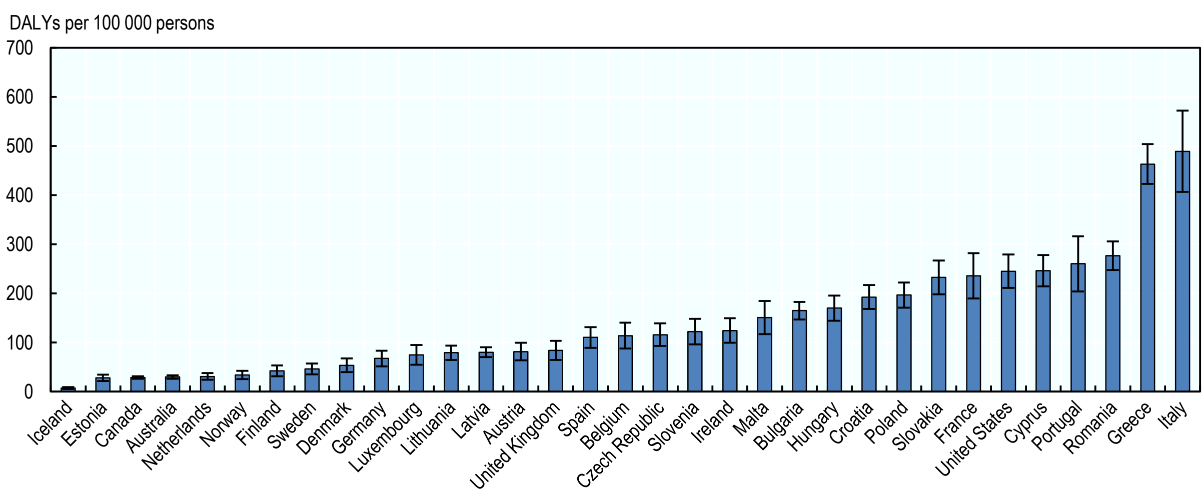
4.4.2. Disease burden of AMR

In terms of burden of disease, the OECD model estimates that each year AMR results in total of 1.75 million and 1 million DALYs lost across the all the modelled countries and EU/EEA countries, respectively. Generally, southern European countries experience the highest burden. Figure 4.4 shows the average annual number of DALYs per 100 000 persons, attributable to AMR. Italy is the hardest hit with an estimated average of 524 DALYs lost each year due to AMR. Five other southern European countries (with the exception of Romania) follow, namely: Greece, Romania, Portugal, Cyprus and France, with estimates ranging between 221 and 376 DALYs per 100 000. Again, in absolute terms, the largest countries experience the highest health burden of AMR. The United States comes first with 724 000 DALYs per year, followed by Italy, France, the United Kingdom, Germany and Spain with estimates ranging from 67 000 to 311 000 DALYs.

Figure 4.4. Average annual burden of AMR in DALYs – 2015-2050



Source: OECD analysis based on the OECD SPHeP-AMR model
Note: For EU/EEA countries, AMR incidence parameters used in the model were provided by the ECDC (Cassini et al., 2018[16]).

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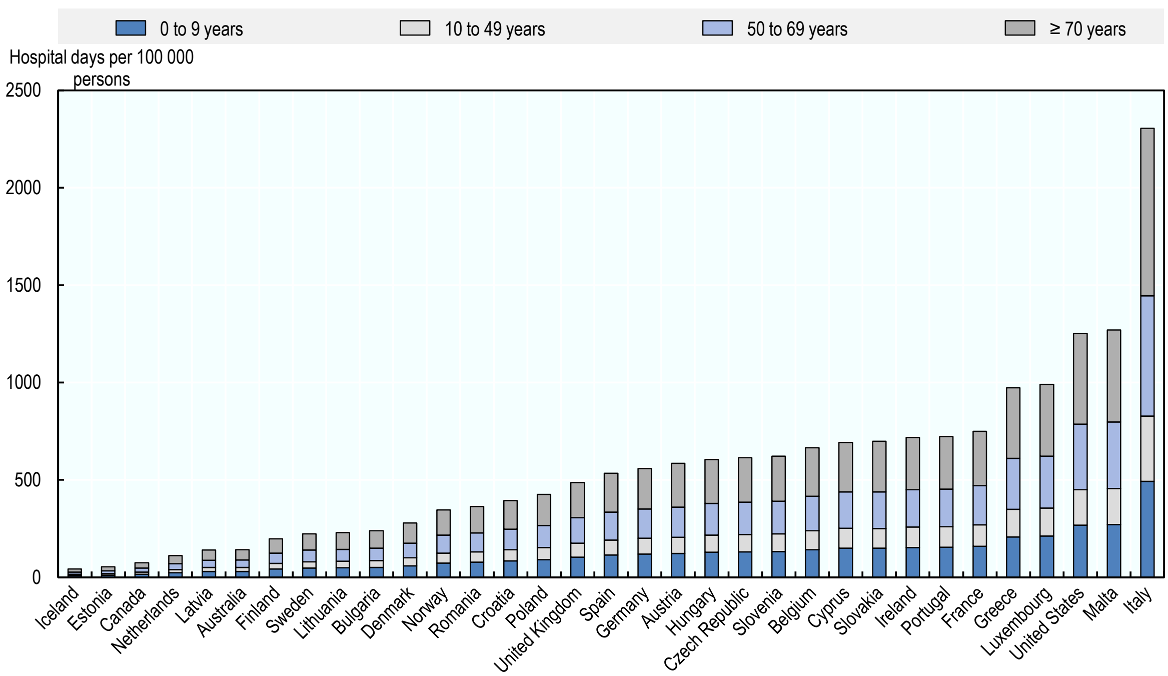
4.5. Impact on hospital resources and health care expenditure

The impact of AMR on health system finances is substantial in a tight fiscal environment and a context of high-cost pressure on the health care sector.

4.5.1. Stretched hospital resources

The OECD analysis estimates that, each year, AMR results in over 700 million EHDs across all the included countries and 568 million in the EU/EEA area. The country-specific estimates follow a pattern similar to the other outcomes. The highest number occurs in Italy with almost 2 300 EHDs per 100 000 persons due to AMR, followed by Portugal and France with around 1 250 EHDs per 100 000 persons. Figure 4.5 shows the distribution of EHDs across different age categories in the population. For all countries, over 60% of the EHDs occur in populations aged over 50 years, while a third occurs in children aged 9 years or under. In this age category, more than 90% of the EHDs are experienced by children under the age of 12 months. Teenagers and adults aged between 9 and 50 years, experience 10-15% of EHDs attributable to AMR. This age-group distribution is to be expected given that the risk of acquiring a resistant infection is partly driven by contact with hospital services. This distribution is strongly reflected in the OECD model, as it includes health care acquired rather than community-acquired infections.

Figure 4.5. Average annual number of extra hospital days associated AMR – 2015-2050



Note: EHD parameters used in the model were provided by the ECDC as well as AMR incidence data for EU/EEA countries (Cassini et al., 2018[16]).
Source: OECD analysis based on the OECD SPHeP-AMR model.

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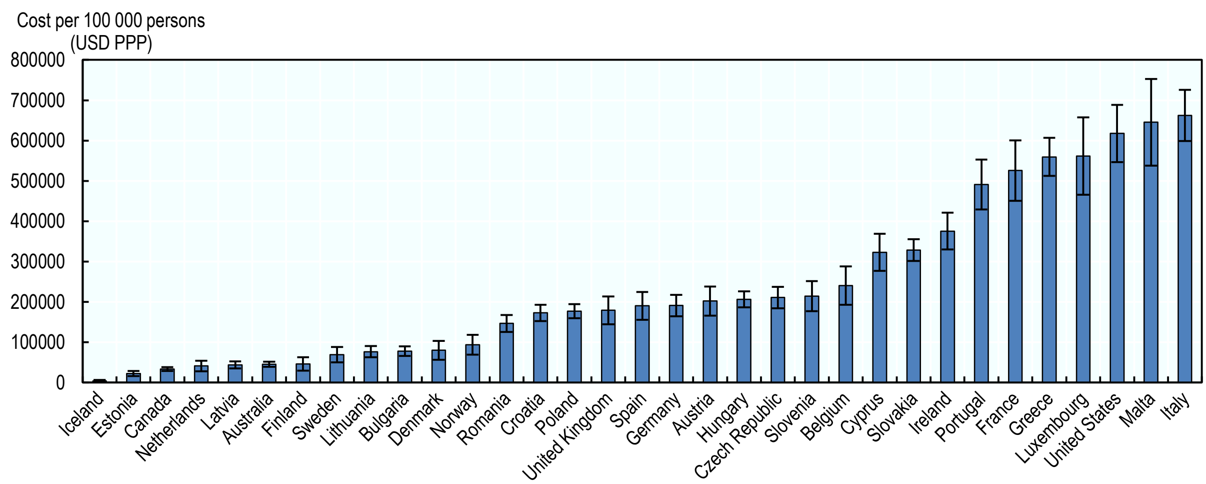
4.5.2. Health care expenditure

The effects of AMR costs the health systems of the countries included in the analysis around USD PPP 3.5 billion per year. In EU/EEA countries that estimate amounts to USD PPP 1.5 billion, per year. Figure 4.5 shows the cost estimates per 100 000 persons for each country. Again, Italy has the highest cost with USD PPP 662 000 per 100 000 persons, followed by Malta and the United States, Luxembourg and Greece with annual cost estimates between USD PPP 559 000 and USD PPP 645 000 per 100 000 persons. In absolute terms, the United States tops the list of the included countries, with annual health expenditure for AMR estimated at around USD PPP 2 billion. Italy and France are second and third with, respectively, USD PPP 393 million and USD PPP 342 million spent each year by the health system as a result of AMR. Far behind these countries come the other large European countries. Germany, the United Kingdom, Spain and Poland spend less than half the amount spent by France with annual estimates for these countries ranging from USD PPP 88 million to USD PPP 157 million per year. Figure 4.6 shows the cumulative cost over the simulation period. The model estimates that by 2050, AMR will have cost the health systems of EU/EEA countries a total of USD PPP 60 billion, while in the United States, Canada and Australia, this amount will reach around USD PPP 74 billion.

These estimates are, overall, consistent with findings from previous studies methodologically close to the OECD model in terms of scope and focus on health care expenditure. For example, the 2009 ECDC analysis of the economic burden of antibiotic resistance (ECDC-EMEA, 2009[7]) estimated, based on 2007 data, that AMR results in EUR 900 million of additional hospital costs per year. A crude comparision of this estimate to the OECD results means that, in less than 10 years, the impact of AMR on the health care budgets of the EU/EEA counties has increased by 60%.

Similarly, for the United States, a recent study, based on the analysis of data from the Medical Expenditure Panel Survey, estimated the total national costs of treating resistant infections at USD 2.2 billion annually, which is in line the OECD model estimate.

Figure 4.6. Annual health care expenditure associated with AMR – 2015-2050



Source: OECD analysis based on the OECD SPHeP-AMR model.

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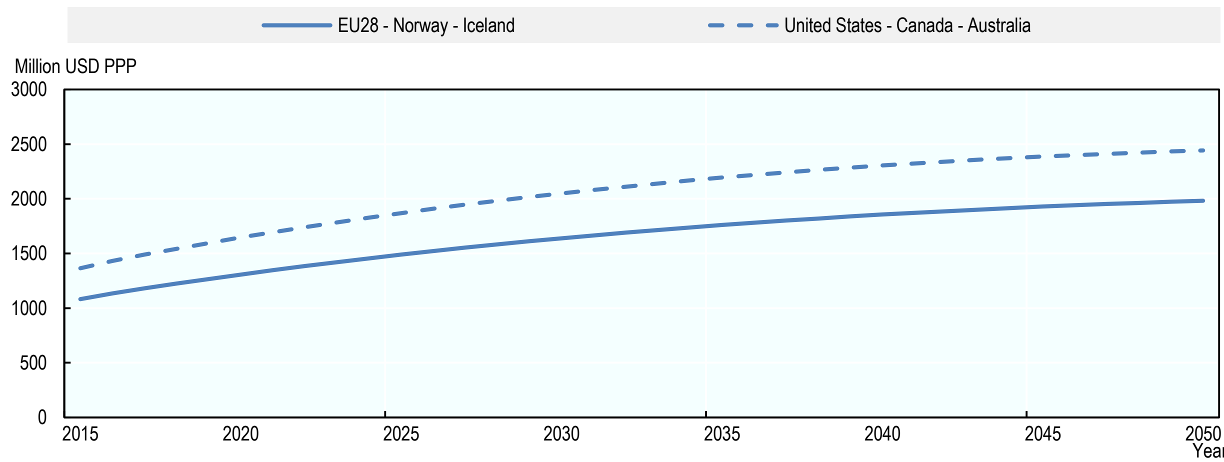
Figure 4.7. Health care expenditure associated with AMR over-time



Note: Future impact on health care expenditure is discounted at a 3% rate.
Source: OECD analysis based on the OECD SPHeP-AMR model.

StatLink http://dx.doi.org/10.1787/888933854953

4.6. AMR jeopardises the safety of many medical procedures

One of the key objectives of the OECD evaluation of the impact of AMR, and the full health system approach adopted, is to assess its potential effects on medical interventions and procedures that rely on effective antimicrobials. The rational for this question is based on the hypothesis that the largest health and economic impact of AMR might come from the impossibility of performing many routine medical interventions due to the high risk of infection that would result from the declining efficacy of current antimicrobials (Smith and Coast, 2013[11]).

Currently, surgical site infections (SSIs) already represent an important public health issue. They are the second most common cause of health care-associated infections (HCAIs) accounting for 20% of all HCAIs (ECDC, 2013[22]). They also constitute a considerable burden in terms of mortality, morbidity, and poor quality of life for patients (Pinkney et al., 2013[23]). Annually, around 800 000 SSIs occur in Europe, leading to over 16 000 deaths (Cassini et al., 2016[24]). The treatment costs for a patient with an SSI is on average three times higher than that of a non-infected patient (Edwards et al., 2008[25]). In Europe, this represents a total annual extra cost to health systems estimated between EUR 1.5 billion and EUR 19 billion (Badia et al., 2017[26]) (Leaper et al., 2004[27]). Considerable and ongoing efforts in terms of infection control in hospitals have been put in place in many countries to prevent SSIs (ECDC, 2017[28]). AMR threatens these efforts, and consequently the safety and feasibility of many invasive procedures.

There is almost no empirical assessment of the potential effects of AMR for the treatment of SSIs. The study by Teillant et al. (2015[9]), mentioned earlier, is to date the only available analysis that has attempted to measure the potential "collateral" effects of AMR in terms of SSIs and associated deaths in the United States. Using a similar approach (see Box 4.3) the OECD investigated the effect of AMR on the risk of infection and death associated with surgical procedures and blood cancer chemotherapy - for which antibiotic prophylaxis treatment is recommended – for individual countries of the EU/EEA area.

Box 4.3. Estimating the effects of AMR in the context of prophylaxis

The Eurostat and EUCAN databases were used to identify the ten most common surgical and blood cancer chemotherapies procedures performed in Europe for which antibiotic prophylaxis is recommended by current guidelines. The included procedures are:

- Cataract surgery
- Caesarean section
- Hip replacement
- Appendectomy
- Knee replacement
- Hysterectomy
- Spinal surgery
- Transurethral prostatectomy
- Colorectal surgery
- Cholecystectomy
- Chemotherapy for blood cancers

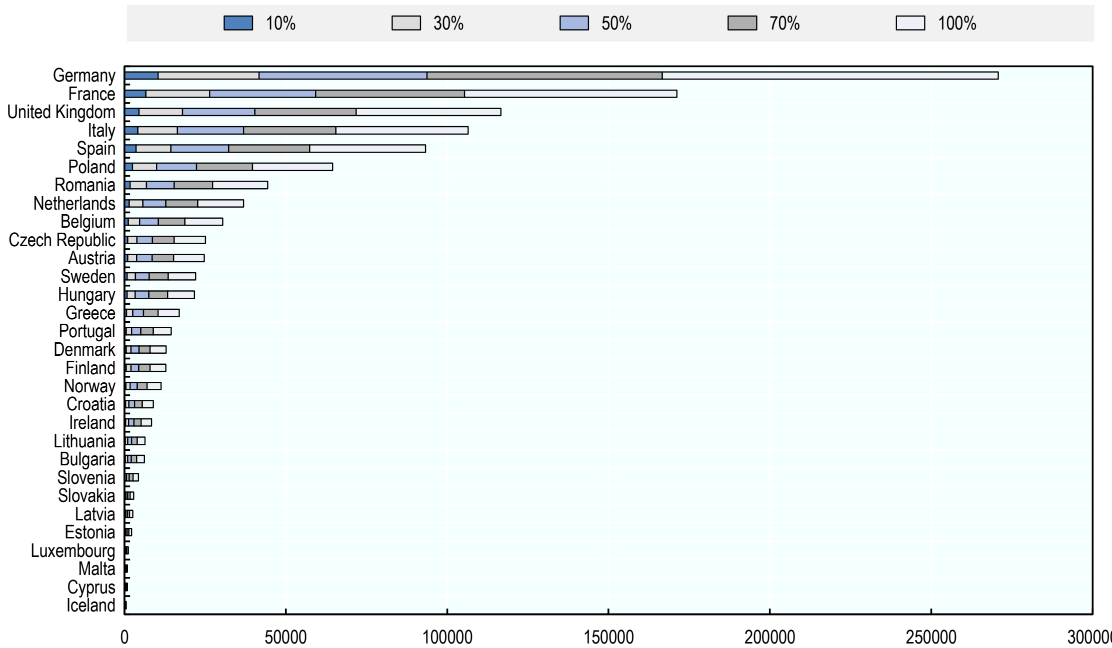
PubMed was consulted to identify meta-analyses of randomised controlled trials reporting estimates of the absolute risk reduction of infections associated with antibiotic prophylaxis for the included procedures.

4.6.1. AMR threatens the safety of many medical procedures

The OECD analysis shows that the potential adverse impact of AMR on the outcomes of some of the most commonly performed surgical procedures in Europe is severe. The 11 surgeries and blood cancer chemotherapies included in the analysis represent approximately 9.5 million procedures performed annually in the EU/EEA area. Figure 4.8 and Figure 4.9 show the additional number of infections and deaths under the different scenarios of efficacy reduction for the counties included in the analysis.

Across the included countries, between 44 000 and 439 000 additional postoperative infections would occur each year under scenarios of 10% and 100% reduction in the effectiveness of antibiotic prophylaxis. This corresponds, respectively, to increases of 5% and 50% in postoperative infections relative to current estimates (ECDC, 2017[29]). In terms of mortality, under a 10% effectiveness reduction scenario, around 3 000 additional deaths would occur each year in the EU/EEA countries, which represents an 18% increase, compared to 2016 estimates. Under the worst-case scenario of resistance, the total number of deaths in the EU/EEA area would amount to around 30 700 per year. This represents an almost 200% increase in deaths due to postoperative infections when compared to current estimates.

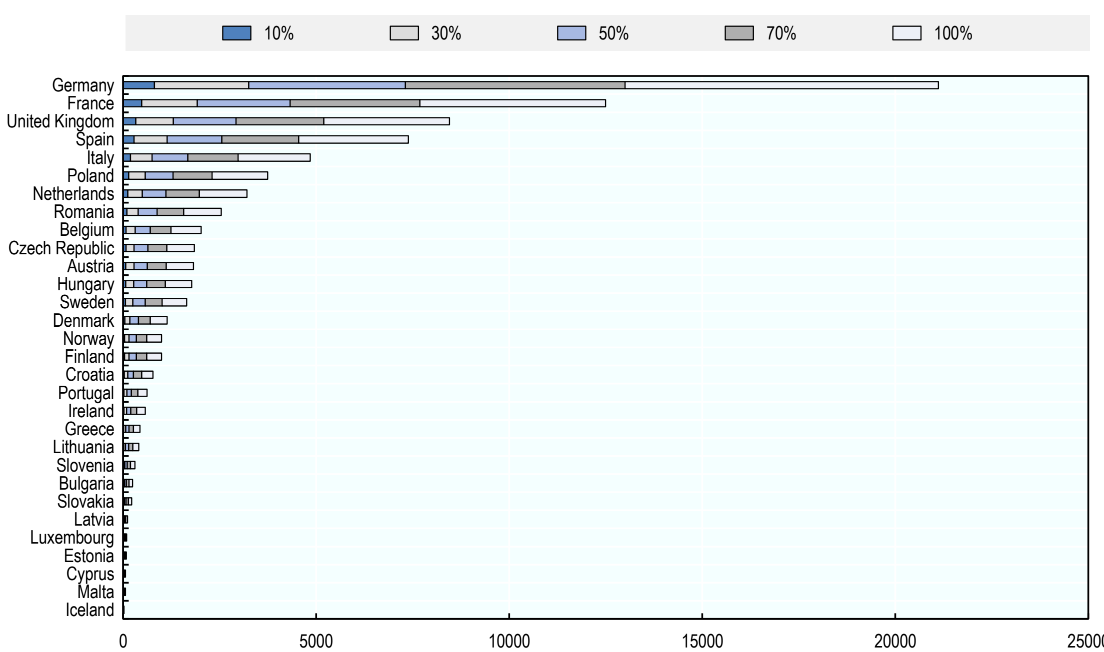
Figure 4.8. Annual number of additional post-intervention infections associated with different scenarios of reduced effectiveness of prophylactic antimicrobial therapy



Source: OECD analysis based on cited sources.

StatLink http://dx.doi.org/10.1787/888933854972

Figure 4.9. Annual number of additional post-intervention deaths associated with different scenarios of reduced effectiveness of prophylactic antimicrobial therapy



Source: OECD analysis based on cited sources.

StatLink http://dx.doi.org/10.1787/888933855257

4.7. What is the worst-case scenario for AMR?

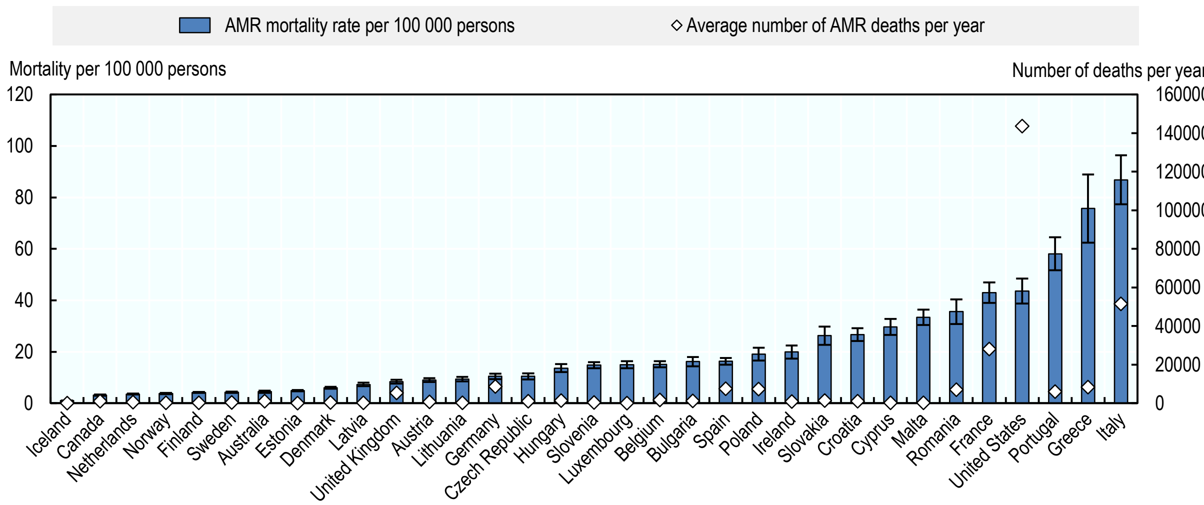
The OECD model was used to estimate the consequences of a hypothetical worst-case scenario in which no antimicrobial treatment is effective. Figure 4.10 and Figure 4.11 report the effects on mortality and health expenditure, respectively. Across the modelled countries, a scenario of absence of effective antimicrobial treatment would result in approximately 288 000 deaths per year and cost the different health systems a total of USD PPP 16.3 billion. In the EU/EEA area, this scenario would result in 142 000 deaths per year for a cost of USD PPP 6.4 billion.

These results are considerably lower than previous analyses that have modelled the potential effects of a hypothetical worst-case scenario for AMR. The RAND study, for example, evaluated that such a scenario would cause around 8 million deaths per year (relative to a 0% resistance scenario) in the OECD/EU/EEA area. As noted previously, a direct comparison between this figure and the OECD estimates cannot be made due to differences in methodology and scope. A potential explanation of the relatively conservative estimates of the OECD analysis, even under an extreme scenario of absolute resistance, might be the fact that the OECD model is based on a much more granular analytical approach (i.e. microsimulation) than previous studies. In addition, the epidemiological model for EU/EEA countries are based on the most reliable and detailed estimates of AMR incidence currently available. These estimates were provided by the ECDC through the European Antimicrobial Resistance Surveillance Network (EARS-Net), which is the largest and most comprehensive system of AMR surveillance (Cassini et al., 2018[16]). As such, the OECD model is more data driven and its outputs are therefore likely to be more realistic.

It is important to acknowledge that a debate exists around the notion of a worst-case scenario analysis for AMR. While in theory it is possible to imagine a world in which antimicrobials are not effective, critics of previous attempts to model such a scenario point to the lack of empirical evidence and the fragility of the assumptions necessary to perform such analyses (De Kraker, Stewardson and Harbarth, 2016[1]).

The scientific limitations of this kind of scenario analyses are acknowledged. Nonetheless, from a public policy and economic perspective, modelling extreme situations, even if the probability of their realisation is small, provides useful indicators and tolls to stimulate research and debate. The findings can also help raise awareness about a threat such as AMR, encourage its prevention, and potentially inform the design of crisis response strategies.

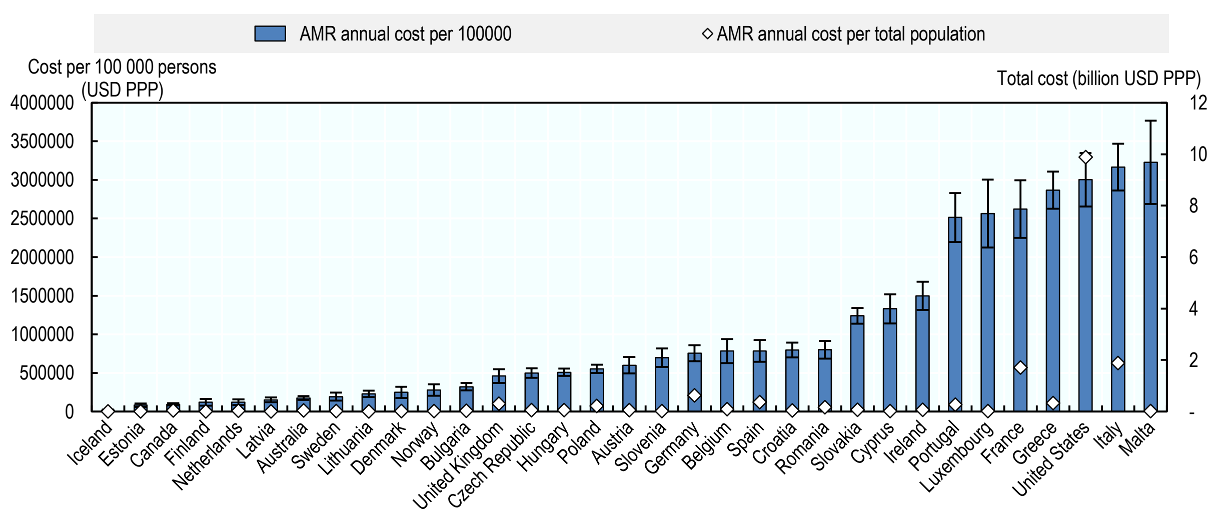
Figure 4.10. Deaths associated with AMR under a 100% resistance scenario



Source: OECD analyses based on the OECD SPHeP-AMR model.

StatLink http://dx.doi.org/10.1787/888933854991

Figure 4.11. Average annual health care expenditure associated with AMR under 100% resistance scenario



Source: OECD analyses based on the OECD SPHeP-AMR model.

StatLink http://dx.doi.org/10.1787/888933854839

Conclusion: still time to react!

AMR is now widely acknowledged as a global threat and a pressing health issue that requires rapid and coordinated international action. It took the efforts of many researchers, analysts and a variety of stakeholders, over many years, to bring AMR to the global stage and to convince the international community of its relevance and the need to act. The available evidence documents part of the potential impact and unpredictable effects of AMR on many sectors of society. But it also highlights many knowledge gaps, the scarcity of data and the fact that our current understanding of AMR – in terms of aetiology, epidemiology and economics – is relatively limited. By developing the microsimulation model described in this chapter, the OECD's aim is to contribute, from a public policy and economics perspective, to the knowledge-generating work currently underway to better identify and apprehend the challenges of AMR.

The main message that can be derived from the results of the OECD model is that the current health burden of AMR and its cost to health care systems are substantial but still relatively limited. However, the economic impact of AMR on the health care system is set to grow significantly over the next 35 years if no effective action is promptly put in place. There are also large differences between countries, with southern European countries carrying the heaviest burden of AMR. These differences are driven by local characteristics in terms of AMR epidemiology, but also by the existence (or absence thereof) and quality of AMR national action plans. The model estimates are broadly in line with the trends reported by previous studies, even though the specific results for each model output are not directly comparable to most of the existing estimates.

This analysis is conducted from a health care system perspective and evaluates, therefore, the health burden and expenditure directly incurred by health systems as a result of AMR. It is also based on a microsimulation approach, which allows a more refined analysis and is likely to produce more precise estimates of the impact of AMR. The model, however, does not assess the costs of AMR that might occur outside of the health care system (i.e. indirect costs). This differs from the approaches used by most of the recent macro-economic studies, whose results include indirect costs based on the analysis of the potential disturbances to the labour market and productivity in the global economy resulting from AMR.

The OECD model estimates, both in terms of the cost and health burden of AMR, are not necessarily large, particularly in comparison to the impact of other public health issues. For example the estimate of USD 1.5 billion in annual health care expenditure due to AMR in EU/EEA countries is dwarfed by the EUR 51 billion spent each year in the EU on cancer care (Luengo-Fernandez et al., 2013[30]). Treatment of lung cancer alone (around EUR 4.2 billion per year) represents almost three times the health care cost of AMR. In terms of mortality, the 33 000 AMR deaths per year compare to the 30 000 annual deaths due to oesophageal cancer – the sixth most common cause of cancer death in the EU (Ferlay et al., 2015[31]).

These comparisons, however, should not convey any sense of reassurance or diminish the urgency with which AMR should be tackled. The current health and economic burden of AMR is indeed currently lower than that of chronic conditions such as cancer, cardiovascular disease or mental health. Yet, in the long run, AMR represents a much bigger threat due to its complexity and potentially far-reaching and enduring health and economic consequences. The specificity of AMR is that it occurs in the realm of infectious diseases. It is caused by a multitude of different bacteria that can be transmitted, evolve constantly, and are genetically designed to ultimately adapt to treatment. Therefore, its evolution and effects are particularly difficult to characterise epidemiologically, and even more challenging to translate in terms of economic and public health impact.

The danger of AMR for high-performing health systems comes from this complexity and the fact that even high-income countries with low AMR infection rates and strong prevention systems in place, can be severely impacted by the spread of resistant bacteria that have developed in a different part of the world and for which no treatment is available. Another source of danger is the potential of AMR to undermine the safety of many invasive and complex medical procedures – i.e. the very characteristics of an advanced and high-performing health system – as shown by the analysis of AMR in the context of prophylaxis.

The reported results should be interpreted with caution and regarded as conservative. It is also important to bear in mind that the OECD model faces several limitations. For example, despite its wide scope in terms of infections and antibiotic-bacterium combinations covered in the analysis, the model does not include many other resistant infections due to lack of data and time constraints. Several assumptions were made to circumvent the many evidence gaps in the current scientific literature on AMR. For example, the assumption of non-transmission prevents the model from fully taking into account the potential effects of the rise in AMR seen in India or the People's Republic of China, on the modelled countries (see Chapter 3). Although, in the case of transmission, resistant infections dynamics, including transmission, are likely to be taken into account by the model through the ECDC incidence data, which reflect the transmission occurring in the population. Similarly, the potential long-term sequelae of AMR and associated costs were not taken into account in the model due to the limited available evidence.

The relatively contained health and cost impacts of AMR produced by the model are consistent with its focus on high-income countries. They confirm the argument made by previous analyses on the fact that most of the current impact of AMR is taking place in LMICs and set to continue to do so in the foreseeable future. The results likely also reflect the positive effects, in terms of AMR prevention, stemming from the efforts and policies put in place over the last ten years by many governments, health care providers and institutions at local and national levels, to reduce inappropriate use of antimicrobials and control the incidence of health care associated infections.

Overall, the OECD model shows existing efforts and initiatives to combat AMR need to be substantially amplified to reduce its current burden, but most importantly to prevent its future unpredictable and potentially catastrophic consequences. AMR is not a fatality. At this stage, the countries included in the model are in the best position to tackle it, as it still appears as a manageable health issue that can be addressed through the right set of policies and coordinated actions. The following chapters present an overview of the current international AMR policy landscape and provide a detailed assessment of the potential impact of selected AMR prevention policies in terms of effectiveness and cost-effectiveness.

Notes

[1] The bacteria included were: methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecium* (VRE), third-generation cephalosporin-resistant *Escherichia coli* (C3EC) and *Klebsiella pneumoniae* (C3KP).

[2] The CDC classified the included resistant bacteria into three categories according to level of concern: i) Urgent: *Clostridium difficile*, carbapenem-resistant *Enterobacteriaceae* and drug-resistant *Neisseria gonorrhoeae*; ii) Serious: multidrug-resistant *Acinetobacter*, drug-resistant *Campylobacter*, fluconazole-resistant *Candida* (a fungus), extended spectrum β-lactamase producing *Enterobacteriaceae*, vancomycin-resistant *Enterococcus*, multidrug-resistant *Pseudomonas aeruginosa*, drug-resistant non-typhoidal *Salmonella*, drug-resistant *Salmonella typhi*, drug-resistant *Shigella*, methicillin-resistant *S. Aureus* (MRSA), drug-resistant *Streptococcus pneumonia*, drug-resistant tuberculosis; iii) Concerning: vancomycin-resistant *Staphylococcus aureus*, erythromycin-resistant Group A *Streptococcus*, clindamycin-resistant Group B *Streptococcus*

[3] The analysis includes: methicillin-resistant *S. Aureus* (MRSA), *Escherichia coli* (*E. Coli*) and *Klebsiella pneumonia* (KP) resistant to third generation cephalosporins, the human immunodeficiency virus (HIV), and tuberculosis (TB).

[4] The model includes: *Escherichia coli, Klebsiella pneumonia, Staphylococcus aureus*, HIV, Tuberculosis and Malaria.

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Annex 4.A.

Annex Table 4.A.1. Characteristics of health economic models identified

Reference	ECDC 2009	RIVM 2011	KPMG 2014	RAND 2014	Teillant et al. 2015	Stewardson et al. 2016
Time perspective	2007	2007-2015	2012-2050	2011-2050	2010	2010-2011
Geographical scope	Europe	Europe	World	World	United States	Europe
Infections	MRSA, VRE, C3EC, C3KP, CRPA, PRSP	MRSA, C3EC	MRSA, C3EC, C3KP, HIV, TB, Malaria	MRSA, C3EC, C3KP HIV, TB, Malaria	MRSA, VRE, C3EC, C3KP, CRPA + other resistant bacteria s	3GCRE, 3GCSE, MRSA, MSSA
Infection site	Bloodstream, respiratory tract, urinary tract, skin/soft tissues	Bloodstream	Bloodstream, respiratory tract, urinary tract, skin/soft tissues	Not specified	Surgical site infections for 10 most common surgical procedures in the US	Bloodstream
Approach	prevalence-based attributable fraction	Prevalence-based attributable fraction	Prevalence-based attributable fraction	General equilibrium model	Prevalence-based attributable fraction	Cox regressions, Non-markov multi-stage model & micro-simulation
Scenarios	-	Linear trend / regression-derived	↑ 40% / 100% current resistance rates Doubling of current resistant rates & ↑ 40% / 100% of MRSA, C3EC. Pneumoniae, HIV, TB, Malaria	↑5% / 40% / 100% current resistance rates	↑10% / 30% / 70% / 100% current resistance rates	-
Outcomes	Infections, aLOS	Number of Infections, aLOS and extra deaths	Number of Infections, aLOS and extra deaths	Working age population loss	Number of Infections, aLOS and extra deaths	Number of Infections, aLOS and extra deaths
Cost inpatient/ outpatient	Both costs included	Only inpatient costs	Only inpatient costs	No cost included	No cost included	Only inpatient costs
Production losses	Included	Not included	Included	Included	Not included	Not included

Note: § The hospitals included in the analysis were located in Italy (3), Germany (2), UK (2), France (1), Spain (1), and Switzerland (1). HAIs: health care acquired infections; HIV: human immunodeficiency virus; TB: tuberculosis; MRSA: Methicillin-resistant *Staphylococcus aureus*; MSSA: Methicillin-susceptible *Staphylococcus aureus*; C3EC: *Escherichia coli* with resistance to third- generation cephalosporins; C3KP: *Klebsiella pneumoniae* with resistance to third-generation cephalosporins; PRSP:Penicillin-resistant *Streptococcus pneumonia*; ColRKP: *Klebsiella pneumoniae* with colistin resistance; CRKP: *Klebsiella pneumoniae* with carbapenem resistance ; CRPA: Carbapenem-resistant Pseudomonas *aeruginosa*; 3GCSE: third-generation cephalosporin susceptible *Enterobacteriaceae*, 3GCRE: third-generation cephalosporin-resistant *Enterobacteriaceae*, aLOS: average length of stay.

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