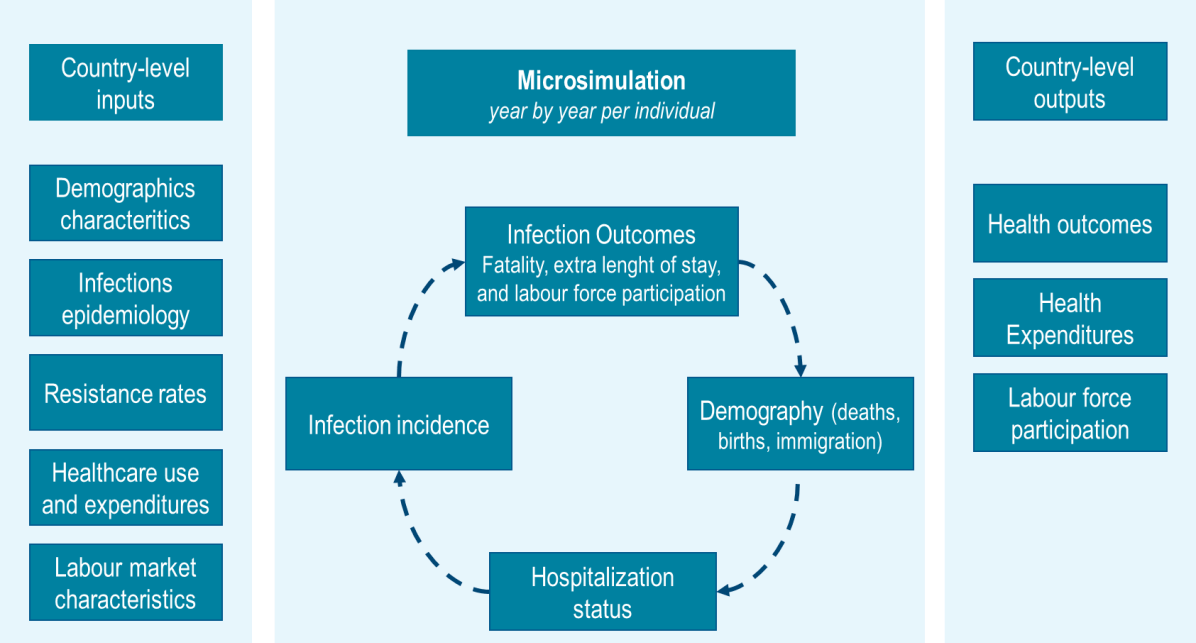
The OECD Strategic Public Health Planning (SPHeP) for antimicrobial resistance

The OECD Strategic Public Health Planning (SPHeP) for infectious diseases model is an advanced systems modelling tool for public health policy and strategic planning. The model is used to predict the health and economic outcomes of the population of a country or a region up to 2050 (Figure 1. 1).

For each country or region, the model uses demographic and risk factor characteristics by age and gender-specific population groups from international databases (see Demographic module) to generate synthetic populations, in which individuals are assigned demographic characteristics and risk factor profiles. Based on these characteristics, individuals have a certain risk of developing a disease each year (see the Disease module). These relative risks are based on different sources, depending on the diseases under consideration. For each year, a cross-sectional representation of the population can be obtained, to calculate health status indicators such as life expectancy, disease prevalence and disability-adjusted life years (DALYs) using disability weights (see Calculating disability weights).

In addition to considering the epidemiology of a country or region, the model is designed to consider the economic impact. Health care costs of disease treatment are estimated based on a per-case annual cost, which is extrapolated from national health-related expenditure data (see Healthcare costs). The labour market module uses relative risks to relate disease status to the risk of absenteeism, presenteeism, early retirement and employment. These changes in productivity and workforce participation are costed based on a human capital approach, using national average wages to calculate lost labour market outputs (see Labour market module).

Figure 1. 1. Graphical representation of the OECD model



Whenever a new country is included in the model, input data and model processing are calibrated and validated against national statistics to ensure that, in the absence of any new policy, the model depicts a reliable scenario *vis-à-vis* country data (see Model validation and uncertainty). The validated model can be subsequently used to model a range of scenario including, for example, the burden of disease and the impact of implementing new policies (see Modelling scenarios and interventions).

1.1. Demographic module

The demographic module is designed to create a synthetic population which reproduces population dynamics for a given country (from 2015-2050). The module initializes the demographic characteristics of every individual based on two key characteristics: i) birth date and ii) gender.

For each country, historical data on the population by age and gender in 2015 are used to initialize the population. The choice of the starting year depends on the availability of the epidemiological data, with the starting year normally set at the first year for which epidemiological data is available. This choice maximizes the historical period for which analyses are carried out and gives more flexibility in the choice of the timeline of the analyses that can start any year thereafter. The case weight of a simulated individual is defined by the number of simulated individuals divided by the total population in 2015. The population evolves until 2050 following a discrete time framework where each timestep is set to 2 months. The choice of the duration of the timestep, as well as of the case weight, considers the trade-offs between computational time to run the analyses and precision of the simulation. At each time-step, new individuals are added to the model (either as new-borns based on birth rates statistics or immigrants from other countries). Similarly, at each time-step, individuals can also exit the model through death or emigration.

1.1.1. Data inputs

Demographic data - populations, births, death rates, life expectancies - are provided by:

- Human Mortality Database (HMD): historical data for 37 countries (HMD, 2022).

- United Nations - World Population Prospects (UN-WPP): historical data (for every country not covered by HMD) and projections for every modelled country (United Nations, 2022).

Migration is taken into account as net-migration and is calculated ex-post by age/gender sub-category and considering population deaths (see Section1.1.4). This approach allows the model to more accurately replicate population dynamics consistent with international datasets.

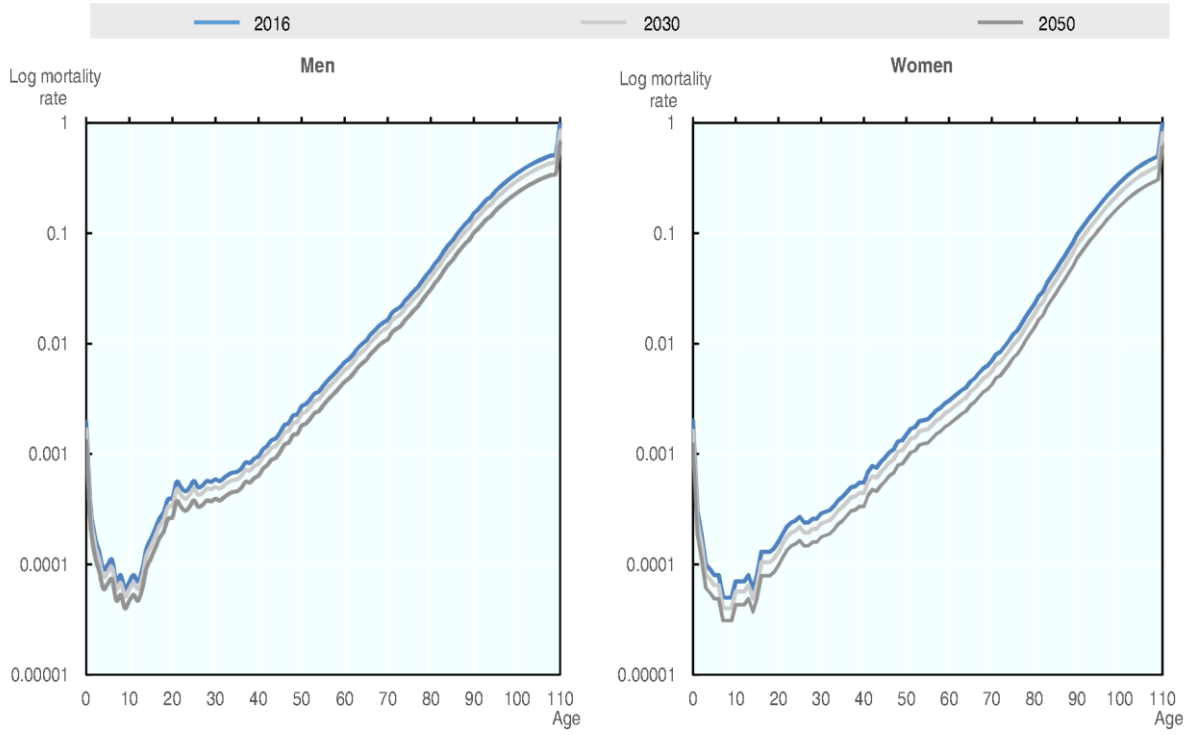
1.1.2. Death rates

Historical mortality rates are derived from the HMD (2022) for countries for which data are available and from the United Nations (2022) otherwise. For diseases included in the model, data on the cause-specific mortality are used. For all other conditions, mortality is captured in the residual mortality that is calculated as the difference between total mortality and the sum of cause-specific mortality.

1.1.3. Projections

Life expectancy projections, provided by the United Nations (2022), are used to project mortality rates until 2050. A scaling factor (multiplicatively) is applied to the last available mortality rates to match the expected level of life expectancy. Life expectancy projections are interpolated to provide yearly estimates and thus yearly estimates for the scaling factor. Figure 1. 2 illustrates the projection using data for Japan as example of how the process is carried out and curves are a translation of the latest available data, in this case, 2016.

Figure 1. 2. Projection of historical mortality rates until 2050 for Japan



Notes: The mortality rates are displayed in log-form.

1.1.4. Migration

Net migration represents the number of incoming migrants minus the number of outward migrants. As previously explained, historical net-migration is reconstructed from population estimates, capturing the difference of populations unexplained by mortality: for year y and age n, net migration flows is as follows:

$$NetMigration(n,y)=Population(n+1,y+1)-Population(n-1,y-1)-Deaths(n-1,y-1)$$

During the projection period, the age-gender pattern of the last 'historically reconstructed' migration flow is combined with projections of migration rates provided by UN-WPP to project immigration flows.

Positive migration flows are converted in a number of new individuals to add every year. Whereas negative flows are converted into hazard rate (year/age/gender-specific) of people leaving the country that exit the simulation.

1.1.5. Simulation

All individuals are simulated from 2015 if they are in the initial population or from their birth or their immigration arrival date to their exit event (by death or outward migration) or until 2050. The following characteristics are initialized i) birth year and ii) gender. Birth date (same for date of arrival) is, then, randomly chosen within the year.

All individuals are, then, simulated simultaneously over the time-step time period. At the end of each period, individual who have experienced an exit event by death or outward migration are removed from the simulation whereas new individuals entering the simulation due to birth or inward migration are integrated in the simulation. Those characteristics reproduce a country-specific demography.

Once they enter the country, migrants are modelled and simulated exactly the same as people who were born in the country. In other words, migrants have the exact same likelihood of experiencing the different modelled events as people born in the country. For each country, every simulated individual, native or migrant, has the same probability of experiencing an emigration event (i.e. to leave the country). Once individuals leave the country, they exit the simulation, thus their course of life no longer affects population outcomes (i.e. they cannot re-enter the country).

1.2. Disease module

The disease module is designed to replicate the epidemiological dynamics of the various infections included in the analysis. Diseases are modelled on the following epidemiological dimensions:

- Incidence representing the rate of occurrence of a disease
- Remission representing percentage of people going back to a state in which the survival prospect is the same of people with no disease
- Risk of *sequalae* representing the rate at which a patient with a given disease develops short or long-term complications
- Fatality representing the rate of occurrence of death due to the disease among those with the disease

Duration of infections is assumed to be lower than the time-step such that the full disease pathway (i.e. incidence, duration, remission or death) with the exception of complications occurs in a single time-step. At the end of the time-step the individual is either healthy, alive with certain complications or dead. Long-term sequelae from infections are modelled through a permanent disability weight that remains attached to the individual until the exit from the simulation.

Infection episodes are assumed to be independent from another such that previous infections (with or without long-term sequelae) do not impact the risk of developing new infections and the risk of hospitalization for those that have developed an infection.

In addition, the module includes a fourth epidemiological dimension referred to as residual mortality that captures the risk of death for any other disease not explicitly included in the model (e.g. chronic diseases and other infectious diseases).

1.2.1. Diseases and bacterial resistance

The bacteria included in the analysis were the following (Table 1. 1): *Acinetobacter* spp., *Campylobacter jejuni* (*C. jejuni*) & *Campylobacter coli* (*C. coli*), *Enterococcus faecalis* (*E. faecalis*) & *Enterococcus faecium* (*E. faecium*), *Escherichia coli* (*E. coli*), *Klebsiella pneumoniae* (*K. pneumoniae*), *Mycobacterium tuberculosis* (*M. tuberculosis*), *Pseudomonas aeruginosa* (*P. aeruginosa*), *Salmonella* spp., *Staphylococcus aureus* (*S. aureus*) and *Streptococcus pneumoniae* (*S. pneumoniae*). Based on the bacteria's characteristics, infections can be developed either in healthcare settings, or in the community, or, for some bacteria, in both healthcare and community settings. For each bacterium, a number of potential resistance strains are considered, which are selected based on prevalence rates – aiming to maximize highly prevalent strains at the global level – and data availability. Combinations of bacteria and resistance and the settings in which infections can be acquired are reported in the table below.

Table 1. 1. List of bug-drug combinations included in the model

Pathogens	Strain characteristics	Setting	
		Healthcare	Community
Acinetobacter spp.	*Acinetobacter* spp. excluding isolates with resistance to carbapenem and/or fluoroquinolones	x	
	Acinetobacter spp. with resistance to carbapenem	x	
	Acinetobacter spp. with multidrug resistance (i.e. three or more of piperacillin ± tazobactam, fluoroquinolones, ceftazidime and aminoglycosides) excluding carbapenem	x	
Campylobacter jejuni (*C. jejuni*) & *Campylobacter coli* (*C. coli*)	*C. jejuni* and *C. coli* excluding isolates with resistance to fluoroquinolones and macrolides		x
	C. jejuni and *C. coli* with resistance to fluoroquinolones		x
	C. jejuni and *C. coli* with resistance to macrolides		x
Enterococcus faecalis (*E. faecalis*) & *Enterococcus faecium* (*E. faecium*)	*E. faecalis* and *E. faecium* excluding vancomycin-resistant isolates	x	
	E. faecalis and *E. faecium* resistant to Vancomycin	x	
Escherichia coli (*E. coli*)	*E. coli* excluding isolates with resistance to third-generation cephalosporins and/or carbapenems	*x*	*x*
	E. coli. with resistance to carbapenem	*x*	*x*
	E. coli with resistance to third-generation cephalosporins excluding carbapenem	*x*	*x*
Klebsiella pneumoniae (*K. pneumoniae*)	*K. pneumoniae* excluding isolates with resistance to third-generation cephalosporins and/or carbapenems	x	x
	K. pneumoniae with resistance to third-generation cephalosporins excluding carbapenem	x	x
	K. pneumoniae with carbapenem resistance	x	
Mycobacterium tuberculosis (*M. tuberculosis*)	*M. tuberculosis* excluding isolates with multidrug resistance (i.e. at least isoniazid and rifampin) and extensive drug resistance (i.e. isoniazid, rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs: amikacin, kanamycin or capreomycin)		x
	M. tuberculosis with multidrug resistance (i.e. at least isoniazid and rifampin) excluding extensive drug resistance		x
	M. tuberculosis with extensive drug resistance (i.e. isoniazid, rifampin, plus		x

Pathogens	Strain characteristics	Setting	
		Healthcare	Community
	any fluoroquinolone and at least one of three injectable second-line drugs: amikacin, kanamycin or capreomycin)		
Pseudomonas aeruginosa (*P. aeruginosa*)	*P. aeruginosa* excluding isolates with carbapenem resistance and/or resistance to three or more of piperacillin ± tazobactam, fluoroquinolones, ceftazidime and aminoglycosides	x	
	P. aeruginosa with carbapenem resistance	x	
	P. aeruginosa with multidrug resistance (i.e. three or more of piperacillin ± tazobactam, fluoroquinolones, ceftazidime and aminoglycosides) excluding carbapenem	x	
Salmonella spp.	*Salmonella spp.* excluding isolates with resistance to fluoroquinolones, cephalosporins and resistance to three or more of ampicillin, chloramphenicol, streptomycin, sulphonamides and/or tetracycline		x
	Salmonella spp. with resistance to fluoroquinolones		x
	Salmonella spp. with multidrug resistance (i.e. three or more of ampicillin, chloramphenicol, streptomycin, sulphonamides and/or tetracycline, and/or cephalosporins) excluding fluoroquinolones		x
Staphylococcus aureus (*S. aureus*)	*S. aureus* excluding methicillin-resistant *Staphylococcus aureus* (MRSA) isolates	x	x
	Methicillin-resistant *S. aureus* (MRSA)	x	x
Streptococcus pneumoniae (*S. pneumoniae*)	*S. pneumoniae* excluding isolates with 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

As general rule, the development of an infection follows a standard 3-step approach:

- At the beginning of each step, any person is predicted to have access to healthcare services or not (as the time-step is 2 months, this allows individuals to have access multiple times to healthcare services for a given year). This probability is based on country-specific hospitalization rates derived from international databases (see section 1.3.2). If a person is hospitalized, then this person can develop a healthcare-acquired infection; otherwise, this person can only develop community-acquired infections under the assumption that individuals who are not hospitalized remain in the community.
- The probability of developing an infection during the time-step is, again, predicted at the beginning of the year based on the country, gender and age-specific incidence rates for each infection bacterium (see section 1.2.2). As previously mentioned, the probability of developing a healthcare-acquired infection is conditional to being admitted to a healthcare facility.
- The site of infection and the probability that the infection is resistant is calculated in the last step, based on the prevalence data (see Section 1.2.2). The site of infection and the probability of each site varies across the different bacteria considered in the analysis. As general rule, the following sites of infections are included in the analysis – with not all the sites necessarily available for all the bacteria: bloodstream, respiratory, urinatory, surgical site and other infection sites.

1.2.2. Data inputs

Data for incidence rates and prevalence rates come from different sources, depending on the country. Data for EU/EEA countries as well as the United Kingdom were provided by the ECDC (European Center for Disease Prevention and Control) to ensure consistency between OECD analyses and ECDC analyses on the health burden of antimicrobial resistance. A full explanation on the methodology used to collect and harmonize this data across countries can be found in the section “Methodology protocol to estimate incidence” of the appendix to the paper by Cassini et al (2018) and, for this reason, this explanation is not

reported in here. To note that data produced by ECDC are comparable across countries part of this database.

The analysis also includes analyses for countries whose data collection and harmonization may not fully comply with the methodology used by the ECDC. To the best of the knowledge of the authors, there is no similar description of the methodology available in the literature for those countries. For the remaining countries, epidemiological data to feed the model were provided by the following institutions: United States (CDC - Centers for Disease Control and Prevention); Switzerland (ANRESIS – Swiss Centre for Antibiotic Resistance); Japan (Drug resistance (AMR) One Health Platform (ncgm.go.jp); Türkiye (by WHO-Europe). In some cases, when not all the data were available (e.g. the proportion of infections by body site and the proportion of infections by age group or gender), average proportions across EU/EEA data were used on country-specific totals.

Projections on prevalence of antimicrobial resistance rates were calculated by the OECD using a methodology explained in the study by Cravo Oliveira Hashiguchi et al (2019), which is based on an ensemble model based on three classes of models including mixed-effects linear regression, exponential smoothing with an additive damped trend and a random forest. It should be noted that these forecasts do not incorporate any potential future policy action or intervention.

1.2.3. Disease models and attributable mortality

1.2.3.1. Generic model

The methodology to determine the health burden of infections follows the same approach used in the paper by Cassini et al (2018). Disease modules (or outcome trees) were developed for all the bacteria and bacteria-resistance combinations. This approach allows to account for all the notable disabilities related to infections, on the basis of published evidence.

A 'baseline' module was developed for the five sites of infection included in the analysis (i.e. bloodstream, respiratory, urinatory, surgical site and other infection sites). Information for the baseline modules were expounded from a previous study by Cassini et al (2016). Building on these baseline modules, specific data for antibiotic-resistant bacteria were retrieved via a systematic review of the literature to model the additional burden caused by resistant infections. Specifically, the additional burden of resistant infections was modelled in terms of attributable case fatality and attributable length of stay. The literature review focused on the effects attributable to these infections compared with a matched non-infected population or to a population infected with susceptible isolates of the same bacteria, when the first option was not available.

This document does not explain in detail the disease modules for susceptible and resistant infections caused by *Acinetobacter spp., E. faecalis & E. faecium, E. coli, K. pneumoniae, P. aeruginosa, S. aureus and S. pneumoniae*, given that all the information related to the methodology used to develop the modules and to prepare the input data can be found elsewhere. Specifically:

- The structure and the data used to feed each of the modules for the baseline modules can be found in the section "Final disease outcome trees" (pages 172-175) of the annex to the study by Cassini et al (2016).
- The structure and the data used to feed the modules for all the antibiotic-resistant bacteria can be found in the section "Final disease outcome trees" (pages 177-186) of the annex to the study by Cassini et al (2016).
- The methodology used in the systematic review to identify the data to simulate the additional burden caused by resistant infections as well as the results and the extraction tables can be found in the sections "Literature review report" (pages 3-141) and "Literature selection grids" (pages 142-167) of the annex to the study by Cassini et al (2016).

Information on the baseline modules for *Salmonella spp.* and for *C. jejuni & C. coli* can be found in the supplementary material number 3 of the study by Colzani et al. (2017). Input data to apply on the baseline module to model resistant variants for the bacteria were collected by the ECDC via a review of the literature. Findings are not yet in the public domain and the ECDC will possibly include this in future analyses.

1.2.3.2. The special case of M. tuberculosis

Incidence of *M. tuberculosis*, resistance rates, and is health outcomes are modelled using WHO TB burden estimates. The development of tuberculosis follows a standard 4-step approach.

- The probability of developing an infection during the time-step is, again, predicted at the beginning of the year based on the country, gender and age-specific incidence rates derived from the WHO TB burden estimates.
- **New versus retreated infections**: *M. tuberculosis* infections can be either a new infection or re-treated infection. Share of re-treated infections is derived from the surveillance database provided by WHO. When data are unavailable for a country, the average by WHO-region and income group is used. For simplification, the share of retreated infections is used to specify the infections instead of implementing the full disease pathway.
- **Resistance**: *M. tuberculosis* infections can be either susceptible, multidrug resistant or extensive-drug resistant. Using again the surveillance data provided by WHO, the probabilities where computed – probability of multidrug resistance in case of a new infection, probability of multidrug resistance in case of a retreated infection and probability of extensive drug resistance in case of a retreated infection. As extensive drug resistances were reported only for retreated cases, the probability of multidrug resistance in case of a new infection is set to be 0. As previous, if data are not available for a country, the average by WHO-region and income group is used.
- **Outcomes**: *M. tuberculosis* prognosis is assumed to be either death or full recovery without sequelae and the case fatality ratio depends on the resistance of the infection. For each of the resistance category it is computed using surveillance data on “tuberculosis outcomes” provided by WHO. When not enough data are available for a country, the average by WHO-region and income group is used.

1.2.4. Calculating disability weights

The health impact of diseases is calculated by producing outputs on various dimensions, including in terms of life spent with disabilities. To do so, and following international standards, the time spent with a disease is multiplied by a disability weight that varies according to the detrimental impact of a disease on people’s health. The less invalidating a disease is, the smaller is the disability weight. Consequently, the more invalidating a disease is, the bigger is the disability weight.

Disability weights used for the various disease statuses are derived from the study by Cassini et al (2016), which is based on data from the European disability weight study (Haagsma, 2015).Disability weights depends only on the site of the infection. Two disability weights are considered. First, the “short-term” disability weight, which reflects the quality of life associated with the duration of the infection and that can take two different values depending on the severity of the infection. Second, the long-term disability weight. If the infection can lead to different sequelae, the disability weight is computed using the weighted-average corresponding to the frequency of each sequela and their associated disability weights. The list of disability weights used for the various diseases can be found in Table 1.2. Impact on disability adjusted life years uses both the disability weights and the duration which varies according to the site, the pathogen and the resistance of the infection.

Table 1.2. List of disability weights used in the model

Site	Short term disability weight			Long term disability weight
	Mild	Moderate	Severe	
Bloodstream	N/A	0.125	0.655	0.0645
Respiratory	N/A	0.125	0.655	0.0645
Urinary	N/A	0.051	0	0
Surgical	N/A	0.051	0	0
Other	N/A	0.051	0	0
Diarrheal	0.073	0.149	0.2390	0
Tuberculosis	N/A	0.308	N/A	0

For short-term disability weight, as infections occurs in a relatively short period of time, an additive approach is used. When an individual experienced multiple sequelae with different disability weights, the multiplicative approach is used (Haagsma, 2011). The multiplicative approach is recommended for combining disability weights of simultaneously occurring health states. The approach allows for an increase of disability when health states are combined, while preventing the total disability level to become larger than 1, which would equal to a quality of life "worse than death".

1.3. Healthcare costs and use of healthcare resources

Use of healthcare services and healthcare costs are modelled following the standard approach used in other OECD SPHeP models, developing previous work on non-communicable diseases and on infectious diseases. The approach is broadly based and further develops the WHO-CHOICE methodology (WHO, 2013) and is based on an ingredient-based approach, in which items consumed in the use of hospital resources have standard costs depending on the country characteristics.

1.3.1. Healthcare costs

Healthcare costs refers to expenses incurred due to treating infections. Medical treatment covers both inpatient care and care in intensive care units. The cost of medical treatment was derived by multiplying the number of attributable hospitalisations by country-specific cost estimates of medical treatment. More specifically, and following the WHO-CHOICE approach, hospital costs are calculated as the product of the average cost for a hospital day in a given country (using a methodology originally provided by Johns, Baltussen and Hutubessy, 2003) multiplied by the average length of stay for each pathogen. The advantages and limitations of this approach have been described elsewhere (Graves et al., 2010). Resulting total costs are calibrated so to match national statistics in the *business-as-usual scenario*.

1.3.2. Use of healthcare resources

The probability of hospitalisation of any given individual simulated in the model is derived from hospital discharge rates reported across the country. For years and countries for which data on hospital discharges were unavailable, a random forest regression model was trained to predict the age- and sex-specific rates of hospital discharges. Using these data and predictions, the probability of hospitalisation for any condition were computed and assumed to be uniform across a given country. The probability of hospitalisation was then used to determine whether a given individual in the simulation would be exposed to the hospital environment.

A total of 18 variables were used in the model to predict annual hospital discharges by age, sex, and country. Demographic and economic predictors included population, sex distribution, age dependency

ratio, population density and gross domestic product. Health system predictors included current health expenditure, diphtheria-pertussis-tetanus immunisation coverage, measles immunisation coverage, hepatitis B immunisation coverage, influenza immunisation coverage, tuberculosis incidence, incidence of infectious and parasitic diseases, incidence of septicaemia, number of physicians, number of doctor consultations per capita, number of hospitals, number of hospital beds, and density of acute care beds. Input data were obtained from the World Bank (2022) and OECD (2022) databases as well as the UN World Population Prospects 2019. Missing data were imputed using multivariate imputation, which models each variable with missing values as a function of other variables.

Hospital discharges per 100 000 population were predicted for countries and age groups over years 1999 to 2019 for which data are not otherwise available. Evaluation of the model revealed good performance with a coefficient of determination (R2) of 0.94 and normalized root mean square error (RMSE) of 0.03.

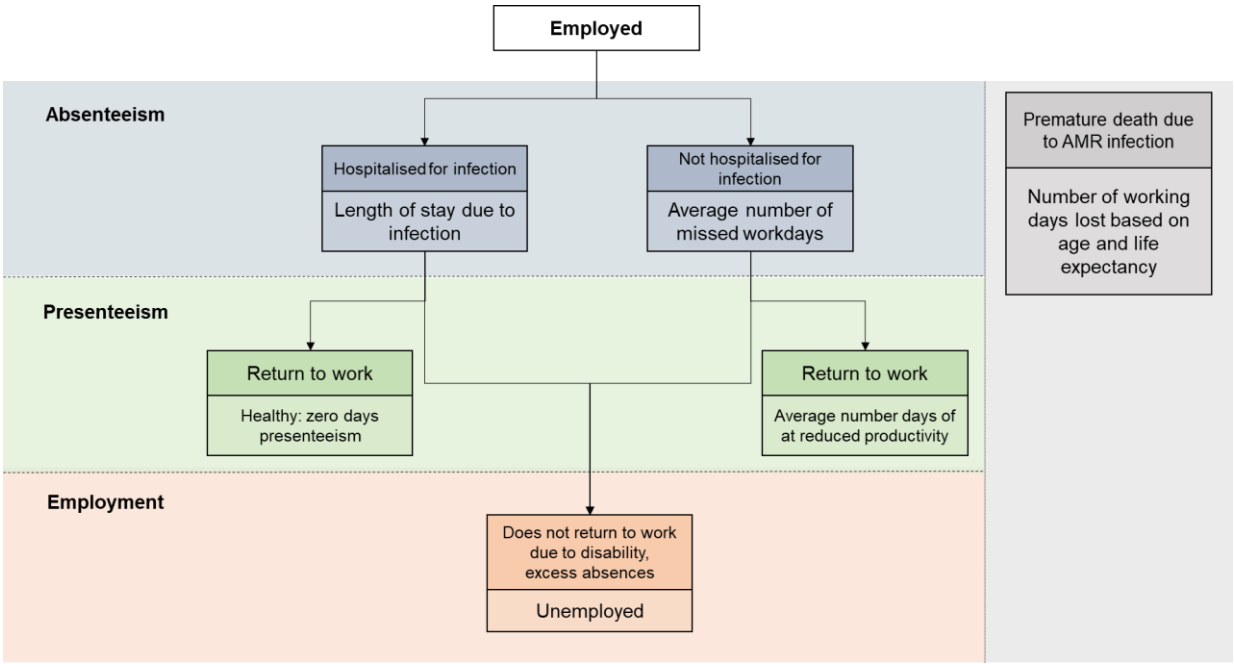
Based on the rate of hospital discharges reported by existing data sources and those predicted by the model, the probability of hospitalisation was computed using the standard equations converting rates to probabilities. The assumption underlying this procedure is that the flow of inpatients into the hospital parallels that of patients being discharged from facilities during a single time-step of the model.

1.4. Labour market module

The labour market module is designed to complements outputs of the health module by evaluating how resistant and susceptible infections affect the following three dimensions (Figure 1. 3): (i) absenteeism (including sick leave), (ii) presenteeism and (iii) employment rate. Early retirement, the fourth dimension normally used to evaluate the total workforce productivity in models as part of the OECD SPHeP framework was not included in this model, considering that no sufficient evidence was found to feed this analysis. All these measures are used to calculate temporary losses in productivity due to ill health. In addition, the model takes into account permanent losses of workforce productivity due to premature mortality. This is calculated as a reduction of the human capital (i.e. number of people in the working age population that are employed in the business-as-usual scenario).

Through these outputs, the model allows for an estimation of productivity loss due to illness caused by infections, which in this context, refers to output loss resulting from work absence and/or reduced labour input due to sickness as opposed to lost individual income (Kigozi et al., 2017). To be consistent with other similar analyses carried out on non-communicable diseases, productivity costs are limited to the context of paid work. Changes in the labour supply and workforce productivity are translated to monetary losses using the human capital approach, in which reductions in productivity as measured by the appropriate unit of duration of work foregone due to illness (e.g. day, month) are multiplied by the national average wage.

Figure 1. 3. Framework to determine inputs for labour market module



1.4.1. Absenteeism

Absenteeism refers to the time or number of workdays missed due to illness (Kigozi et al., 2017). The module outputs the number of additional absentee days due to infections. For infections requiring hospitalisation, the length of the hospital stay is considered to be the number of absentee days for a particular individual. For infections in which infected individuals are not admitted to the hospital, the average number of missed workdays due to illness is considered absentee days.

Review of the academic literature examining the impact of infectious diseases on absenteeism resulted in at least 17 studies reporting a duration of absenteeism among ill patients. The majority of articles studied absenteeism related to influenza or influenza-like illnesses. Because of the challenges discerning viral and bacterial infections based on symptoms alone, it is probable that some illnesses characterised by flu-like symptoms are, in fact, caused by bacterial infections. For this reason and due to the dearth of studies on bacterial infections and absenteeism, values for number of missed workdays due to influenza and influenza-like illnesses are used to inform the model inputs on absenteeism.

Susceptible respiratory infections reported an average of 12.9 absentee days (range 5-14 days), urinary tract infections reported an average 3.09 days (range 2.29-3.89 days), and other body site infections reported an average of 2.8 days (range 0.99-5.8 days). Infections caused by bacteria resistant to antibiotics generally reported an additional two to four days of absenteeism compared to susceptible infections. These values are used to inform absenteeism for non-hospitalised infections. For types of resistant infection for which data are unavailable, it is conservatively assumed that the number of days of absenteeism for non-susceptible infections is comparable to that of susceptible infections.

1.4.2. Presenteeism

Presenteeism, defined as the time or number of days an individual works with limitations (i.e. reduced productivity) due to illness, has rarely been studied in economic evaluations (Pritchard and Sculpher, 2000). Reviews of the literature suggest that presenteeism generates significantly higher cost estimates

than does absenteeism, emphasizing the importance of considering the role of presenteeism in efforts to appropriately estimate the value of interventions that affect worker productivity (Kigozi et al., 2017).

Accurately estimating the role of presenteeism is plagued by limited research and data, particularly with respect to antimicrobial resistance. There are limited data available to inform the number of days employees engage in presenteeism as a result of infections caused by bacteria resistant to antibiotics. Research on presenteeism is also based on self-reported information, which can be subject to bias. Surveys on presenteeism collect self-reported information on the number of days an employee is present at work while sick as well as an employee's estimated productivity level compared to their productivity when healthy.

A systematic review on the prevalence, reasons and risk factors for workplace presenteeism attributable to infectious illness published in 2019 included 24 studies, 20 of which were survey-based, and reported prevalence rates of presenteeism ranging from 35% to 97% among study participants (Webster et al., 2019). Most studies on presenteeism focus on influenza-like illnesses, respiratory tract infections, and general symptoms of infectious illness. A longitudinal study of older adults in the United States reported an average of 21 days of workplace presenteeism due to community-acquired pneumonia (Wyrwich et al., 2015). Presenteeism associated with the common cold and influenza-like illnesses was between 5.9 hours and 3.5 days per episode (Bramley, Lerner and Sarnes, 2002; Keech, Scott and Ryan, 1998). Urinary tract infection was associated with an average 3.45 days of workplace presenteeism (Wagenlehner et al., 2018). These values have been used to inform the baseline data inputs for the labour market module of the model.

There is no evidence quantifying the differential impact of resistant infections on workplace presenteeism. However, presenteeism arguably occurs primarily among those with non-severe illness and who do not require hospitalisation. It is assumed that people return to the workplace upon reaching a certain productivity threshold (i.e. upon beginning to feel better) and that this threshold is similar on average across the population. At such a point, assuming that the time to full health is similar for non-severe susceptible and non-susceptible infections, presenteeism will be for these individuals will be similar. Model inputs outlining presenteeism for community-acquired, non-hospitalized susceptible and non-susceptible infections, therefore, are the same. Critical differences between susceptible and resistant infections are observed in absenteeism rather than presenteeism.

On the other hand, severe infection – whether susceptible or resistant – increases the likelihood of hospitalisation. There is a lack of research on the duration of presenteeism following hospitalisation for illness. For this reason, upon being hospitalized in the model, it is assumed that the individual will return to work only upon reaching full health and productivity (i.e. zero days of presenteeism).

To determine productivity loss over the duration of presenteeism, it is necessary to understand to what extent productivity has been limited during this time. Participants in a study of the effects of influenza vaccine on presenteeism reported that their productivity level during days of reduced productivity was 50% (range 20-100) (Nichol, Mallon and Mendelman, 2003). Because the symptoms of non-severe influenza are often similar to that of bacterial infections, for the purposes of the model, 50% has been used as the proportion of productive time lost due to infection. Productivity costs attributable to presenteeism were also computed according to the human capital approach, accounting for reduced levels of productivity over the duration of presenteeism.

1.4.3. Employment rate

National employment rates from Eurostat and the International Labour Organization (ILO) inform simulated individuals' initial employment status. Morbidity and premature mortality due to bacteria resistant to antibiotics contribute to changes in the employment rate over time. For example, a simulated person may change from employed to unemployed status as a result of an excessive number of absent workdays due to infections resistant to antibiotics.

A friction period or the time until another worker fully replaces an absent worker has not been considered in previous studies. Failing to assign a friction period in practice assumes that absent workers will not be replaced by previously unemployed individuals, thereby reducing the labour supply over time. Similar to other models in the literature, the model does not currently implement a friction period, assuming that absence from work due to infection is generally not long enough for a worker to be replaced (ECDC and EMEA, 2009).

1.4.4. Sick leave

Characterising how sick leave plays a role in labour market outcomes is another dimension by which to understand the impact of infections. Depending on the country, sick leave will be paid by employers and/or governments. In either case, these losses in productivity add societal costs, while failing to generate outputs of value for those costs. When considering impacts on labour supply, employer and/or government policies often provide an allotted period of sick leave, after which period, the employer can dismiss the worker and the individual will become unemployed. Through this mechanism, cases of prolonged absence from work due to infection may contribute to changes in employment rate. Based on the average duration of sick leave by country and availability of such information, the costs attributable to paying sick leave either by employer or governments can be computed. It will thereby be possible to understand the proportion of estimated productivity costs that is attributable to paid sick leave.

1.5. Model uncertainty and validation

Significant efforts are made to ensure that findings from the model correctly represent the grade of uncertainty surrounding the input data and the effectiveness of interventions. Similarly, a number of validation and calibration steps are taken to ensure the correctness of outputs. With regards to this, and consistently with other analyses carried out using the OECD SPHeP model, outputs of the model are assessed by using both internal and external validation mechanisms.

1.5.1. Modelling uncertainty

Simulation uncertainty was calculated by running both the *business-as-usual* and intervention scenarios independently and randomly 20 times. This process resulted in 20 independently drawn subsamples. Each intervention scenario was run nine times in order to calculate the uncertainty associated with each modelled intervention. In each of these runs, the effectiveness value used in the analysis was set such that it was uniformly distributed between the minimum, middle and maximum values of the 95% confidence intervals of relative risk values calculated based on systematic reviews of the literature and meta-analyses. The middle value of the effectiveness of each intervention and its 95% confidence intervals were estimated by quantifying the difference between the i^th subsample of the *business-as usual scenario* with the i^th subsample in the intervention scenario, where i was comprised between 1 and 20 (the mid-effectiveness of each intervention and its 95% confidence intervals considered both the simulation and intervention uncertainty). This process was repeated nine times – one for each draw of the intervention effectiveness – each time maintaining the same value for the i^th subsample in the *business-as-usual scenario*. In the final step, the middle value of the effectiveness of the intervention and its 95% confidence intervals were derived on the 180 non-independent subsamples by using the quantile estimation from a sample methodology.

1.5.2. Model validation

Model outputs are validated by using both internal and external validation mechanisms.

Internal validation is carried out by comparing data inputs used to feed the model against the same dimensions produced to by the model. In principle, at the net of the uncertainty produced by the sampling process (see Section 1.5.1) a model is validated when these two dimensions coincide, meaning that the model correctly predicts its input data. The process is mainly used to validate the mechanics of the model (i.e. all the algorithms and code are correctly written) and the correctness of the feeding process of the input data to the model

Figures 1.4 through 1.11 report the number of infections by country comparing input data and output data produced by the model. At the net of the noise caused by, for example, sampling and statistical rounding, outputs from the OECD SPHeP-AMR model match well input data for all the antibiotic-bacterium combinations and consistently across countries.

Figure 1. 4. Hospital-acquired *Acinetobacter* spp.: comparison between input cases and model output cases for 2016

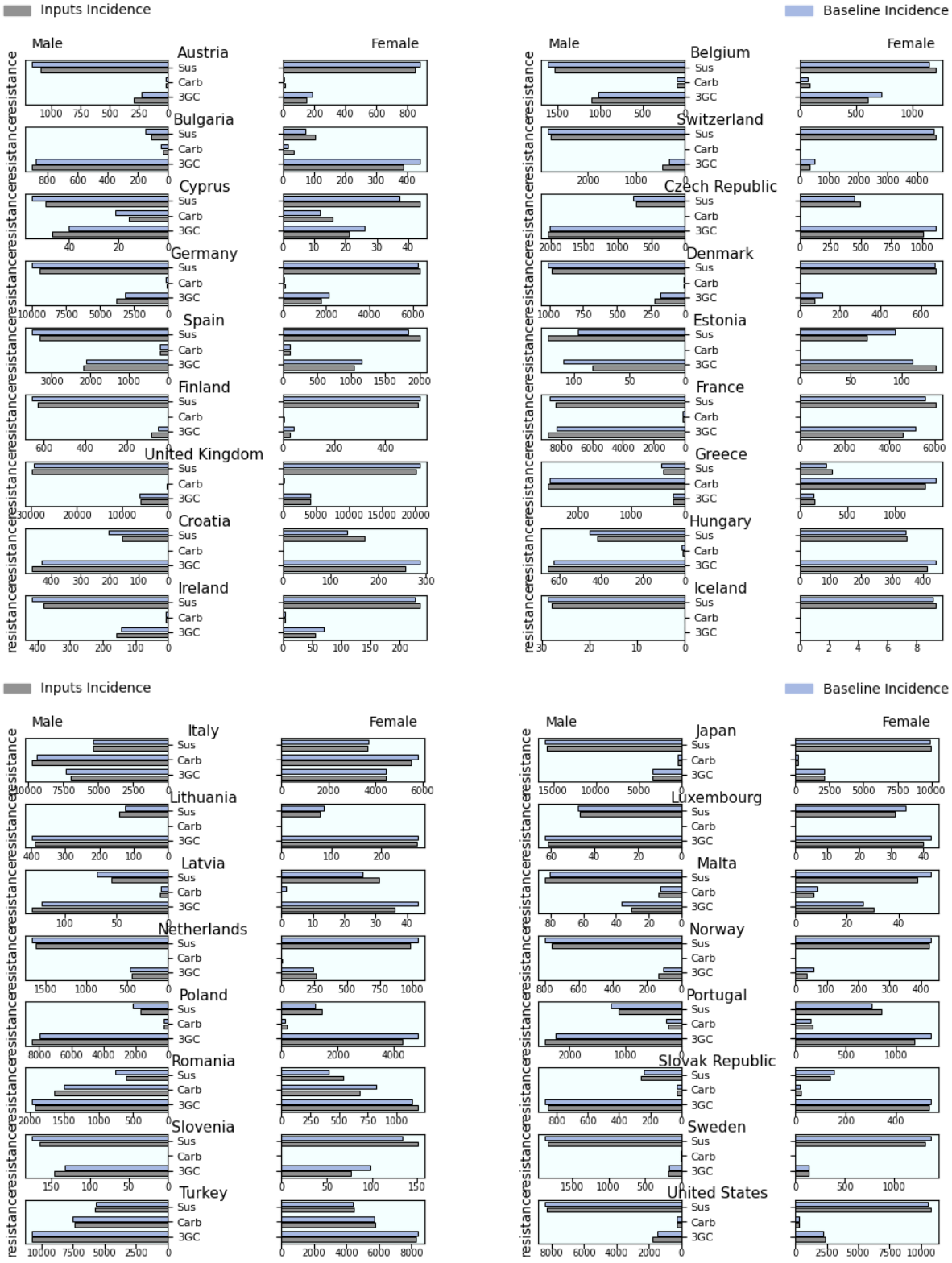
Source: OECD estimates and input data sources described in section 1.2.2.
Note: Sus: Susceptible cases, MD: Multi drug resistant cases, Carb: Carbapenem resistant cases.

Figure 1. 5. Hospital-acquired *E. coli* spp.: comparison between input cases and model output cases for 2016

Source: OECD estimates and input data sources described in Section 1.2.2

Note: Sus: Susceptible cases, Carb: Carbapenem resistant cases, 3GC: 3rd generation cephalosporins resistant cases.

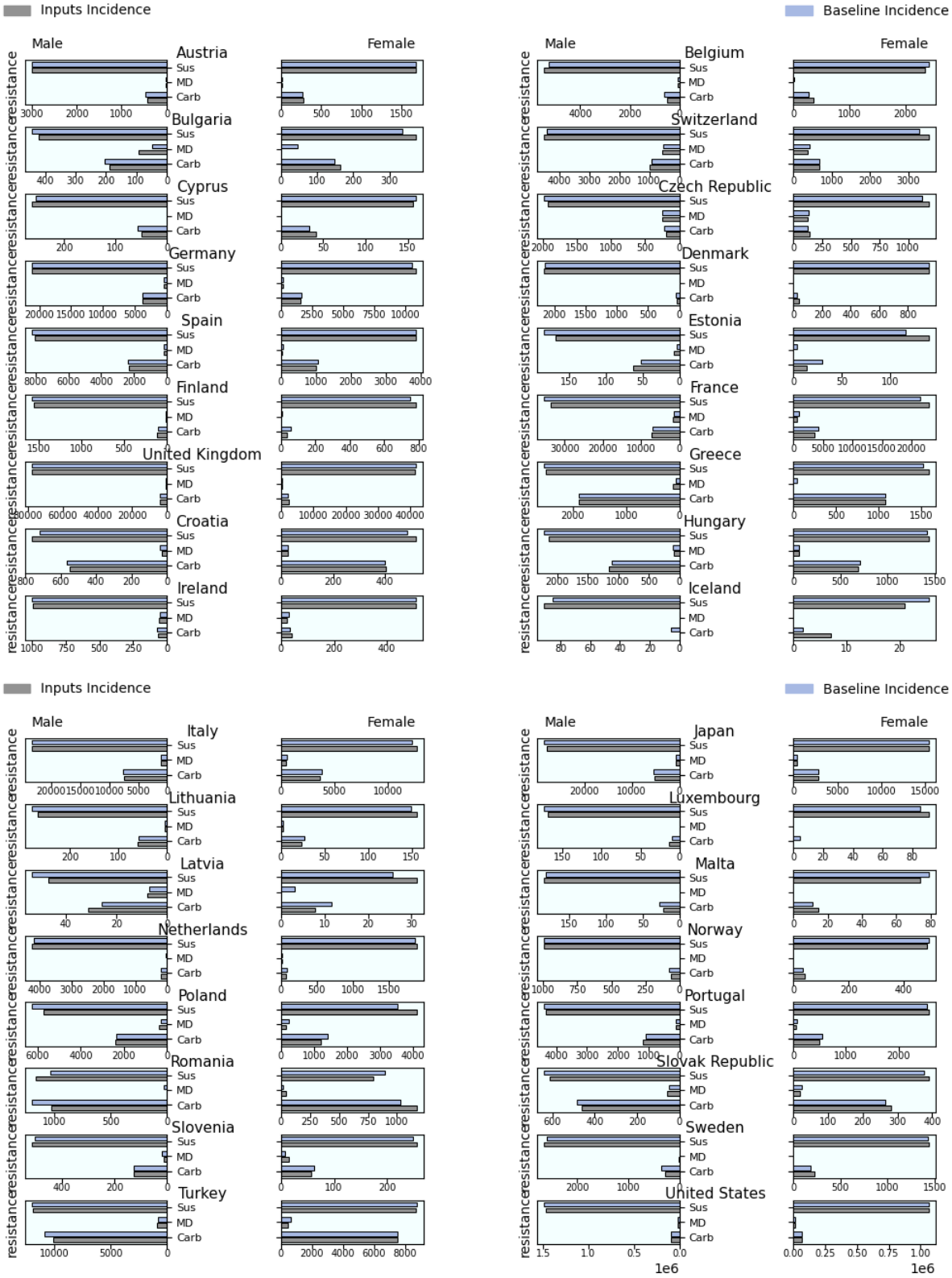
Figure 1. 6. Hospital-acquired *K. pneumoniae:* comparison between input cases and model output cases for 2016



Source: OECD estimates and input data sources described in Section 1.2.2

Note: Sus: Susceptible cases, Carb: Carbapenem resistant cases, 3GC: 3rd generation cephalosporins resistant cases.

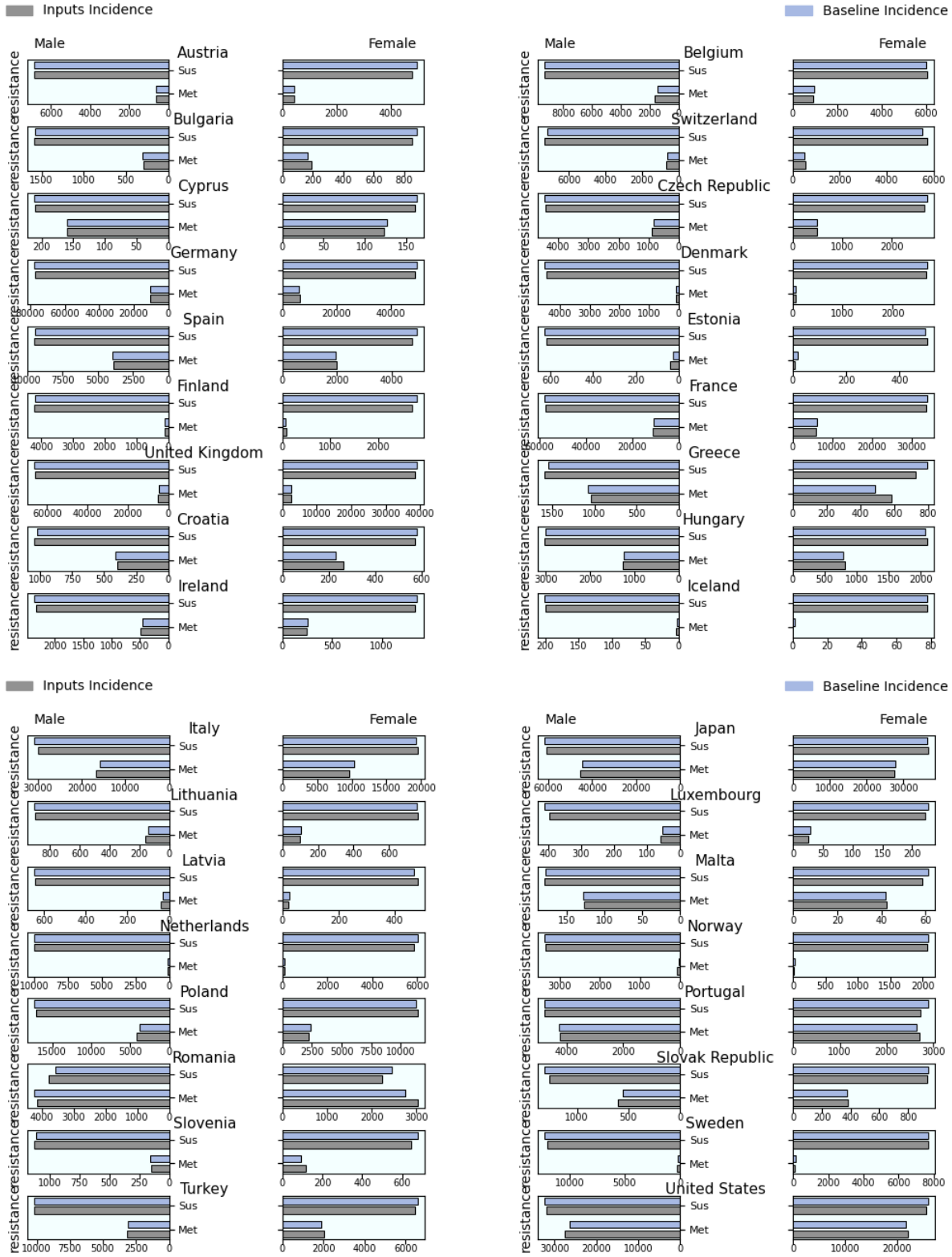
Figure 1. 7. Hospital-acquired *P. aeruginosap:* comparison between input cases and model output cases for 2016



Source: OECD estimates and input data sources described in Section 1.2.2

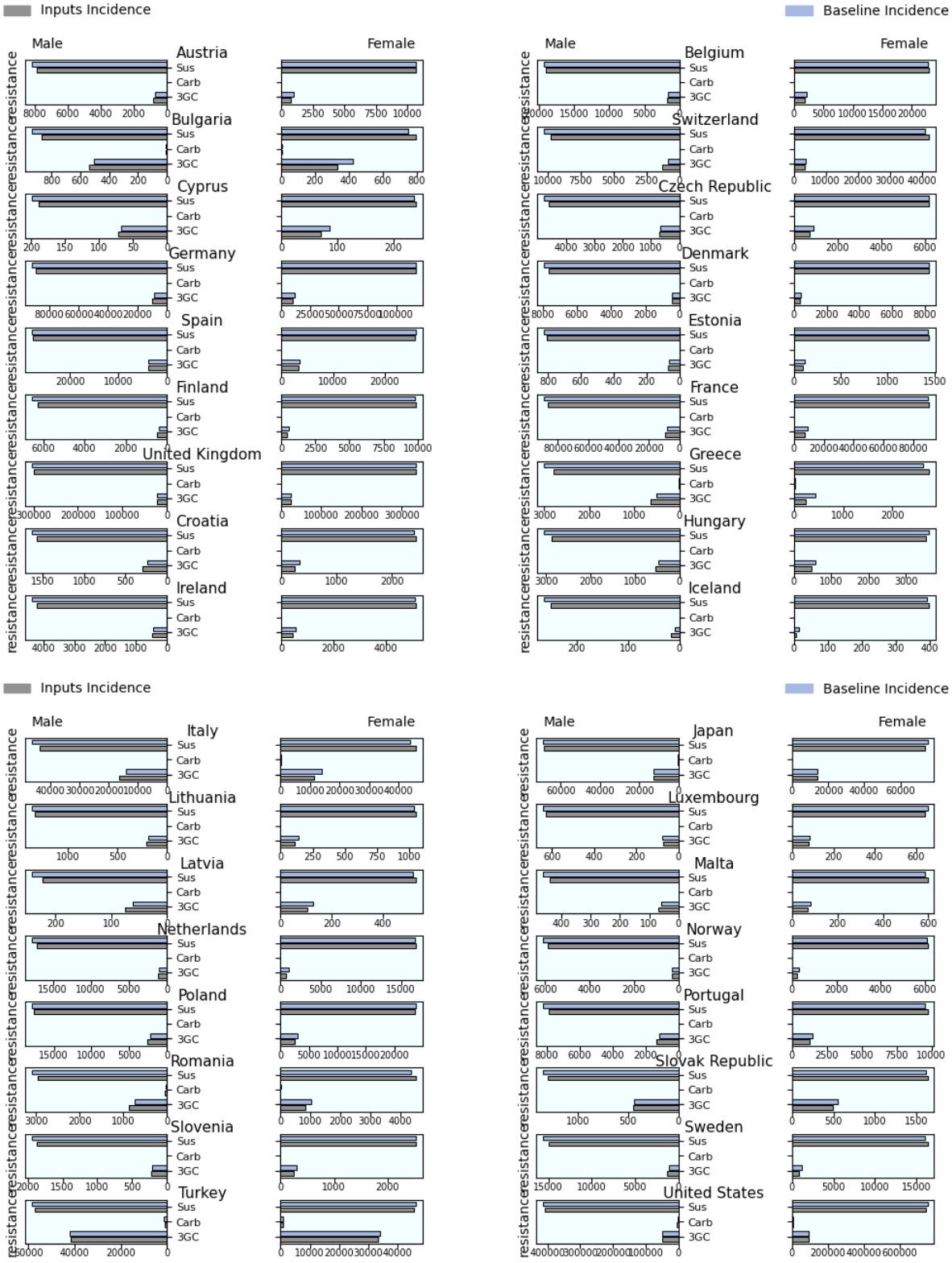
Note: Sus: Susceptible cases, MD: Multi drug resistant cases, Carb: Carbapenem resistant cases.

Figure 1. 8. Hospital-acquired *S. aureus:* comparison between input cases and model output cases for 2016



Source: OECD estimates and input data sources described in Section 1.2.2
Note: Sus: Susceptible cases, Met : Methicillin resistant cases.

Figure 1. 9. Community-acquired *E. coli:* comparison between input cases and model output cases for 2016



Source: OECD estimates and input data sources described in Section 1.2.2

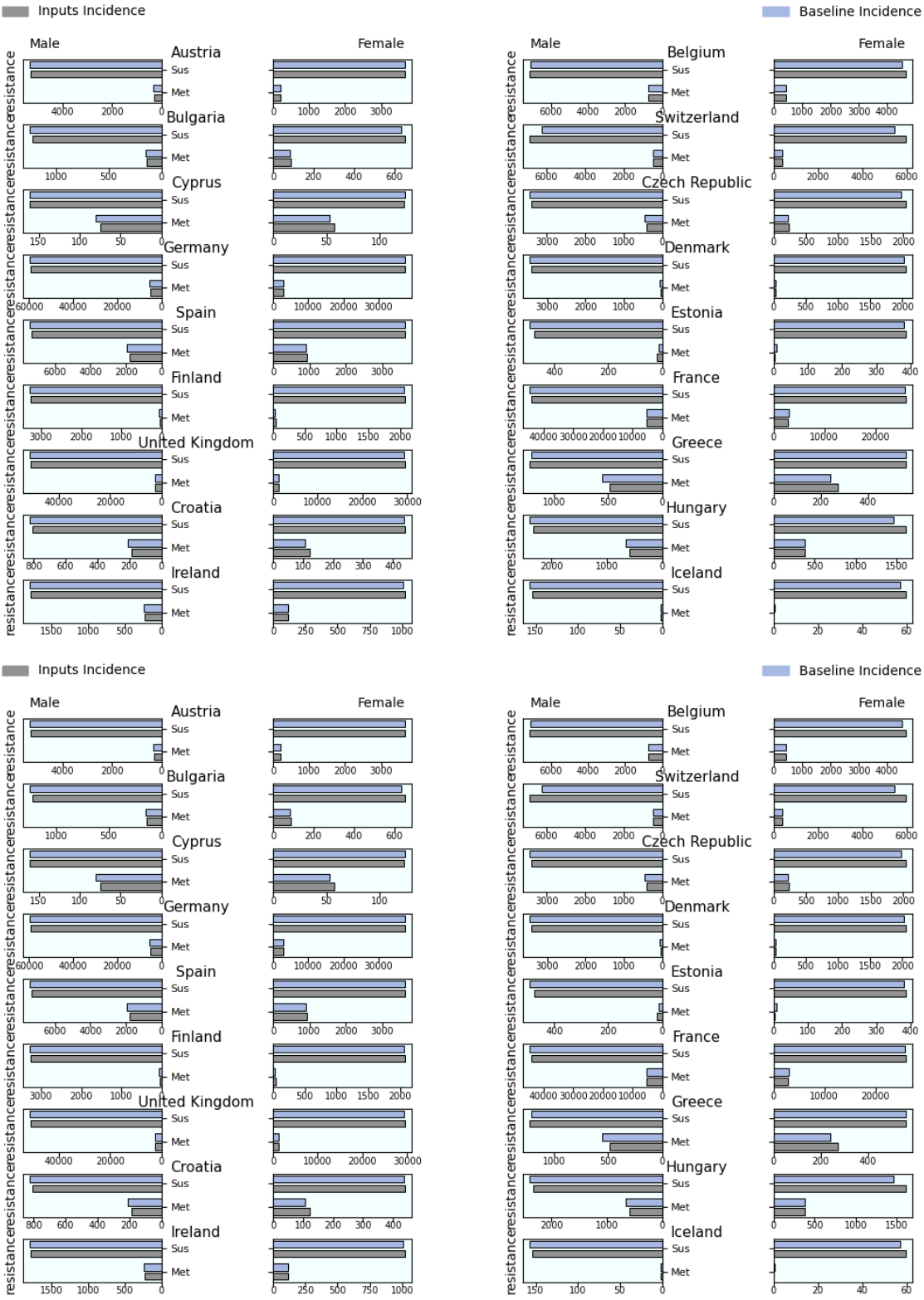
Note: Sus: Susceptible cases, Carb: Carbapenem resistant cases, 3GC: 3rd generation cephalosporins resistant cases.

Figure 1. 10. Community -acquired *K. pneumoniae:* comparison between input cases and model output cases for 2016

Source: OECD estimates and input data sources described in Section 1.2.2

Note: Sus: Susceptible cases, Carb: Carbapenem resistant cases, 3GC: 3rd generation cephalosporins resistant cases.

Figure 1. 11. Community-acquired *S. aureus:* comparison between input cases and model output cases for 2016

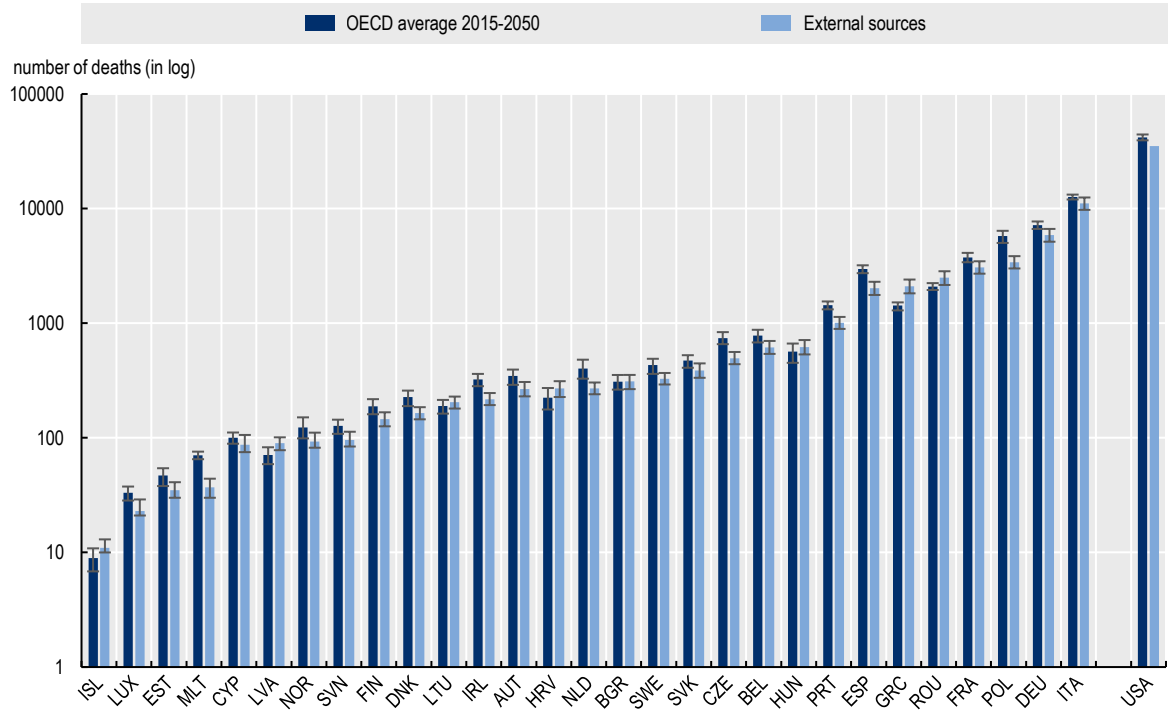


Source: OECD estimates and input data sources described in Section 1.2.2

Note: Sus: Susceptible cases, Met: methicillin-resistant. External validation is carried out by comparing outputs from the model against external outputs that were produced independently from the OECD SPHeP model for example, either by other models or vis-à-vis real-word statistics, if these are available. In the case of the analysis on antimicrobial resistance, the model was externally validated by comparing outputs from the OECD SPHeP model against outputs from a similar analysis produced by the European Centre for Disease Prevention and Control (ECDC, 2022) for EU/EEA countries and the United Kingdom as well as from an analysis on the United States produced by the Centers for Disease Control and Prevention (CDC, 2019).

The validation is particularly useful as the OECD SPHeP-AMR and the ECDC models use many of the same incidence data to feed their analyses. A significant difference across the two models is, however, that the OECD models is a dynamic model projecting AMR rates until 2050 while the ECDC model is a static model, calculating the retrospective burden of disease. For this reason, a cross-validation is possible, but some caveats apply (Figure 1. 12). Also of great potential for validation is the comparison of the outputs from the OECD SPHeP-AMR model against the analyses produced by the CDC, considering that the outputs are produced by using completely different – and independently developed – methodological approaches, although the OECD SPHeP-AMR model uses input data on the incidence of infections provided by the CDC.

Figure 1. 12. Total number of deaths due to resistant infections per year by country, comparison of outputs produced by the OECD and other sources



Note: Results are presented based on the sources of input data, with data for countries in the group on the left that are all from the same source and calculated with a comparable methodology. Results are not directly comparable for countries on the left- and right-hand sides of the panel due to the methodological differences in data collection and data extraction practices.
Source: (ECDC, 2022[1]) for EU-EEA countries, (CDC, 2019[2]).

Overall, outputs from the OECD SPHeP-AMR model matches well with outputs produced by both the ECDC and the CDC, confirming the goodness of the analyses of the OECD model as well as the validity of the approach. Differences between outputs can be explained by the following factors:

- OECD analyses calculate the average number of deaths per year, over the period 2015-2050, while ECDC and CDC analyses are calculated as the number of deaths in 2019. Given that OECD is taking into account the growth and the ageing of the population and that OECD forecast predicts a growth in most of AMR rates over the simulated period (e.g. by 9% in the European region), it is plausible that the average in OECD analyses results higher compared to a single year in other analysis that is at the beginning of the simulation;
- In the case of the United States, the set of antibiotic-bacteria combinations slightly differ from the one included in the OECD analyses. Specifically, OECD analyses include multidrug-resistant Acinetobacter and 3rd-generation cephalosporins resistant ESBL-producing Enterobacteriaceae that are not included in CDC analyses. Conversely, CDC analyses include drug-resistant N. gonorrhoeae, Candida auris, erythromycin resistant group A Streptococcus, drug-resistant Candida, drug-resistant Shigella, and clindamycin resistant group B Streptococcus that are not included in the OECD analyses. While no solid evaluation can be carried out, it is expected that once that these differences are taken into account the difference between the OECD and the CDC analyses becomes smaller than showed in the graph.

It is also important to note that the total number of deaths due to resistant infections per year showed in the graph above does not match the results presented in the publication. In fact, following the standard approach used for all the other modelling-based analyses in public health, the OECD findings are represented by the change in the number of deaths following the elimination of antimicrobial resistance. This number is a product of two dimensions: the number of deaths due to antimicrobial resistance avoided (i.e. what showed in the graph above) and the number of additional deaths due to other causes that would take place following the elimination of antimicrobial resistance. The second number is particularly significant given that elderly individuals are those most affected by antimicrobial resistance and these persons are also very likely to have other diseases (for example non-communicable diseases) that are likely to cause the death of the person, even in the absence of a resistant infection. The OECD report shows the total number of deaths as this is what would happen in reality following the hypothetical elimination of AMR. Conversely, analyses by ECDC and CDC only take into account the number of deaths attributable to AMR.

Conversely, outputs from the OECD SPHeP-AMR model are conservative compared to those generated by the European Antibiotic Resistance Collaborators (Mestrovic et al., 2022). In this study, deaths due to AMR in 2019 are estimated to average around 541 thousand under a scenario similar to the OECD's elimination scenario and around 133 thousand using a scenario similar to the replacement scenario, suggesting around 25-to-21-fold difference in mortality estimates compared to the OECD estimates. These large differences between the two analyses are driven primarily by the differences in the analytical scope, methodologies, and data sources. For example, the study by Mestrovic and colleagues covered 23 pathogens and 88 antibiotic-bacterium combinations. Whereas consistent with the analyses carried out by the ECDC (ECDC, 2022) and other studies carried out at the national level (CDC, 2022; Council of Canadian Academies, 2019), the OECD model focuses on a more limited set of 10 pathogens and 18 antibiotic-bacterium combinations that are regarded as priority across the OECD countries and EU/EEA countries. This study provides estimates for 53 countries included in the WHO European Region, many of which are shown to have substantially high AMR burden. In comparison, the OECD analysis focuses on 34 OECD countries and EU/EEA countries that generally estimated to have a lower AMR burden. A final significant driver of difference between the two studies is the number of infections used as input data to feed the two models. The OECD model uses estimates on the number of infections provided by EARS-Net and other official sources for non-EU/EEA member OECD countries including the Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR). In comparison, the European Antibiotic

Resistance Collaborators use a variety of sources combined through a meta-analytical approach. A direct comparison between the inputs of the two models is not currently possible, because data on the number of infections is not publicly available. However, it should be noted that, particularly for some specific antibiotic-bacterium combinations, the number of deaths estimated by the European Antibiotic Resistance Collaborators is significantly higher than the number of infections officially reported by countries included in the OECD analysis.

1.6. Modelling scenarios and interventions

To gauge the population-level effectiveness and the return on investment of interventions designed to tackle susceptible and resistant infections, interventions are evaluated against a "*business-as-usual*" scenario, in which age- and sex-specific exposures to risk factors remain unchanged during the simulation period and the provision of preventive and health services is implemented at the current levels, specific to a country. Thus, the "*business-as-usual*" scenario, which is used as baseline, assumes that no new policy relevant to the public health threat under consideration is implemented and that trends (e.g. demography, epidemiology for the public health threat under consideration, etc.) continue following the identified patterns using data up to the most recent ones.

Scenarios and interventions are modelled by applying a shock to the business-as-usual scenario, usually in the most recent year for which historical data are available. Depending on the available evidence, or the type of scenario that it is simulated, the shock can be applied to one or multiple parameters, with incidence rates for infections, or prevalence rates of resistant infections being among the most common parameters being shocked.

The comparison between the business-as-usual and the scenarios in which the shock is applied corresponds to the impact of the intervention or of the scenario. The comparison is carried out by considering all the relevant dimensions including, for instance, differences in health, health costs, labour market productivity and so on. (additional information on how the uncertainty is calculated can be found in section 1.5.1).

1.6.1. Parameters used to simulate scenarios (e.g. the burden of disease)

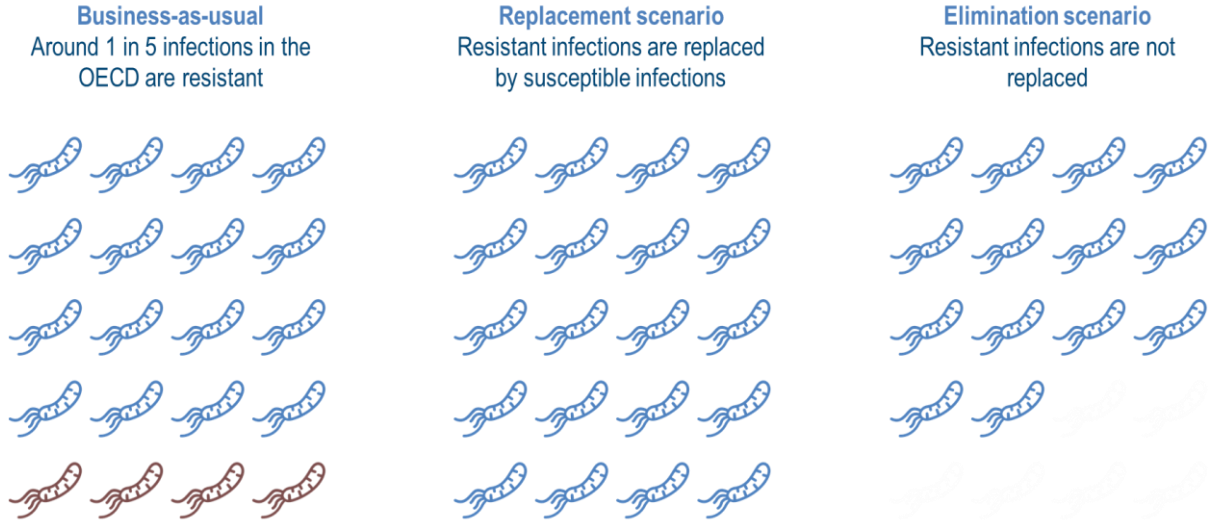
The impact of scenarios, such as the burden of disease scenarios, are evaluated by completing eliminating the public health threat. For example, this is done by shocking the incidence rate or the prevalence rates of specific infections, or of groups of infections, to zero. In the case of the analysis on antimicrobial resistance, two different burden scenarios are calculated following a decision taken by the OECD Expert Group on the Economics of Public Health (EGEPH).

- In a first scenario, the replacement scenario, the total incidence of infections (i.e. incidence of susceptible infections and incidence of resistant infections) is maintained constant as in the 'business-as-usual' scenario, while the prevalence of resistant infections is set to 0. In practice, this means that all the resistant infections are completely replaced by susceptible infections.
- In a second scenario, the elimination scenario, the incidence of susceptible infections is maintained constant while the incidence of resistant infections is set to 0 which results in a complete elimination of all the resistant infections.

The two burden scenarios can be seen as an optimistic scenario (i.e. the elimination scenario) and a pessimistic, or conservative, scenario (i.e. the replacement scenario) as their impact on population health and all the related dimensions is significantly different due to the lower (but still sizable) burden caused by susceptible infections. Both of the two scenarios are seen as potentially plausible given that there is no concluding evidence in the literature on which one is more likely to take place in the case of an elimination

of antimicrobial resistance. A graphical representation of the business-as-usual scenario as well as of the two burden scenarios is provided in Figure 1. 13.

Figure 1. 13. Graphical representation of the business-as-usual as well as of the two burden scenarios



1.6.2. Parameters used to simulate interventions

Interventions differ from scenarios as the inputs to feed the analyses are not hypothetical (e.g. the complete elimination of all resistant infections) but are based on empirical evidence or the literature. Differently from scenarios, the modelling of interventions aims to show the potential impact of scaling up to the desired level interventions already in place in the country, or to introduce innovative policy options or best practices. For this reason, modelling interventions is based on a more complex set of input data, coming from different sources.

Whether a particular policy intervention will work in a given context depends on a number of factors, some of which are likely to be location-specific. For example, the return on investment of an intervention may depend not only on its general efficacy but also on the local medical costs of treating related diseases and complications; demographic structure; epidemiological burden and the cost of intervention implementation. Within the OECD SPHeP models, interventions are modelled using the following four key parameters: i) effectiveness of interventions at the individual level, ii) effectiveness over time, iii) the Intervention coverage and iv) the implementation costs.

1.6.2.1. Effectiveness of interventions at the individual level

This parameter captures the extent to which the modelled intervention changes the probability of developing an infection or a resistant infection. For example, in the case of the analyses on infectious diseases (including on antimicrobial resistance), this may consist in changes in use of antibiotics, or better hygiene. Normally, this dimension is modelled as a decrease in the incidence or prevalence rates of infections, whether susceptible or resistant or both. Consistently with the guidelines decided by the OECD Expert Group on the Economics of Public Health (EGEPH), the evidence to model the interventions is taken from peer-reviewed studies privileging meta-analyses – preferably from randomised controlled trials – when these studies are available. Normally, the parameter is the same across countries, meaning that the effectiveness of the intervention at the individual level is assumed not to vary across countries for the individuals that are reached by the intervention. In other words, for example in the case of an intervention

targeting prescription rates of healthcare workers, the reaction to the intervention from a healthcare worker exposed to the intervention remains the same across countries. An exception to this rule is sometimes made when both OECD and non-OECD countries are included in the analysis. In this case, a different effectiveness may be used across these two regions, if there is strong suggestion from the available evidence that this is the case. Finally, it is to note that this assumption has been considered reasonable given that another parameter (intervention coverage – see section 1.6.2.2.) is used to model cross-country differences in implementation of the intervention.

It is assumed that interventions are maintained over time with repeated investments, trainings, media coverage etc. Effectiveness of the interventions is then assumed to be maintained over time. This is a strong assumption but reflects countries progress in the fight against AMR.

1.6.2.2. Intervention coverage

This composite parameter is based on three different inputs and aims to describe the eligible population as well as its incremental exposure level following the scale up (or the introduction) of the intervention. All the parameters used to model this dimension are intervention-specific and country-specific and are those explaining probably the most significant share of the cross-country variability in the results.

- A first parameter is based on the calculation of the current level of coverage of the policy. For innovative policies, this parameter is set to zero (i.e. as the policy is new, no target person in the population is already covered by the intervention in the business-as-usual scenario). For other policies that are already in place, an estimate of the level of coverage is based on available data, including the 2020-21 Tripartite AMR Country Self-Assessment Survey and studies based on the 2019 Hand Hygiene Self-Assessment Framework and the 2019 Infection Prevention and Control Assessment Framework Survey conducted by the WHO.
- A second parameter refers to the population group targeted by the intervention. While some interventions may target the whole population, others may only affect a subset of a population. For example, the intervention may target individuals in certain age groups or particular categories such as patients of primary care services. The modelling of the target group is based on the information contained in the literature about the modelled intervention – e.g. the description of the intervention contributing most of the evidence underlying the meta-analysis or the one with the value closest to the meta-analysis result.
- The final parameter takes into account the share of the target group that is actually exposed to the intervention. For example, an intervention targeting patients in primary care would only reach those who visit primary care providers and are willing to participate. Data to model this dimension come from various sources, mainly from datasets by OECD, WHO and the World Bank for statistics (e.g. those related to access to primary care services) and information contained in the studies used to model the interventions (e.g. on the share of targeted individuals accepting to be exposed to the intervention).

1.6.2.3. Implementation costs

Total costs of interventions are calculated as the sum of two budget lines: i) programme-level costs, which include administration, training and other activities taking place above the individual-level; and ii) expenditures at the individual-level, which include the material used to deliver the intervention on the ground including the use of goods and services such as rapid diagnostic tests, vaccination or other material (e.g. media material). A standardised, ingredient-based approach was used to calculate expenditures for both cost lines. The approach required information about the quantities of physical inputs needed and their respective unit cost. Where prices and inputs varied (e.g. due to the country-specific context), we attempted to use country-specific estimates. Conversely, the same inputs and costs were used across countries when this was considered a credible assumption. For example, the same price was used across countries for goods that are traded internationally, such as for soap and other material for hygiene. Similarly, the quantity

of material for a given target in the population or the amount of training provided to healthcare workers were maintained as a constant across countries given that the quantity of these inputs was based on standards (e.g. international guidelines).

Costs are calculated by taking a governmental and healthcare perspective. The governmental perspective is broadly defined in the sense that, for example, interventions that would be delivered by social health insurances, or by hospitals (independently from the ownership of the hospital) are included into the calculation of the costs. Conversely, costs that are covered by other agents due to the implementation of the policy (e.g. the cost for personal protective equipment bought by farmers following the improved farm hygiene intervention) are not included in the analysis.

Multiple sources of data were used to identify both the inputs and the unit price costs. The key data to model inputs and costs for programme-level costs were derived from the WHO-CHOICE database, as well as from forthcoming OECD publications on infectious diseases that focused on promoting hand hygiene and enhanced environmental hygiene in healthcare services. Costs are calculated by taking into account differentials in relative prices (as measured by differences in purchasing power parities and exchange rates) and are expressed in 2020 USD PPPs.

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