Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Economic burden of antimicrobial resistance:

An analysis of additional costs associated with resistant infections

July 2021

This research was part-funded through an extension of the grant agreement by the Health Research Board (HRB) for the HRB-Collaboration in Ireland for Clinical Effectiveness Reviews (HRB-CICER 2016-1871).

About the Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) is an independent statutory authority established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.
HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children, Equality, Disability, Integration and Youth, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.

- **Regulating social care services** — The Chief Inspector within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.

- **Regulating health services —** Regulating medical exposure to ionising radiation.

- **Monitoring services** — Monitoring the safety and quality of health services and children's social services, and investigating as necessary serious concerns about the health and welfare of people who use these services.

- **Health technology assessment** — Evaluating the clinical and cost-effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.

- **Health information** — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland's health and social care services.

- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health services, in conjunction with the Department of Health and the HSE.

Foreword

Antimicrobial resistance (AMR) occurs when micro-organisms adapt over time and no longer respond to antimicrobials. When micro-organisms become resistant to antimicrobials, infections become more difficult and more expensive to treat. AMR presents a significant threat to public health globally, as it is associated with substantial levels of mortality and morbidity. The financial cost of treating resistant infections places a significant burden on society, as patients infected with drug-resistant micro-organisms are more likely to remain in hospital for a longer period of time, to have poorer outcomes and to be unable to work.

Ireland's National Action Plan (iNAP) on Antimicrobial Resistance (2017-2020) was co-launched by the Minister for Health and the Minister for Agriculture, Food and the Marine on 25 October 2017. iNAP is based on the five strategic objectives in the 'World Health Organization (WHO) Global Action Plan on AMR' and recognises the critical importance of a One Health approach, in that human health, agriculture and environment sectors need to work together to effectively tackle AMR. One of the five key strategic objectives of iNAP is to 'promote research and sustainable investment in new medicines, diagnostic tools, vaccines and other interventions'. Aligned with this objective, is a strategic intervention to undertake an economic analysis of AMR. The purpose of this study was to estimate the current costs associated with select antimicrobial-resistant micro-organisms of public health concern in the public acute hospital setting in Ireland. The study will inform understanding of the economic costs associated with AMR in Ireland and the development of the second National Action Plan (2021 – 2025), iNAP 2.

Work on the economic analysis was undertaken by the Evidence for Policy Evaluation Team within the HTA Directorate in HIQA. A multidisciplinary Expert Advisory Group was convened to advise HIQA during the course of the study.

HIQA would like to thank its Evaluation Team, the members of the Expert Advisory Group and all who contributed to the preparation of this report.

Dr Máirín Ryan

Deputy Chief Executive and Director of Health Technology Assessment

Health Information and Quality Authority

About Evidence for Policy

The Evidence for Policy Team was established within the Health Technology Assessment (HTA) Directorate of the Health Information and Quality Authority (HIQA) in 2018 following a request from the National Patient Safety Office (NPSO) in the Department of Health. The Evidence for Policy Team is responsible for implementing evidence synthesis programmes to deliver high-quality evidence to support the development of policy by the Department of Health.

Funding

The Evidence for Policy Team is part-funded through an extension of the grant agreement by the Health Research Board (HRB) for the HRB Collaboration in Ireland for Clinical Effectiveness Reviews (HRB-CICER).

Acknowledgements

HIQA would like to thank all of the individuals and organisations who provided their time, advice and information in support of this analysis. In particular, HIQA would like to thank Stephen Murchan, the Health Protection Surveillance Centre (HPSC), Dr Alessandro Cassini, the World Health Organization (WHO), and the European Centre for Disease Prevention and Control (ECDC) for their assistance with providing access to data and templates.

Particular thanks are due to the Expert Advisory Group (EAG) and the individuals within the organisations listed below who provided advice and information.

The membership of the EAG was as follows:

EAG members	
Dr Máirín Ryan (Chairperson)	Director of Health Technology Assessment & Deputy Chief Executive Officer, Health Information and Quality Authority (HIQA)
Dr Patricia Harrington	Deputy Director of Health Technology Assessment, HIQA
Professor Martin Cormican	Health Service Executive (HSE) National Lead for Healthcare Associated Infection and Antimicrobial Resistance, Antimicrobial Resistance & Infection Control (AMRIC) Division of Health Protection Surveillance Centre (HPSC)
Rosarie Lynch	Head of Clinical Effectiveness, AMR and Surveillance, National Patient Safety Office, Department of Health

	(DOH)
Dr Teresa Maguire*	Head of Research Services and Policy, DOH
Christopher Ryan†	Head of Research Services and Policy, DOH
Bernie O'Reilly†	Chairperson, Patients for Patient Safety Ireland
Sean Egan	Head of Healthcare Regulation, HIQA
Dr Karen Burns	Consultant Clinical Microbiologist, Beaumont Hospital & HPSC, HSE
Dr Eoghan de Barra	Consultant in Infectious Diseases, Beaumont Hospital. Infectious Diseases Society of Ireland.
Thérèse Dalchin	AMRIC General Manager, Acute Operations, AMRIC Division of HPSC, HSE
Shirley Keane	Programme Manager, AMRIC Division of HPSC, HSE
Marie Philbin†	Chief Antimicrobial Pharmacist, AMRIC Division of HPSC, HSE
Professor Susan Smith	Professor of Primary Care Medicine, Royal College of Surgeons in Ireland (RCSI).

*Until November 2020. †Since March 2021

Membership of the Evaluation Team

Dr Kieran A. Walsh, Dr Christopher G. Fawsitt, Dr Kirsty O'Brien, Natasha Broderick, Dr Patricia Harrington, Dr Conor Teljeur, Michelle O'Neill, Professor Susan M. Smith and Dr Máirín Ryan.

Conflict of Interest

None declared.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

3GCREC	third-generation cephalosporin resistant *E. coli*
3GCRKP	third-generation cephalosporin-resistant *K. pneumoniae*
ABF	activity based funding
AIDS	acquired immunodeficiency syndrome
AR-DRG	Australian Refined Diagnosis Related Group
AMR	antimicrobial resistance
AMRIC	Antimicrobial Resistance and Infection Control
BCoDE	Burden of Communicable Disease in Europe
BSI	blood stream infection
CHEPA	Centre for Health Economics and Policy Analysis
CHO	community healthcare organisation
CI	confidence interval
COVID-19	coronavirus disease 2019
CPE	carbapenemase-producing *Enterobacteriaceae (Enterobacterales)*
CRE	carbapenem resistant *Enterobacteriaceae*
CSF	cerebrospinal fluid
CPI	consumer price index
CSO	Central Statistics Office
DALY	disability-adjusted life years
DRG	diagnosis related group
EAG	expert advisory group
EARS-Net	European Antimicrobial Resistance Surveillance Network

ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EMA	European Medicines Agency
ESBL	extended-spectrum beta lactamase
EQA	external quality assessment
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
EUnetHTA	European Network for Health Technology Assessment
GDP	gross domestic product
GLASS	Global Antimicrobial Resistance and Use Surveillance System
HPO	Healthcare Pricing Office
HIPE	Hospital In-Patient Enquiry
HIQA	Health Information and Quality Authority
HIV	human immunodeficiency virus
HCAI	healthcare-associated infection
HPSC	Health Protection Surveillance Centre
HRB	Health Research Board
HSE	Health Service Executive
HTA	health technology assessment
ICU	intensive care unit
iNAP	Irish National Action Plan on Antimicrobial Resistance
IPC	infection prevention and control
KPI	key performance indicator
KPMG	Klynveld Peat Marwick Goerdeler

LOS	length of stay
MDR	multidrug resistant
MRSA	meticillin-resistant *Staphylococcus aureus*
NICE	National Institute for Health and Clinical Excellence
NPHET	National Public Health Emergency Team
NCCHTA	National Coordinating Centre for Health Technology Assessment
OECD	Organisation for Economic Co-operation and Development
PICo	Population, Interest and Context
PPE	personal protective equipment
PPS	point prevalence survey
RAND	Research and Development corporation
RTI	respiratory tract infection
RQ	research question
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SPHeP-AMR	strategic public health planning for antimicrobial resistance
SSI	surgical site infection
TB	tuberculosis
UI	uncertainty interval
UK	United Kingdom
US	United States
UTI	urinary tract infection
VRE	vancomycin-resistant enterococci
WHO	World Health Organization
XDR	extensively drug-resistant

Executive Summary

Background to the request

Antimicrobial resistance (AMR) is defined as the ability of a micro-organism to stop an antimicrobial from working against it. AMR is driven largely by excessive and inappropriate use of antimicrobials in human and animal populations. Additionally the crucial role that the environment plays in the persistence and spread of AMR is increasingly being acknowledged, specifically in relation to water, sanitation and hygiene factors. Importantly, the resistant nature of infections can be transferred across humans, animals and the environment, and so the consequences of AMR go beyond the inability of an antimicrobial to work in a given individual.

AMR is a global public health concern; as standard antimicrobial treatments become ineffective, infections persist and spread, increasing morbidity and mortality, impacting on the both the individuals affected and society. Rising rates of AMR will make it increasingly difficult and expensive to control and treat infections and could affect the sustainability of some modern healthcare interventions. AMR also causes significant disruption to routine hospital services, as operating theatres and other settings need to be decontaminated and left vacant for a period of time after treating patients with resistant infections. The financial cost of treating resistant infections places a significant burden on society, as patients infected with drug-resistant micro-organisms are more likely to remain in hospital for a longer period of time, to have poorer outcomes and to be unable to work.

Economic evidence of the current cost of AMR could inform investment and policy prioritisation decisions, however, this evidence is currently limited in Ireland. The Evidence for Policy Team within the Health Technology Assessment (HTA) Directorate of the Health Information and Quality Authority (HIQA), was requested to carry out this economic analysis on behalf of the Department of Health.

Description and scope of the study

A literature review followed by an economic analysis was undertaken. The scope of the project was restricted to the costs of excess length of hospital stay associated with the following eight pathogens of concern, which were categorised into 16 discrete antibiotic resistance-bacterium combinations:

- *Acinetobacter* spp., Colistin-resistant
- *Acinetobacter* spp., Carbapenem-resistant (excluding isolates also resistant to colistin)
- *Acinetobacter* spp., Aminoglycoside- and fluoroquinolone-resistant (excluding

isolates also resistant to colistin and/or carbapenem)

- *Enterococcus faecalis* and *Enterococcus faecium (E. faecalis* and *E. faecium)*, Vancomycin-resistant
- *Escherichia coli (E. coli)* , Colistin-resistant
- *E. coli*, Carbapenem-resistant (excluding isolates also resistant to colistin)
- *E. coli,* Third-generation cephalosporin-resistant (excluding isolates also resistant to colistin and/or carbapenem)
- *Klebsiella pneumoniae (K. pneumoniae)*, Colistin-resistant
- *K. pneumoniae*, Carbapenem-resistant (excluding isolates also resistant to colistin)
- *K. pneumoniae*, Third-generation cephalosporin-resistant (excluding isolates also resistant to colistin and/or carbapenem)
- *Pseudomonas aeruginosa (P. aeruginosa)*, Colistin-resistant
- *P. aeruginosa*, Carbapenem-resistant (excluding isolates also resistant to colistin)
- *P. aeruginosa,* Resistance to three or more antibiotic groups (excluding isolates also resistant to colistin and/or carbapenem)
- *Staphylococcus aureus (S. aureus)*, Meticillin-resistant
- *Streptococcus pneumoniae (S. pneumoniae)*, Penicillin-resistant (excluding isolates also resistant to macrolides)
- *S. pneumoniae*, Penicillin- and macrolide-resistant (excluding isolates only resistant to penicillin).

Purpose of the study

The purpose of this study was to estimate the current costs associated with select antimicrobial-resistant micro-organisms of public health concern in the public acute hospital setting in Ireland. The perspective adopted is that of the publicly funded health and social care system in Ireland.

This costing study was undertaken in fulfilment of listed activities aligned with Strategic Objective 5 of Ireland's National Action Plan (iNAP) on Antimicrobial Resistance (2017-2020). Establishing the current cost of AMR is useful to inform

future investment decisions thereby promoting, and providing a metric against which to measure the use of proposed evidence-based, cost-effective solutions to challenges faced as a result of AMR. Additionally, this study presents a preferred standardised methodology for estimating the economic burden of AMR on public acute hospitals in Ireland, which may be used in the future by the Department of Health and other agencies. Hence, findings from this current study provide a baseline cost estimate upon which future iterations of this study can build. This is particularly relevant as Ireland moves towards the second National Action Plan for Antimicrobial Resistance 2021 - 2025, iNAP 2.

The following two research questions (RQs) were conducted:

- RQ1: What methodologies have been used to estimate the costs of AMR (including outbreaks) in acute hospital settings?
- RQ2: With respect to public acute hospital care in Ireland, what are the costs associated with AMR?

Expert advisory group

An expert advisory group (EAG) was convened for this study, comprising representation from key stakeholders including clinical experts, policy makers, service providers, patients and methodological experts. The role of the EAG was to inform the process and provide expert advice. One face-to-face and one online EAG meeting occurred.

RQ1: Literature review of methodological approaches

Estimation of the economic burden of AMR is of critical importance for policy-making, but is challenging. Widely diverging cost estimates have been reported in the literature and hence the true burden of AMR is unclear. The objective for this research question was to identify, and appraise the quality of, methods that have been used to estimate the costs of AMR (including outbreaks) in acute hospital settings. Findings from this research question informed the development of an appropriate methodology to estimate the current healthcare costs associated with AMR in the public acute hospital setting in Ireland. A targeted literature review was undertaken focussing on studies linked to four seminal systematic reviews, and supplemented by a comprehensive grey literature search and a database search of PubMed.

A total of 1,233 records were identified and screened, resulting in a finalised list of 27 studies included in this review. Of these 27 included studies, nine estimated the cost of outbreaks of antimicrobial-resistant pathogens, 17 estimated the cost of AMR in general at a population-level (henceforth called 'population & modelling studies')

and one study estimated the cost of both. A quality appraisal tool developed by the Welsh Public Health Observatory was used to assess the quality of the included studies. The quality of the included studies varied; some studies were found to have consistently high quality across all domains, whereas others, particularly outbreak studies, were poor in the majority of domains. The absence of sensitivity analysis and limited reporting of uncertainties were common weaknesses in most included studies.

Outbreak studies generally adopted a healthcare system/hospital perspective, and used predominantly a combination of top-down and bottom-up approaches to costing. Outbreak studies were mostly conducted in single wards or hospitals, and required in-depth data on unit cost and resource utilisation, as well as data on the organisational disruption that occurred as a result of the outbreak. These studies tended to combine the direct costs for the hospital in containing the outbreak, with the revenue losses associated with bed closures and elective surgery cancellations. The accurate costing of outbreaks is particularly challenging given the requirement for extensive local data. The only way to effectively ascertain these costs would be to survey and or interview individual hospitals directly. This is further complicated by the fact that outbreaks can often be contained within wards, and so activity may be transferred from an affected ward to another ward to mitigate revenue losses. The economic impact of AMR may also be mitigated by planning elective surgery in such a way as to minimise disruptions to an operating theatre. For example, by scheduling an operation involving a person with a resistant infection for a Friday, so that the theatre is closed for two days afterwards regardless, this means that any required decontamination measures do not result in any unplanned cancellations. Hence, in order to get an accurate picture of the overall impact of an outbreak, data may be required from multiple wards and operating theatres within a hospital.

Population & modelling studies varied much more substantially in terms of perspective, epidemiological approach and methodology. The analytical methods used included modelling, matching, regression, burden of disease/cost-of-illness, evidence synthesis, expert opinion, and various combinations of the above. In spite of these differences, there were a number of important similarities in the way population & modelling studies estimated and reported costs. For instance, most studies estimated the additional costs associated with treating resistant infections relative to susceptible infections, with outcomes commonly reported as the additional cost per bed day. Additionally, all of the population & modelling studies used predominantly top-down or econometric approaches, with some studies also incorporating bottom-up approaches.

A limitation of this review is that a pragmatic targeted search was undertaken as opposed to a systematic search, and so there is a possibility that some studies were

missed. However, a strength of the review is that a comprehensive range of costing methodologies were identified. Analysis of these provided detailed information to inform the development of an appropriate methodology to address the second research question.

Based on this review of international literature, there does not appear to be a universally accepted, or gold standard, approach to costing AMR. This reflects both the diverse models of health and social care delivery systems internationally, as well as the differing ways in which cost and resource utilisation data are collected. However, it is clear from the literature that the choice of costing methodology is largely influenced by the quality and type of data available. The three population & modelling studies that were assessed as having the highest quality overall were those by the Organisation for Economic Co-operation and Development (OECD), Bartsch et al. and Wozniak et al., all of which used simulation modelling approaches. The OECD approach has the advantage of using European AMR surveillance data and also uses an evidence-based burden of disease analysis that was developed by the European Centre for Disease Prevention and Control (ECDC), thus allowing for cross-country comparisons. This methodological approach formed the basis for the second research question, and was used to estimate the additional cost associated with treating resistant infections relative to susceptible infections. The cost of managing outbreaks associated with specific antimicrobial-resistant pathogens was not estimated due to lack of appropriate data and timing constraints. The significant impact of the coronavirus disease 2019 (COVID-19) pandemic on the health service presented an additional challenge to data collection during this period.

RQ2: Economic analysis

The aim of this research question was to estimate the costs associated with AMR with respect to public acute hospital care in Ireland. This research question comprised two parts. Part 1 estimated the burden of disease due to AMR, the outputs of which informed Part 2 which estimated the additional cost to the public acute hospital system of treating resistant relative to susceptible infections.

For the purpose of this current study, AMR surveillance data, as collated by the Health Protection Surveillance Centre (HPSC) and reported to the European Antimicrobial Resistance Surveillance (EARS-Net) system, were used as the primary data source.

The burden of disease is specifically concerned with the measurement of health loss. The disability-adjusted life year (DALY), is a utility measure, commonly used in burden of disease studies that refers to the loss of one year of full health. A DALY is equal to the sum of the years of life lost (YLL) due to premature mortality plus the years lost due to disability (YLD) for people living with a health condition or its

consequences.

Part 1 used a step-wise approach to estimate the burden of disease due to AMR in all 50 public acute hospitals in Ireland for the year 2019. This population-modelling methodology developed by the European Centre for Disease Prevention and Control (ECDC) focusses exclusively on the above listed 16 antibiotic resistance-bacterium combinations that are considered to be of public health concern within the European Union and European Economic Area (EU/EEA). Part 2 used a simulation model to estimate the additional costs associated with treating resistant infections relative to susceptible infections, with outcomes reported as the additional cost per excess bed day. Excess bed days refers specifically to the time spent in hospital by one group (that is, those with resistant infections) over and above the time spent in hospital by the other group (that is, those with suspectible infections). As this outcome relates specifically to the incremental time spent in hospital by those with resistant relative to susceptible infections, it does not reflect the totality of time spent in hospital.

Based on the Irish EARS-Net data for public acute hospitals in 2019, 814 of the 6,117 blood stream infections (BSIs) of the eight bacterial pathogens of concern were resistant to at least one of the antimicrobials examined, representing an AMR rate of 13.31%. The total number of resistant infections in all 50 public acute hospitals in Ireland in 2019 was estimated to be 4,787 (95% confidence interval (CI), 2,432-14,764), which resulted in an expected total additional cost, relating to excess LOS, of €12,020,068 (95% CI: €4,879,603 - €23,267,352), relative to susceptible infections. These resistant infections accounted for an estimated 215 (95% uncertainty interval (UI), 208-222) attributable deaths and 4,961 (95% UI: 4,861-5,062) DALYs. The burden of disease was found to be highest in males, and in infants (<1 year) and older adults (≥65 years).

The base case analysis assumed an average cost per inpatient bed day of €737 for excess length of stay (LOS), which might underestimate the true economic burden on public acute hospitals, due to more costly intensive care unit (ICU) admission, for example. The number of ICU admissions and the excess LOS spent in ICU due to AMR, are currently unknown. Scenario analyses were undertaken to assess the influence of higher hospital costs arising from potential ICU admission and duration of stay on expected costs. In particular, three scenarios were considered to assess the impact of:

1. ICU admission by pathogen-infection type combinations with 100% of excess LOS spent in ICU (for admitted cases)

2. different durations of stay in ICU as a proportion of excess LOS (for all cases)

3. ICU admission by infection type with different durations of stay in ICU as a

proportion of excess LOS (for admitted cases).

When interpreting the findings of the scenario analyses, it is important to remember that the outcome relates specifically to the incremental time spent in hospital by those with resistant relative to susceptible infections, rather than the totality for each. The evidence-based assumptions underpinning the economic model are that those with resistant infection spend at least the same amount of time in hospital as those with equivalent susceptible infections. While there are evidence-based estimates for the excess LOS for each of the 16 antibiotic resistance bacterium combinations, the evidence base is relatively poor with regards to excess ICU duration. It is possible that none, some, or the entirety of excess time in hospital, for a patient with a resistant infection, may be spent in ICU. It is also possible that patients with certain resistant infections are more likely to get admitted to ICU than patients with other resistant infections. Hence the need for these scenario analyses, which explore these interacting possibilities.

In the first scenario, which looked at potential ICU admission for each pathogen-infection type combination, with 100% of excess LOS spent in ICU (for admitted cases), the total additional cost was estimated to be €11,561,842 (95% CI: €4,574,594 - €22,528,949). In this scenario, the difference in the proportion of individuals with resistant relative to susceptible infections that experienced complications was used as a proxy for ICU admission. In the second scenario, which looked at different durations of stay in ICU as a proportion of excess LOS (for all cases), the total additional cost was estimated to be €33,916,175 (95% CI: €14,060,290-€64,224,879) when 100% of the excess LOS was spent in ICU, representing a worst-case scenario. In the third scenario that looked at the risk of ICU admission by infection type and different durations of stay in ICU as a proportion of excess LOS for admitted cases, the total additional cost was estimated to be €15,515,044 (95% CI: €6,594,222-€28,723,702) when 100% of the excess LOS was spent in ICU (assuming a fixed proportion of cases in ICU for each infection type).

Models are simplifications of complex systems and rely heavily on the underpinning data and assumptions. AMR is a complex phenomenon that can affect individuals differently, resulting in very different outcomes and costs, and models may not be able to accurately reflect these complexities. It is important to consider these inherent limitations when interpreting the findings of this study. Another limitation of this study was that it was restricted in terms of the included pathogens and costs considered, and so the costs estimated in this report are acknowledged to be an underestimate of the total costs of AMR to public acute hospitals.There are costs associated with AMR screening, changes to empiric prescribing, capital investment in national governance structures, infrastructure, information technology systems and hospital wastewater treatment, as well as the potential for costs arising from AMR-

related litigation. None of these costs are included in this study.

Discussion

This study estimated that it cost the Health Service Executive (HSE) an additional €12 million to treat patients with selected resistant infections, in public acute hospitals in 2019. This figure is a conservative estimate as it only reflects the additional cost due to excess LOS for a select number of resistant pathogens. The estimated €12 million reflects an opportunity cost of displaced care; that is, if the 4,787 patients with these selected resistant infections had susceptible infections instead, the reduction in length of stay would have allowed for greater efficiencies in care elsewhere in the system through increased bed capacity, for example. This is particularly important given the very high bed occupancy rates (often greater than 90%) in the Irish public acute hospital system, which is among the highest in the OECD. Higher occupancy rates lead to bed shortages which may contribute to higher rates of infection. While acknowledging that not all infections are preventable, and that AMR rates are currently stable in Ireland, or even in decline for some pathogens, it must be noted that, at a global level, resistance rates are growing. This emphasises the requirement for appropriate measures to be place, to avert future AMR cost increases for the healthcare system.

Compared with the European average, Ireland has low numbers of ICU beds per 100,000 population and consequently has consistently high ICU occupancy rates. During the COVID-19 pandemic, there was a potential for ICUs to become overwhelmed when there was high transmission rates of SARS-CoV-2 in the community and in secondary healthcare settings. While the same rapid onset pattern is unlikely for AMR, the situation exemplifies what might happen if a single infectious disease diagnosis accounts for a high proportion of ICU bed availability, either due to frequent admission or prolonged length of stay. Not only is there a greater cost associated with ICU admissions as illustrated in this study, but there are also significant opportunity costs associated with avoidable admissions to ICU. Once capacity is reached, clinicians have to decide how critical care is allocated. This can cause a knock-on effect in terms of cancellation of elective and semi-elective procedures. Therefore, AMR may be associated with delays in provision of elective care for other conditions, potentially contributing to adverse outcomes and and overall reduction in the efficiency of the healthcare system.

Patients with infections caused by resistant organisms are more likely to have poorer health and to experience worse outcomes including morbidity and mortality, when compared with those whose infections are caused by antimicrobial susceptible organisms. Beyond mortality and morbidity, patients and their carers and families experience other significant health and economic burdens due to AMR such as

increased healthcare and other out-of-pocket costs, loss of earnings and leisure time, increased anxiety and depression, fear of transmitting infections to others, stigmatisation, reduced treatment options and side effects from last-line antimicrobials

The growth of AMR places a strain on healthcare professionals in that the choice of effective antimicrobial therapies is continuously being reduced, while the development of newer antimicrobials has stalled. For some multidrug-resistant gram negative bacterial infections, healthcare professionals are resorting to last line therapies, such as colistin, which have significant toxicity issues. The reduction in effective antimicrobial therapy options produces particularly significant challenges for clinicians working with patients who rely on effective antimicrobials to treat infections, such as patients undergoing chemotherapy or transplants. The data included in this study relate to 2019 and therefore pre-date COVID-19. The impact of COVID-19, including the wide range of IPC measures implemented to prevent transmission of SARS-CoV-2, on antibiotic prescribing and or the burden of AMR are as yet unknown.

The financial cost of treating resistant infections places a significant burden on society, as patients infected with drug-resistant micro-organisms are more likely to remain in hospital for a longer period of time, to have poorer outcomes and to be unable to work. At a macro-economic level, reduced productivity due to illness or death among working populations can result in the loss of gross domestic product. Though estimating the societal costs of AMR is particularly challenging, given the current rate of AMR growth globally, and the significant impact it is currently having on patients, healthcare professionals and healthcare systems, it is likely that these societal costs in the future will be substantial. There may be other societal consequences to high levels of AMR, which may include a loss of confidence in the healthcare system.

The findings from this study will be used to directly inform iNAP 2. Establishing the current cost of AMR is useful to inform future investment decisions thereby promoting, and providing a metric against which to measure the use of proposed evidence-based, cost-effective solutions to challenges faced as a result of AMR. Additionally, this study presents a preferred standardised methodology for estimating the economic burden of AMR on public acute hospitals in Ireland based on an international review of the economic literature, which may be used in the future by the Department of Health and other agencies. This methodology allows for comparisons to be made between countries. Hence, findings from this current study provide a baseline cost estimate for which future iterations of this study can build upon.

The need to develop and implement policies to combat the spread of AMR is evident from the findings of this study. To protect the health and economic wellbeing of the population from the harmful effects of AMR, policies should focus on promoting the prudent use of antimicrobials in humans, animals and the environment, increasing vaccination uptake and improving IPC measures. Investment is needed to improve infrastructure and increase capacity, with the aim of reducing the risk of onward transmission of infectious diseases within the congregated environments where health and social care is delivered. There is a need for expanded surveillance of AMR in Ireland, given the increasing number of antimicrobials for which resistance is developing and the projected increase in resistance levels globally. Greater resources are required to enhance surveillance activities and public health capacity in Ireland in order to effectively identify and manage AMR threats rapidly, as well as to allow broader evaluations of the economic cost of AMR in Ireland.

AMR also has an important impact on empiric antimicrobial prescribing, which was not captured in the current study. Should resistance to a pathogen exceed a certain threshold for a particular antimicrobial in a population, this agent can no longer be used empirically, and so a second or third line agent will have to be used, which has implications on costs and effectiveness. With regards to third line antimicrobials in particular, these are usually less effective, more toxic and more costly than first or second line agents. The older agents may be unlicensed medicinal products, can be difficult to source and can be very costly. The newly developed agents tend to be very expensive given the impact of drug patents. In the future, consideration may need to be given to alternative funding models (both for the older unlicensed products and the newly developed agents) to safeguard their availability.

The main strength of this study was the rigorous methods that were used by the evaluation team who are experienced in the areas of evidence synthesis, health economics and pharmacotherapy. Input from the EAG which provided contextual knowledge and significant clinical experience of managing AMR added important insights to this study. The robustness of the study has led to evidence-based findings that are relevant and important for informing national health policy.

The main limitation of this study was that its scope was restricted to the costs of excess length of hospital stay associated with 16 antibiotic resistance-bacterium combinations. It is important to acknowledge that these 16 antibiotic resistance-bacterium combinations do not represent the entire spectrum of AMR in Ireland, and that the costs considered are limited to a proportion of all costs. Hence, the estimated figures from this study are acknowledged to be an underestimate of the total costs of AMR on the public acute hospital system in Ireland. Future research, aligned with iNAP 2 should endeavour to estimate the broader costs associated with AMR, that is, to include a broader range of drug-resistant pathogens, in a wider

range of settings (including community settings) and over a longer time period. Consideration should also be given to surveying acute hospital staff on the management of discrete pathogen-specific AMR outbreaks, and to examine empiric prescribing practices in response to AMR concerns.

Plain English Summary

Antimicrobials are medicines that are used to treat infections. Antimicrobials work by killing or stopping the growth of bugs. The most common bugs that cause infections in humans are bacteria, fungi, and viruses. Commonly used antimicrobials are antibiotics, which specifically treat bacterial infections. Antimicrobial resistance (AMR) happens when bugs change so much that an antimicrobial no longer works to fight it and the antimicrobial can't treat the infection. This means that treatment options become limited and common infections become more difficult to treat.

Treating AMR is becoming more expensive, as more and more people become infected with bugs that are resistant to antimicrobials. AMR can mean that people spend a longer time in hospital, are sicker and have a higher chance of dying. It was not known how much it costs Irish hospitals to treat AMR. This information would help predict and set aside enough funding to tackle the problem of AMR. This is why the current study was done.

The aim of this study was to find out how much more it costs hospitals to treat infections that are resistant to antimicrobials compared with treating infections that respond well to antimicrobials. This study included two research questions. The first research question for this study involved reviewing the literature to see how researchers across the world estimated these costs. Twenty-seven studies were found. Many different approaches were used in these studies. It found that the approach used by researchers had a large influence on the cost estimate that they reported. No gold standard approach was identified. However, it was clear that the approach taken by different researchers was generally based on the quality and type of data that they had access to.

The second research question for this study involved estimating the costs of treating important types of resistant bacterial infections in all publicly-funded hospitals in Ireland in 2019. Findings from the first research question helped to shape the methods that were used in the second research question. First of all, the number of the selected resistant infections that occurred in publicly-funded hospitals in Ireland in 2019 was estimated. This information was used to estimate the burden of disease, using a particular outcome measure called a disability-adjusted life year (DALY). DALYs are a combination of years lost due to disease, and time spent disabled by the disease, with one DALY being equal to one year of full health lost. The literature on the impact of AMR on patients was also reviewed, and highlighted the significant burden, both health and financial, that AMR places on patients, as well as their carers and families.

This study found that over 4,700 resistant infections occurred across all 50 public

hospitals in Ireland in 2019. These resistant infections resulted in about 215 deaths and almost 5,000 DALYs, or years of full health lost. Providing hospital beds for these patients cost around €12 million extra in 2019. This estimate is based on the longer time spent in hospital (on average) by these patients, compared with patients with infections that respond well to antimicrobials. It was also limited to eight resistant bacteria. There is a lot of uncertainty around this cost estimate. There are other important resistant bugs and costs that were not examined in this study, including for example costs to prevent the spread of infection, costs in the community and patient-related costs. This €12 million is acknowledged therefore to be an underestimate of the total annual cost of managing all resistant infections in Ireland.

To protect people, the healthcare system and the economy from the harmful effects of AMR, Governments and other public health agencies across the world, need to put in place effective measures to stop AMR getting worse. These measures can include improving knowledge about how to use antimicrobials better, increasing vaccination uptake and promoting other measures such as better hand hygiene and respiratory etiquette. There is also a need for better computerised systems for monitoring AMR in Ireland. This would allow earlier identification and management of AMR threats, as well as allow better ways of determining the true cost of AMR in Ireland.

1 Introduction

1.1 Background to the request

Antimicrobial resistance (AMR) is defined as the ability of a micro-organism to stop an antimicrobial from working against it.[1] AMR is driven largely by excessive and inappropriate use of antimicrobials in human and animal populations.[2] Additionally the crucial role that the environment plays in the persistence and spread of AMR is increasingly being acknowledged, specifically in relation to water, sanitation and hygiene factors.[2, 3] Importantly, the resistant nature of infections can be transferred across humans, animals and the environment, and so the consequences of AMR go beyond the inability of an antimicrobial to work in a given individual.[4]

AMR is a global public health concern; as standard antimicrobial treatments become ineffective, infections persist and spread, increasing morbidity and mortality; impacting on the both the individuals affected and society.[5, 6] Rising rates of AMR will make it increasingly difficult and expensive to control and treat infections and could affect the sustainability for some modern healthcare interventions. The financial cost of treating resistant infections places a significant burden on society, as patients infected with drug-resistant micro-organisms are more likely to remain in hospital for a longer period of time, to have poorer outcomes and to be unable to work.[7-9] The Organisation for Economic Co-operation and Development (OECD) estimates that, between 2015 and 2050, approximately 2.4 million individuals could die due to AMR and that treating AMR could cost healthcare systems across OECD and European Union (EU) countries up to US $3.5 billion per year.[10] A seminal United Kingdom (UK) government report, chaired by the economist Lord Jim O'Neill, estimated that globally by 2050, 10 million lives a year and a cumulative US $100 trillion of economic output are at risk due to the rise of drug-resistant infections.[11]

Carbapenemase-producing *Enterobacteriaceae* (or *Enterobacterales*) are a significant public health concern as these 'superbugs' are resistant to most, if not all, antibiotics.[12] *Enterobacteriaceae* include (but are not restricted to) the following genera of bacteria: *Escherichia, Klebsiella, Citrobacter, Enterobacter, Serratia, Proteus, Morganella, Salmonella,* and *Shigella*. Carbapenem resistance and carbapenemase production can also be problematic in non-*Enterobacteriaceae* including *Acinetobacter* spp. and *Pseudomonas* spp..[13] The terms carbapenemase producing *Enterobacteriaceae* (CPE) and carbapenem resistant *Enterobacteriaceae* (CRE) are often used interchangeably,[14] however subtle differences exist, with CPE referring to *Enterobacteriaceae* that produce an enzyme (carbapenemase) that breaks down carbapenem antibiotics (ertapenem, meropenem, doripenem, or imipenem), whereas CRE refers to *Enterobacteriaceae* that are resistant to carbapenem antibiotics, but do not necessarily have

carbapenemase enzymes.[12, 15] For the purpose of this report, the term CPE will be used throughout, except specifically where CRE was the focus of an included study.

In October 2017, CPE was declared a national Public Health Emergency in Ireland by the Minister of Health.[16] The Public Health Emergency was declared in an attempt to halt or reverse the spread of CPE. This included the establishment of the CPE National Public Health Emergency Team (NPHET) and Expert Group. Outbreaks of CPE present not only significant mortality (as high as 40% to 50%)[17] and morbidity risks, but also significant cost implications to the health service. In 2017, the Health Service Executive (HSE) estimated that a CPE outbreak in University Hospital Limerick which resulted in 60 cases of CPE since 2015 cost €4 million, while CPE outbreaks in Tallaght Hospital since 2016 were estimated to have cost €2 million, with 700 operations postponed as a direct consequence of the outbreak.[18]

In recognition of the serious and increasing threat of AMR, and the requirement for a 'whole of Government' approach, the Department of Health's Chief Medical Officer and the Department of Agriculture, Food and the Marine's Chief Veterinary Officer established a high level National Interdepartmental AMR Consultative Committee in 2014. This Committee acts as an Interagency Co-ordination Mechanism as recommended by the World Health Organization (WHO) and European Commission. The Committee takes a 'One Health' approach and enables a multidisciplinary collaborative effort across health, agriculture and environment sectors. It also provided guidance in relation to the development of Ireland's National Action Plan on Antimicrobial Resistance (iNAP) 2017-2020.[18] This national action plan was developed in line with the five strategic objectives established in the World Health Organization (WHO) Global Action Plan on AMR[5] to:

- improve awareness and understanding of antimicrobial resistance
- strengthen knowledge through surveillance and research
- reduce the incidence of infection
- optimise the use of antimicrobial agents
- develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions.

The iNAP recognises the urgent and growing problem of AMR for human health worldwide.[18] It aimed to implement policies and actions to prevent, monitor and combat AMR across the health, agricultural and environmental sectors. Reducing the inappropriate use of antimicrobial medicines, as well as preventing the transmission of infections and disease, is recognised as being vital to stop the development and spread of resistant micro-organisms.

Development of the successor plan, iNAP 2 is now underway. This plan will continue

to focus on the five strategic objectives established in the WHO Global Action Plan on AMR.[5] It will build on the work achieved under iNAP, and the experience from the Public Health Emergencies on coronavirus disease 2019 (COVID-19) and CPE infections.

National governance structures were established in 2017 to respond to the CPE Public Health Emergency and expanded in 2018 to incorporate Antimicrobial Resistance and Infection Control (AMRIC). The AMRIC team reports to the HSE Chief Clinical Officer. The AMRIC team operates at a national level to develop and provide infection prevention and control (IPC) guidance, education, training and expert advice to services on all issues pertaining to IPC and antimicrobial stewardship. The AMRIC team identifies structural and resource requirements, develops funding proposals to address IPC resource deficits, designs and oversees resource allocation to Community Healthcare Organisations (CHOs) and Hospital Groups, designs and implements service improvement programmes and plans and rolls out integrated communications for patients, staff and members of the public.[19] The Department of Health allocated in the region of €7 million between 2018-2019 (€2 million in 2018 and €5 million in 2019) to AMRIC to meet the strategic objectives of iNAP,[20] and progress initiatives in the context of the CPE Public Health Emergency. Specifically, this included substantial funding for:

- improving compliance by acute hospitals with revised national guidance for screening patients for asymptomatic carriage of CPE
- IPC and antimicrobial stewardship
- addressing the wider impact on the healthcare system of increased detection of CPE, and operational costs related to the management of CPE outbreaks.[21]

The overall goal of iNAP was to ensure, for as long as possible, the availability of effective antibiotic treatment options for both human and animal populations, with safe medicines that are quality assured, used in a responsible way, and accessible to all who need them.[18] One of the key strategic objectives of iNAP was to 'promote research and sustainable investment in new medicines, diagnostic tools, vaccines and other interventions'. Aligned with this key strategic objective, was a strategic intervention to 'carry out health economic analysis of cost of HCAI/AMR'.[18] A driver for this particular activity was the limited cost data for AMR at a national level in Ireland. Economic evidence of the current cost of AMR could inform investment decisions, and provide a metric against which to measure the use of proposed evidence-based, cost-effective solutions to challenges faced as a result of AMR. The Evidence for Policy Team was requested to carry out this economic analysis on behalf of the Department of Health.

1.2 Description and scope of the study

In order to ensure the successful completion of the study within the available time and resource constraints, a select number of pathogens with good data availability, were used as the basis for estimating the economic burden of AMR on public acute hospitals in Ireland. As there is a continuously expanding range of pathogens displaying novel resistance patterns, a finite list of resistant pathogens was decided upon by the evaluation team based on extensive scoping work, in conjunction with the Expert Advisory Group (EAG). For the purpose of this costing study, a pathogen-based approach (for example, *Acinetobacter* spp.), as opposed to a syndrome-based approach (for example, urinary tract infection), was used to define AMR. Antimicrobial resistant pathogens were defined in accordance with the European Antimicrobial Resistance Surveillance Network (EARS-Net).[22] EARS-Net is the main European surveillance system for AMR in bacteria that cause serious infections. EARS-Net is managed and coordinated by the European Centre for Disease Prevention and Control (ECDC), and is supported by a coordination committee composed of disease-specific experts. Data reported from EARS-Net serve as important indicators on the occurrence and spread of AMR in Europe. Use of the EARS-Net data for an Irish study, is supported by the national coverage of participating laboratories (96% in 2019) and the high level of sample representiveness (in terms of geography, hospital, patient and isolate).[23] Hence, the following 16 antibiotic resistance-bacterium combinations were used to define AMR in this study as they are considered to be of public health concern within the European Union and European Economic Area (EU/EEA), are currently under surveillance by EARS-Net, and have reliable Irish data:[22]

- *Acinetobacter* spp., Colistin-resistant
- *Acinetobacter* spp., Carbapenem-resistant (excluding isolates also resistant to colistin)
- *Acinetobacter* spp., Aminoglycoside- and fluoroquinolone-resistant (excluding isolates also resistant to colistin and/or carbapenem)
- *Enterococcus faecalis* and *Enterococcus faecium (E. faecalis* and *E. faecium)*, Vancomycin-resistant
- *Escherichia coli (E. coli)* , Colistin-resistant
- *E. coli*, Carbapenem-resistant (excluding isolates also resistant to colistin)
- *E. coli,* Third-generation cephalosporin-resistant (excluding isolates also resistant to colistin and/or carbapenem)
- *Klebsiella pneumoniae (K. pneumoniae)*, Colistin-resistant
- *K. pneumoniae*, Carbapenem-resistant (excluding isolates also resistant to colistin)
- *K. pneumoniae*, Third-generation cephalosporin-resistant (excluding isolates also resistant to colistin and/or carbapenem)

- *Pseudomonas aeruginosa (P. aeruginosa)*, Colistin-resistant
- *P. aeruginosa*, Carbapenem-resistant (excluding isolates also resistant to colistin)
- *P. aeruginosa,* Resistance to three or more antibiotic groups (excluding isolates also resistant to colistin and/or carbapenem)
- *Staphylococcus aureus (S. aureus)*, Meticillin-resistant
- *Streptococcus pneumoniae (S. pneumoniae)*, Penicillin-resistant (excluding isolates also resistant to macrolides)
- *S. pneumoniae*, Penicillin- and macrolide-resistant (excluding isolates only resistant to penicillin).

It is important to acknowledge that these 16 antibiotic resistance-bacterium combinations do not represent the entire spectrum of AMR in Ireland. For example, fluoroquinolone-resistant *E. coli* and *K. pneumoniae* are not included in this list, despite 20% and 17% of all tested invasive isolates of *E. coli* and *K. pneumoniae* being resistant to fluoroquinolones in Ireland in 2019.[23] Additionally, though relatively rare in Ireland,[24] the healthcare costs for patients with multidrug resistant (MDR) or extensively drug-resistant (XDR) tuberculosis (TB) are substantial.[25] Furthermore, drug-resistant viral (for example, Human Immunodeficiency Virus (HIV)) and fungal infections (for example, *Candida auris)* can have substantial clinical and economic impacts on patients, healthcare systems and society.[26, 27] The methodology selected to estimate the burden of infection associated with AMR, which underpins the approach used in this study, focusses on the 16 antibiotic resistance-bacterium combinations listed above.[28] Therefore, it is acknowledged to be an underestimate of the total cost of AMR in Ireland. This population-based modelling methodology developed by the ECDC (henceforth called the ECDC study) was informed by substantial evidence syntheses and in-depth modelling, and provides a strong framework for the conduct of this study. Adaptation of this model to include additional pathogens was considered to be beyond the scope of this study.

The scope was further impacted by the onset of the COVID-19 pandemic in early 2020. Specifically, cost and resource utilisation data for infection prevention and control measures used for the control of AMR-related outbreaks prior to the pandemic, are likely to be of limited applicability in the context of COVID-19 due to the widespread changes to healthcare provision that have occurred. These include deferral of scheduled care, changes to patient flow and bed occupancy rates, and widespread use of, and high demand for PPE in healthcare settings. Given the lack of a centralised cost database in Ireland, cost and resource utilisation data would have to be obtained from individual hospitals. In light of the increased demands on acute services as they deal with the ongoing impact of COVID-19, it was agreed that it would be neither feasible nor appropriate to seek these data from acute hospital

staff at this time.

Considering all of these factors, the scope of the project was restricted to the costs of excess length of hospital stay associated with the above listed 16 antibiotic resistance-bacterium combinations. Hence, the estimated figures from this study are acknowledged to be an underestimate of the total costs of AMR on the public acute hospital system in Ireland. A number of other costs (beyond excess length of stay) may also be attributable to AMR, such as the costs associated with governance, surveillance, screening, and prevention and control of AMR (including the management of discrete pathogen-specific AMR outbreaks).

1.3 Purpose of the study

The purpose of this study was to estimate the current costs associated with selected antimicrobial-resistant micro-organisms of public health concern in the public acute hospital setting in Ireland. The perspective adopted is that of the publicly funded health and social care system in Ireland.

This costing study was undertaken in fulfilment of listed activities aligned with Strategic Objective 5 of Ireland's National Action Plan (iNAP) on Antimicrobial Resistance (2017-2020).[18] Establishing the current cost of AMR is useful to inform future investment decisions thereby promoting, and providing a metric against which to measure the use of proposed evidence-based, cost-effective solutions to challenges faced as a result of AMR. Additionally, this study presents a preferred standardised methodology for estimating the economic burden of AMR on public acute hospitals in Ireland based on an international review of the economic literature, which may be used in the future by the Department of Health and other agencies. Hence, findings from this current study provide a baseline cost estimate upon which future iterations of this study can build. This is particularly relevant as Ireland moves towards the second National Action Plan for Antimicrobial Resistance 2021 - 2025, iNAP 2.

With respect to public acute hospital care, the terms of reference of this study were to:

- review the methodologies used in costing AMR in general, and in discrete pathogen-specific AMR outbreaks
- develop and apply (where possible) a methodology for estimating current health service costs associated with AMR in Ireland.

The following research questions (RQs) are conducted to address the objectives outlined in the terms of reference:

- RQ1: What methodologies have been used to estimate the costs of AMR

(including outbreaks) in acute hospital settings?
- RQ2: With respect to public acute hospital care in Ireland, what are the costs associated with AMR?

1.4 Expert Advisory Group

An expert advisory group (EAG) was convened for this study, comprising representation from key stakeholders including clinical experts, policy makers, service providers, patients and methodological experts. The role of the EAG was to inform the process and provide expert advice. Advice from the EAG was used to inform a decision as to the most appropriate methodology to use for RQ2 as well as the available Irish data sources, clinical pathways and experiences. The Terms of Reference for the EAG were to:

- contribute to the provision of high quality research by HIQA
- contribute fully to the work, debate and decision-making processes of the group by providing expert guidance, as appropriate
- be prepared to provide expert advice on relevant issues outside of group meetings, as requested
- provide advice to HIQA regarding the scope of the analysis
- support the Evaluation Team led by HIQA during the research process by providing access to pertinent data, as appropriate
- review the project protocol and advise on priorities, as required
- review the draft report from the Evaluation Team and recommend amendments, as appropriate
- contribute to HIQA's development of its approach to evidence synthesis by participating in an evaluation of the process on the conclusion of the assessment
- notify the project lead if a nominee can no longer participate or contribute to the process as non-participation may require alternative EAG membership to be sought.

2 Research question 1: Literature review of methodological approaches

2.1 Key points

- Estimation of the economic burden of antimicrobial resistance (AMR) is of critical importance for policy-making, but is challenging. Widely diverging cost estimates have been reported in the literature and hence the true burden of AMR is unclear.
- The objective for this research question was to identify, and appraise the quality of, methods that have been used to estimate the costs of AMR (including outbreaks) in acute hospital settings. Findings from this research question informed the development of an appropriate methodology to estimate the current healthcare costs associated with AMR in the public acute hospital setting in Ireland.
- A targeted literature review was undertaken focussing on studies linked to four seminal systematic reviews, and supplemented by a comprehensive grey literature search and a database search of PubMed.
- A total of 1,233 records were identified and screened, resulting in a finalised list of 27 studies included in this review. Of these 27 included studies, nine estimated the cost of outbreaks of antimicrobial-resistant pathogens, 17 estimated the cost of AMR in general at a population-level (henceforth called 'population & modelling studies') and one study estimated the cost of both.
- The quality appraisal tool used in this review was developed by the Welsh Public Health Observatory. The quality of the included studies varied; some studies were assessed to be of consistently high quality across all domains, whereas others, particularly outbreak studies, were assessed to be of poor quality in the majority of domains. The absence of sensitivity analysis and limited reporting of uncertainties were common weaknesses in most included studies.
- Outbreak studies generally adopted a healthcare system/hospital perspective, and used predominantly a combination of top-down and bottom-up approaches to costing. Outbreak studies were mostly conducted in single wards or hospitals, and required in-depth data on unit cost and resource utilisation, as well as data on the organisational disruption that occurred as a result of the outbreak. These studies tended to combine the direct costs for the hospital in containing the outbreak, with the revenue losses associated with bed closures

and elective surgery cancellations.

- The accurate costing of outbreaks is particularly challenging given the requirement for extensive local data. The only way to effectively ascertain these costs would be to survey and or interview individual hospitals directly. This is further complicated by the fact that outbreaks can often be contained within wards, and so activity may be transferred from an affected ward to another ward to mitigate revenue losses, or elective surgery may be rescheduled. In order to get an accurate picture of the overall impact of an outbreak, data may therefore be required from multiple wards and operating theatres within a hospital.
- Population & modelling studies varied much more substantially in terms of perspective, epidemiological approach and methodology. The analytical methods used included modelling, matching, regression, burden of disease/cost-of-illness, evidence synthesis, expert opinion, and various combinations of the above.
- In spite of these differences, there were a number of important similarities in the way population & modelling studies estimated and reported costs. For instance, most studies estimated the additional costs associated with treating resistant infections relative to susceptible infections, with outcomes commonly reported as the excess cost per bed day. Additionally, all of the population & modelling studies used predominantly top-down or econometric approaches, with some studies also incorporating bottom-up approaches.
- The three population & modelling studies that were assessed as having the highest quality overall were those by the OECD (Organisation for Economic Co-operation and Development), Bartsch et al. and Wozniak et al.The OECD approach has the advantage of using European AMR surveillance data, uses an evidence-based burden of disease analysis that was developed by the European Centre for Disease Prevention and Control (ECDC), and allows for cross-country comparisons.
- A potential limitation of this review is that a systematic search was not undertaken, and so there is a possibility that some studies were missed. However, a strength of this pragmatic, comprehensive review is the addition of an extensive grey literature search. The review identified a broad range of costing methodologies, which provided detailed information to inform the development of an appropriate methodology to address the second research question.

- Based on this review of international literature, there does not appear to be a universally accepted, or gold standard, approach to costing AMR. This reflects both the diverse models of health and social care delivery systems internationally, as well as the differing ways in which cost and resource utilisation data are collected. However, it is clear from the literature that the choice of costing methodology is largely influenced by the quality and type of data available.

2.2 Introduction

Estimation of the economic burden of antimicrobial resistance (AMR) is of critical importance for policy-making, but is challenging.[9, 29] These difficulties are often compounded by limited good quality, clinically-linked, and representative microbiological data.[30] Providing inaccurate or unclear estimates may potentially undermine the fight against AMR.[29] Widely diverging cost estimates have been reported in the literature and this contributes to uncertainty among the public, clinicians, researchers and policy-makers alike.[10, 31] For example, a 2018 systematic review by Naylor et al. reported that excess healthcare system costs due to AMR relative to susceptible infection ranged widely from no additional costs to $1 billion per year in additional costs.[9] Such variability in economic burden estimates may lead to inaccurate intervention evaluations and poor policy and investment decisions.[9]

Factors that have contributed to the variability in estimates include differences in the perspective adopted and in the methodological approach used.[9, 29] The economic perspective adopted by a study impacts substantially on cost estimates. For example, the patient perspective will include out-of-pocket costs, the healthcare system perspective will include costs associated with excess length of stay (LOS) in hospitals, and the societal perspective will generally also include the broader costs to society such as productivity losses due to mortality and morbidity.[32] The analytical approach undertaken also impacts cost estimates, with different methodologies noted in AMR economic burden studies such as regression analysis, survival analysis, matching and multi-state models.[9]

Assessing the quality of methods used to estimate the economic burden of AMR is important to ensure that decisions are made based on the best available evidence.[29] Excess LOS is considered the most significant cost of infections in hospitals.[33] However, methods to estimate the excess LOS attributable to infection have been shown to be subject to bias, including in particular, failure to adjust for time-dependent exposure.[34] Simulation research has shown that excess LOS is greatly overestimated when the infection onset time is ignored, leading to an overestimate of the associated economic costs.[34] Other sources of bias relate to insufficiently controlling for co-morbidities or inappropriate empiric antimicrobial therapy due to their potential influence on patient outcomes.[29]

The objective for this research question was to identify and appraise the quality of methods that have been used to estimate the costs of AMR (including outbreaks) in acute hospital settings, with a focus on methodologies that are relevant and applicable to the Irish healthcare system. Findings from this research question informed the development of an appropriate methodology to address the second research question, the primary objective of which was to estimate the additional cost of treating resistant infections relative to susceptible infections, in the public acute hospital setting in Ireland.

2.3 Methods

2.3.1 Review question

What methodologies have been used to estimate the costs of AMR (including outbreaks) in acute hospital settings?

The following Population, Interest and Context (PICo) framework was developed to address the above research question (Table 2.1).

Table 2.1: PICo for RQ1

	PICo Elements
Population	Patients (of any age) attending/admitted to acute hospitals with an infection that is resistant to antimicrobials (must include at least one of the 16 antibiotic resistance-bacterium combinations considered to be of public health concern within the European Union/European Economic Area (EU/EAA)). Antibiotic resistance-bacterium combinations considered to be of public health concern within the EU/EEA: ▪ *Acinetobacter* spp., Colistin-resistant ▪ *Acinetobacter* spp., Carbapenem-resistant ▪ *Acinetobacter* spp., Aminoglycoside- and fluoroquinolone-resistant ▪ *Enterococcus faecalis* and *Enterococcus faecium*, Vancomycin-resistant ▪ *Escherichia coli*, Colistin-resistant ▪ *Escherichia coli,* Carbapenem-resistant ▪ *Escherichia coli,* Third-generation cephalosporin-resistant ▪ *Klebsiella pneumoniae*, Colistin-resistant ▪ *Klebsiella pneumoniae*, Carbapenem-resistant ▪ *Klebsiella pneumoniae*, Third-generation cephalosporin-resistant ▪ *Pseudomonas aeruginosa*, Colistin-resistant ▪ *Pseudomonas aeruginosa*, Carbapenem-resistant ▪ *Pseudomonas aeruginosa*, Resistance to three or more antibiotic groups ▪ *Staphylococcus aureus*, Meticillin-resistant ▪ *Streptococcus pneumoniae*, Penicillin-resistant ▪ *Streptococcus pneumoniae*, Penicillin- and macrolide-resistant.
Interest	▪ methodology used to estimate costs ▪ costs considered ▪ author-reported costs.
Context	▪ acute hospital setting ▪ must be able to disaggregate costs for acute hospital setting ▪ regional or national-level population required for the cost of AMR in general ▪ individual hospital-level data acceptable for discrete pathogen-specific AMR outbreaks ▪ multinational studies as long as they include at least one of the above listed 16 antibiotic resistance-bacterium combinations.

2.3.2 Search strategy

A pragmatic approach to searching the literature was adopted in an attempt to find the most commonly used costing methodologies in this area, within a relatively short period of time. This approach was undertaken as opposed to a traditional systematic or scoping review due to a strategic decision to focus more on applying the methodology, rather than searching for all potential methodologies in an exhaustive manner. During the scoping phase of this project, four key systematic reviews were identified that included studies relevant to the research question.[9, 29, 35, 36]

1. Wozniak, Barnsbee et al. Using the best available data to estimate the cost of antimicrobial resistance: a systematic review. BMC Antimicrobial Resistance and Infection Control. 8:26 (2019)[29]

2. Naylor, Atun et al. Estimating the burden of antimicrobial resistance: a systematic literature review. BMC Antimicrobial Resistance and Infection Control. 7:58 (2018)[9]

3. Birgand, Moore et al. Measures to eradicate multidrug-resistant organism outbreaks: how much do they cost? Clinical Microbiology and Infection 22, 162.e1-e9 (2015)[35]

4. Zhen, Lundborg et al. Economic burden of antibiotic resistance in ESKAPE organisms: a systematic review. BMC Antimicrobial Resistance and Infection control. 8:137 (2019)[36]

These four systematic reviews were used as the starting point for this targeted literature review. Backward (that is, screening studies that were included in these reviews) and forward citation searching (that is, screening the studies that referenced any of these reviews) and use of the 'similar articles' function on PubMed was conducted in the first instance. This was supplemented by an electronic search of PubMed restricted to 2009 onwards (Appendix 1), and a comprehensive grey literature search (Appendix 2).

Any systematic review that was identified as relevant during this process, was also screened to ensure that no included study relevant to this review had been missed.

For data management purposes, all studies identified from the backward and forward citation searching of the four key systematic reviews as well as from the PubMed, and grey literature search were exported to Covidence (www.covidence.org). The original search was conducted on 22 December 2019, and this was updated on 9 November 2020.

2.3.3 Eligibility criteria

Cost-of-illness or other costing studies that described the methodology used to estimate the cost to the healthcare system, of AMR in general, or of discrete pathogen-specific AMR outbreaks, were included, in accordance with the inclusion and exclusion criteria listed in Table 2.2. Studies must have:

- included at least one of the 16 key antibiotic-pathogen combinations listed in Table 2.1
- been population-based, unless describing an outbreak (as these are generally only conducted at a ward- or hospital-level)
- presented costs to acute hospital settings, regardless of the perspective undertaken by the researchers.

Due to the emergence of new strains of resistance (such as CPE) and the development of innovative strategies to prevent, control and treat AMR, it was decided that the most relevant costing methodologies were likely to be found in studies published within the last 10 years (2009 onwards). Finally, only studies reported in English were included. While this may limit the range of reports, the focus on the methodology means that a particularly high quality of translation is necessary in order to fully understand the potentially complex methodology used.

Table 2.2: Inclusion and exclusion criteria for RQ1

Inclusion Criteria	Exclusion Criteria
▪ The subject of the article is the cost of AMR to the healthcare system OR the subject relates to the cost of an outbreak of discrete AMR pathogens to the healthcare system (or hospital).	▪ Studies that do not present the cost of AMR.
▪ Cost-of-illness or costing studies.	▪ Studies that focus on HCAI and do not present data on AMR.
	▪ Studies that do not specify the methodology used in the calculation of costs.
	▪ Studies that do not include or present the cost to the healthcare system (regardless of perspective).
	▪ Studies that do not include or present the cost to acute hospital settings.
	▪ Studies that focus on pathogens that are not one of the 16

	key antibiotic-pathogen combinations listed in Table 2.1.
	▪ Studies that do not explicitly state what pathogens were included in their costs.
	▪ Studies where the costs in the acute hospital setting cannot be disaggregated from other settings such as primary care.
	▪ Studies that focus on the cost-effectiveness of interventions.
	▪ Studies that are based in single hospitals (unless there is an explicit mention of outbreaks – defined as *"two or more linked cases of the same illness, or the situation where the observed number of cases exceeds the expected number."*[37]).
	▪ Publication before 2009.
	▪ Reviews, editorials or commentaries.
	▪ Non-English Language.

Key – AMR –antimicrobial resistance; HCAI – healthcare associated infection.

2.3.4 Study selection

Following removal of duplicates, two reviewers independently screened the titles and abstracts of all potentially relevant citations and identified those which warranted full-text review. A flow diagram was generated to report the selection process and all results (Figure 2.1).[38]

Studies which met the inclusion criteria (Table 2.2) following full-text review by two independent reviewers, were then screened for relevance and applicability to Irish healthcare system based on three key questions:

1. Is the costing methodology described in enough detail to replicate?
2. Are some or all of the cost inputs relevant to an Irish setting?
3. Are the necessary data likely to be available in Ireland?

Studies which met all three of the above criteria were included in this review. These three screening questions were used to eliminate costing methodologies which could not be replicated due to insufficient detail, or would have no relevance or applicability for the Irish public healthcare system. For example, some studies had hospitalisation costs for every included patient, as well as linked routine clinical data, allowing better linking of AMR-related treatment to costs.[39] Hospital In-Patient

Enquiry (HIPE) is the principal source of national data on discharges from public acute hospitals in Ireland. HIPE collects demographic, clinical and administrative data on discharges from, and deaths in, public acute hospitals nationally.[40] Healthcare costs in Irish public acute hospitals are not calculated for every aspect of a patient's care, but rather are based on the entire episode of hospitalisation using diagnosis related groups (DRGs). The DRGs are designed to group cases which are clinically similar and which are expected to consume similar amount of resources.[41] Of the 807 DRGs in the classification system used in Ireland in 2019 (the Australian Refined DRG system (AR-DRG v8.0)), none specifically relate to AMR. After patients are discharged from, or die in hospitals, they are assigned via a computer algorithm using data from HIPE to one of the 807 DRGs, all of which have designated costs. These DRGs determine budget allocation to public acute hospitals in Ireland.[41] Therefore, while there is the possibility of linking clinical data to resource utilisation and cost data in public acute hospitals in Ireland, this is not feasible for AMR given that there are no relevant DRGs. Additionally, there are issues with data linkage, so that while possible at an individual hospital, where individual patient-level data may be used, it is not feasible to conduct individual patient-level data linkage for all 50 public acute hospitals in Ireland as these data are aggregated at a population-level. Ethical issues also arise regarding linking data without patient consent, due to the possibility of potentially identifying patients.[42, 43] Therefore, AMR costing methodologies which are based on linked patient-level clinical and cost data were not considered applicable at this time.

Other studies reported patient charges as the economic outcome as opposed to costs to the healthcare system.[44, 45] In public acute hospitals in Ireland, the charge for inpatient or day services is fixed at €80 per day up to a maximum of €800 for an individual in a rolling 12 month period regardless of the number, purpose or duration of attendances in that period. There are also certain exemptions to these charges, including those with medical cards, people receiving treatment for prescribed infectious diseases (including COVID-19), women receiving maternity care and children up to six weeks of age. There is also a fixed €100 charge for people attending the Emergency Department (ED), with certain exemptions for this charge including those with medical cards, those referred by a general practitioner (GP), and those being treated for prescribed infectious diseases (including COVID-19). There are also separate charges for patients who opt for private services in public hospitals, and these charges vary depending on the duration of hospital stay, the type of hospital and the occupancy of the room.[46] Therefore, the reported patient charges have limited bearing on the cost to the public acute hospital system in Ireland, and methodological approaches which collect this type of economic data would have limited usefulness in the Irish context.

2.3.5 Data extraction and quality appraisal

Relevant data were extracted and quality assessment was conducted for each included study by one reviewer and double-checked by another. Where disagreements occurred between the reviewers during the review process, discussions were held to reach consensus, and where necessary a third reviewer was consulted.

The following data were extracted for each included study:

- author name
- year of publication
- country
- study design
- study objective
- outbreak or population & modelling study
- setting
- subpopulation, if relevant
- year of valuation
- currency
- sample size
- methodology used
- economic perspective
- cost-of-illness approach used (prevalence- vs. incidence-based)*
- approach to estimating costs (top-down vs. bottom-up vs. econometric)**
- direct costs considered
- indirect costs considered
- definition of AMR
- type of infection
- prevalence/incidence of AMR
- comparison group
- burden of disease outcome
- discounting rate
- confounder adjustment
- author reported economic costs
- sensitivity analysis.

*The approach to cost-of-illness studies can be prevalence or incidence-based depending on how the epidemiological data are used. Prevalence-based approaches

estimate the cost of a condition over a specific period, usually a year. Incidence-based approaches estimate the lifetime costs of a condition from onset until cure or death.

**The approach to estimating costs were categorised as follows. A top-down approach uses aggregated costs (for example, the average cost per bed day), whereas a bottom-up approach uses disaggregated costs (for example, unit cost per swab). The econometric approach estimates the difference in costs between a cohort with the disease and another matched cohort without the disease.[47]

The quality appraisal tool used in this review was developed by the Welsh Public Health Observatory, and is derived from another tool developed by Larg et al. (Appendix 4).[48] The quality appraisal tool assessed the quality of studies across 11 domains focussing on two main areas. These were the methodology and data used in the study (that is, how well were resources measured and valued), as well as the study analysis and reporting (that is, how well were the data analysed and the findings reported).

2.3.6 Data synthesis

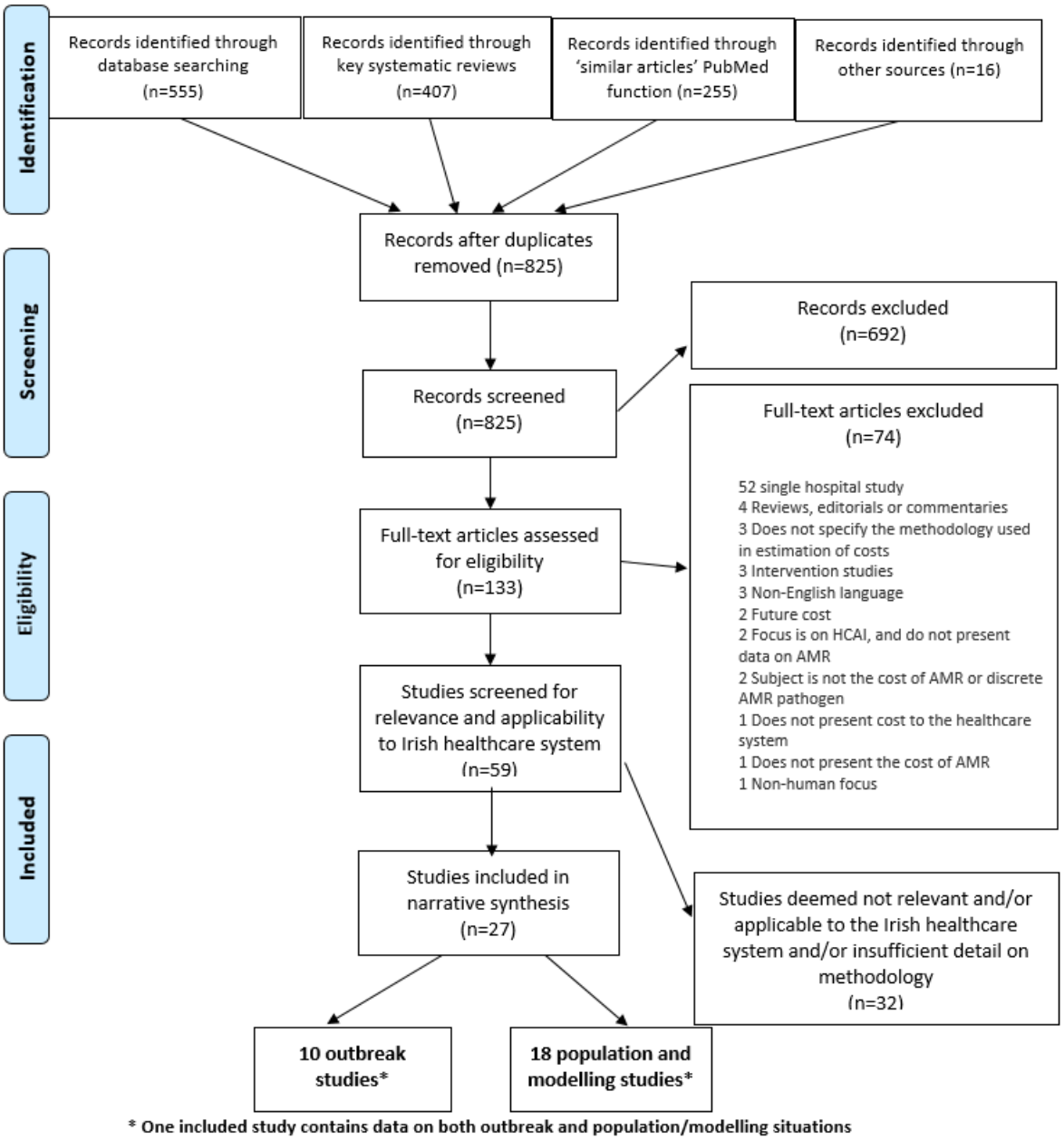
Included studies were synthesised narratively due to the huge variation in how studies were conducted, analysed and reported. Outbreak and population & modelling costing studies are reported separately due to the inherent differences in how these studies were conducted.

2.4 Results

2.4.1 Search results

A total of 1,233 records were identified from all sources (Figure 2.1). After removal of duplicates, the titles and abstracts of 825 citations were independently screened by two reviewers and 692 records excluded at this stage. A total of 133 full-texts were independently assessed by the two reviewers applying the predefined inclusion and exclusion criteria. Seventy-four records were subsequently excluded at this stage, resulting in 59 studies to be screened for relevance and applicability to the Irish healthcare system. Of the 59 studies, 32 were excluded on this basis, resulting in a final inclusion of 27 studies, 10 of which reported costs of outbreaks (outbreak costing studies),[49-58] 18 reported costs relating to AMR more generally over a defined time period (population & modelling costing studies).[10, 58-74] with one population & modelling study also estimating costs for an outbreak (Figure 2.1).[58]

Figure 2.1: PRISMA flow diagram of included studies



2.4.2 Characteristics of included studies

Across all 27 included studies, six were conducted in the US,[54, 59, 63, 64, 67, 68] five were conducted in France,[49, 50, 52, 53, 71] four were conducted across a number of European and or OECD countries,[10, 61, 62, 70] two each were conducted in the Netherlands,[51, 55] the UK,[56, 66] and Australia,[72, 73] and one each was conducted in Japan,[57] Sweden,[58] Spain,[74] Canada,[60] Colombia[65] and Germany (Table 2.3).[69] The year of epidemiological data collection used to inform the cost estimates of included studies ranged from 2005[67] to 2018.[60] No included study was conducted

since the onset of the COVID-19 pandemic.

Eight of the 10 outbreak studies were case series,[49-56] and two were cross-sectional surveys.[57, 58] The sample size of the outbreak studies ranged from five[53] to 104 individual cases.[58] Seven of the outbreak studies involved individual wards or hospitals,[49-55] another outbreak study involved five hospitals,[56] while two outbreak studies surveyed 21[58] and 23[57] infection control units or hospitals, respectively, for data on outbreaks (Table 2.3).

Six of the 18 population & modelling studies were cross-sectional studies,[61-64, 68, 74] five were economic modelling studies,[10, 58, 59, 67, 72] four were cohort studies,[65, 66, 70, 73] two were case-control studies,[69, 71] and one was an evidence synthesis.[60] The sample size of the population & modelling studies ranged from 165[65] to 8,933,326 (Table 2.3).[66]

Table 2.3: Table of characteristics for outbreak and population & modelling studies

First author (year) Country	Study design (n)	Sub-population	Perspective	Methodology Approach to estimating costs Epidemiological approach	Antimicrobial resistance (infection site)
Outbreak studies					
Ayraud-Thevenot (2012)[49] **France**	Retrospective case series (n=27)**	Surgical ICU patients	Healthcare system perspective - hospital	Costing (Top down and bottom-up)	MDRAB (not reported)
Daroukh (2014)[50] **France**	Retrospective case series (n=16)**	None reported	Healthcare system perspective – hospital	Costing (bottom-up)	CPE (peritonitis, catheter infection, obstructive pyelonephritis)
Dik (2016)[51] **The Netherlands**	Retrospective case series (n=90)	None reported	Healthcare system perspective – hospital	Costing (Top down and bottom-up)	MRSA, ESBL, VRE, Pantoea spp. Norovirus, S. marcescens (not reported)
Escaut (2013)[52] **France**	Retrospective case series (n=13)**	Hepato-biliary patients	Healthcare system perspective - hospital	Costing (Top down and bottom-up)	VRE (not reported)
Gagnaire (2017)[53] **France**	Retrospective case series (n=5)**	Neuro-surgery patients	Healthcare system perspective - hospital	Costing (Top down and bottom-up)	CP-AB (not reported)
Jiang (2015)[54] **US**	Retrospective case series (n=9)	General surgery ICU and trauma ICU patients	Healthcare system perspective - hospital	Costing (bottom-up)	MDRAB (not reported)
Mollers (2017)[55] **The Netherlands**	Retrospective case series (n=29)	None reported	Healthcare system perspective - hospital	Costing (Top down and bottom-up)	CPE - (NDM)-producing Klebsiella pneumoniae (not reported)

First author (year) Country	Study design (n)	Sub-population	Perspective	Methodology Approach to estimating costs Epidemiological approach	Antimicrobial resistance (infection site)
Morii (2020)[57] **Japan**	Cross sectional survey (n=104 outbreaks, 23 provided cost data. Unclear n for patients)	None reported	Healthcare system perspective – hospital	Costing of multiple outbreaks (Top down and bottom-up)	VRE; CRE; MRSA; multidrug-resistant Pseudomonas aeruginosa; ESBL-producing Enterobacteriaceae, multidrug resistant Acinetobacter; Clostridioides difficile and multidrug-resistant Corynebacterium striatum (unclear)
Otter (2017)[56] **UK**	Retrospective case series (n=40)	None reported	Healthcare system perspective – hospital	Costing (Top down and bottom-up)	CPE - (NDM)-producing Klebsiella pneumoniae (not reported)
Public Health Sweden (2018)[58]* **Sweden**	Cross- sectional survey (n=106 cases, 21 infection control/care hygiene units surveyed)	None reported	Healthcare system	Costing (Top down and bottom-up)	MRSA, VRE (not reported)
Population & modelling studies					
Bartsch (2017)[59] **US**	Economic modelling study (N/A)	None	Hospital, third-party payer, and societal perspectives	Decision-tree analysis (Top-down and bottom-up) Incidence based	CRE (Bacteraemia, pneumonia, complicated intra-abdominal infection, complicated UTI)
Canton (2020)[74] **Spain**	Cross-sectional study (n=12,090)	Nosocomial, excluding community-acquired infections	Societal perspective, but direct costs also reported	Burden of disease (Top down) Prevalence based	Carbapenem resistant Klebsiella pneumoniae, Pseudomonas aeruginosa and Acinetobacter baumannii (Not specified)
CCA (2019)[60] **Canada**	Evidence synthesis (N/A)	None	Healthcare system and societal perspectives	Evidence synthesis and expert opinion (Top down) Prevalence based	MRSA, ESBL bacteria, VRE, C. dif (BGI, BSI, CDI, IAI, MSI, pneumonia, STI, SSTI, TB, UTI)

First author (year) Country	Study design (n)	Sub-population	Perspective	Methodology Approach to estimating costs Epidemiological approach	Antimicrobial resistance (infection site)
de Kraker (2011)[61] **31 European countries**	Cross-sectional study (n=42,894)	None	Healthcare system perspective	Burden of disease (Top down) Prevalence based	MRSA and 3GC-resistant *E. Coli* (BSI)
ECDC (2009)[62] **30 EU/EEA countries**	Cross-sectional study (NR)	None	Healthcare system and societal perspectives	Cost-of-illness (Top-down and bottom-up) Prevalence based	MRSA, vancomycin-resistant Enterococcus faecium, Penicillin-resistant Streptococcus pneumoniae, third-generation cephalosporin-resistant Escherichia coli and Klebsiella pneumoniae and carbapenem-resistant Pseudomonas aeruginosa (BSI, LRTI, SSTI and UTI)
Johnston (2019)[63] **US**	Cross-sectional study (n= 6,385,258)	None	Healthcare system perspective - hospital	Regression analysis (Econometric) Prevalence based	MRSA, C. diff, other non-specified MDROs (Meningitis, Encephalitis, Cellulitis, Endocarditis, Pneumonia, Pyelonephritis, Septic arthritis, Osteomyelitis, Bacteraemia, Sepsis/severe sepsis, SSI, UTI, Complicated IAI, Intestinal infections due to other organisms/enteritis, Bacterial infection in conditions classified elsewhere and of unspecified site)
Klein (2019)[64] **US**	Cross-sectional study (n=616,070)	None	Healthcare system perspective - hospital	Matching (Econometric) Prevalence based	MRSA (Septicaemia, Pneumonia and unspecified infection)
Lee (2020)[73] **Australia**	Retrospective case-cohort study (n=96,025)	None specified	Healthcare system	Matching, multistate survival model, logistic regression. (Econometric) Prevalence based	3GC-resistant *K. pneumoniae*; 3GC-resistant *E. coli*; Ceftazidime-resistant *P. aeruginosa*; Meticillin-resistant *S. aureus* (MRSA); Vancomycin-resistant *E. faecium* (VRE); (BSI, UTI and RTI)
Lemos (2013)[65] **Colombia**	Prospective cohort study (n=165)	ICU patients	Third party payer perspective - hospital	Regression analysis (Econometric) Prevalence based	CRAB (Pneumonia, bacteraemia, central venous catheter-associated infection, surgical infection, UTI, soft tissue, intra-abdominal infections)

First author (year) Country	Study design (n)	Sub-population	Perspective	Methodology Approach to estimating costs Epidemiological approach	Antimicrobial resistance (infection site)
Naylor (2019)[66] **UK**	Retrospective cohort study (n=8,933,326)	None	Healthcare system perspective – hospital	Multistate modelling (Top down) Prevalence based	Resistant E. Coli (BSI)
Nelson (2016)[67] **US**	Economic modelling study (N/A)	None	Hospital and third-party payer perspectives	Multistate modelling and matching (Top down) Incidence based	MDRAB (not reported)
Nguyen (2019)[68] **US**	Cross-sectional study (n=546,305)	Older patients (≥65 years)	Healthcare system perspective – hospital	Regression analysis (Econometric) Prevalence based	MRSA, beta-lactam resistance, multidrug-resistance, quinolone resistance and other unspecified AMR (UTI)
OECD (2018)[10] **33 OECD and EU/EEA countries**	Economic modelling study (N/A)	None	Healthcare system perspective – hospital	Micro-simulation modelling study (Top-down) Incidence based	Resistance to†: Acinetobacter spp., S. pneumoniae, S. aureus, E. coli, K. pneumoniae, P. aeruginosa, E faecalis and E faecium (BSI, RTI, UTI, surgical site and other infections)
Public Health Sweden (2018)[58]* **Sweden**	Economic modelling study (N/A)	None	Societal and healthcare system	Micro-simulation modelling study (Top down) Incidence based	ESBL, MRSA, PNSP, VRE (not reported)

First author (year) Country	Study design (n)	Sub-population	Perspective	Methodology Approach to estimating costs Epidemiological approach	Antimicrobial resistance (infection site)
Resch (2009)[69] **Germany**	Retrospective case-control study (n=313,943)	None	Healthcare system perspective – hospital	Matching (Econometric) Prevalence based	MRSA (not reported)
Stewardson (2016)[70] **6 European countries**	Retrospective cohort study (n=606,649)	None	Healthcare system perspective – hospital	Multistate modelling (Top down) Prevalence based	MRSA, 3GCRE (BSI)
Touat (2019)[71] **France**	Retrospective case-control study (n=318,234)	None	Public health insurance perspective	Matching (Econometric) Prevalence based	Resistance to: E. coli, Klebsiella, other Enterobacteriaceae, S. aureus, other Staphylococcus, Pneumococcus, Enterococcus, other Streptococcus, GNB (urinary and genital tract, devices and prosthesis-related infection, SSTI, LRTI, bacteraemia and sepsis (alone), gastrointestinal and abdominal, bone and joint, during pregnancy, heart and mediastinum, infection in newborn, ear, nose and throat, eye, and nervous system)
Wozniak (2019)[72] **Australia**	Economic modelling study (N/A)	None	Healthcare system perspective – hospital	Simulation model (Top-down and bottom-up) Prevalence based	Ceftriaxone resistant E. coli; ceftriaxone-resistant K. pneumonia; ceftazidime-resistant P. aeruginosa; VRE; and MRSA (BSI, UTI and RTI)

Key: AMR – antimicrobial resistance; BGI - bacterial gastro-intestinal infection; BSI – bloodstream infection; CDI – *Clostridioides/Clostridium difficile* infection; CP-AB - Carbapenemase-producing *Acinetobacter baumannii*; CPE - carbapenemase-producing Enterobacteriales (Enterobacteriaceae); CRE - carbapenem-resistant *Enterobacteriaceae;* CRAB - carbapenem-resistant *Acinetobacter baumannii*; DRG - Diagnosis-related Group; ESBL - extended-spectrum beta-lactamases; GNB – gram negative bacilli; IAI - intra-abdominal infection; ICU – intensive care unit; IPC – infection prevention and control; MDRAB – multidrug resistant Acinetobacter Baumannii; MRSA – meticillin-resistant Staphylococcus aureus; MSI - musculoskeletal infection; NDM - New Delhi metallo-beta-lactamase 1; PNSP - penicillin-non-susceptible pneumococci; (U)/(L)/RTI – (upper)/(lower) respiratory tract infection; STI – sexually transmitted infection; SSI – surgical site infection; SSTI – skin and soft tissue infection; TB – tuberculosis; UK – United Kingdom; US – United States; UTI – urinary tract infection; VRE - vancomycin-resistant enterococci; 3GC - third-generation cephalosporin; 3GCRE - third-generation cephalosporin-resistant Enterobacteriaceae.

*Public Health Sweden 2018 presented both population & modelling and outbreak data separately, this report has therefore been included twice in this table.

2.4.3 Quality appraisal

The quality of the included studies varied, some studies were assessed to be of consistently high quality across all domains,[59, 72] whereas others were assessed to be of poor quality in the majority of domains.[49, 60] With regards to the outbreak studies (Table 2.4), none performed any sensitivity analysis. The majority did not provide a range of estimates for costs,[49-55, 58] or identify any uncertainties[49, 50, 52-56, 58] nor did they discuss the implications of any such uncertainties.[49-55, 58] The outbreak studies that were assessed as having the highest quality overall were those by Morii et al.[57] and Otter et al..[56]

With regards to population & modelling studies (Table 2.5), the quality varied substantially. Most studies did not clearly identify the main uncertainties[58, 60, 63-66, 68-71, 74] or discuss the implications of those uncertainties.[10, 58, 60, 63, 64, 67, 69-71, 73, 74] Nine of the population & modelling studies did not conduct any sensitivity analysis.[58, 60, 61, 64-67, 74] The three population & modelling studies that were assessed as having the highest quality overall were those by the OECD,[10] Bartsch et al.[59] and Wozniak et al..[72]

Table 2.4: Quality appraisal of outbreak studies (n = 10)

	Methodology and data: how well were resource use and productivity losses measured?			What did they find (analysis and reporting)?							
Author	Were quantification methods appropriate?	Was resource quantification method well executed?	Were healthcare resources valued appropriately?	Did the analysis address the study question?	Was a range of estimates presented?	Were the main uncertainties identified?	Was a sensitivity analysis performed?	Was adequate documentation and justification given for cost components, data and sources, assumptions and methods?	Was uncertainty around the estimates and its implications adequately discussed?	Were important limitations discussed regarding the cost components, data assumptions and methods?	Were the results presented at the appropriate level of detail to answer the study question
Ayraud-Thevenot 2012[49]											
Daroukh 2014[50]											
Dik 2016[51]											
Escaut 2013[52]											
Gagnaire 2017[53]											
Jiang 2016[54]											
Mollers 2017[55]											
Morii 2020[57]											
Public Health Sweden 2018[58]*											
Otter 2017[56]											

Key: Green box means yes. Red box means no. Yellow box means unclear.
*Public Health Sweden 2018 presented both population & modelling and outbreak data separately, this report has therefore been included in both sets of tables.

Table 2.5: Quality appraisal of population & modelling studies (n = 18)

	Methodology and data: how well were resource use and productivity losses measured?			What did they find (analysis and reporting)?							
Author	Were quantification methods appropriate?	Was resource quantification method well executed?	Were healthcare resources valued appropriately?	Did the analysis address the study question ?	Was a range of estimates presented?	Were the main uncertainties identified?	Was a sensitivity analysis performed ?	Was adequate documentation and justification given for cost components, data and sources, assumptions and methods?	Was uncertainty around the estimates and its implications adequately discussed?	Were important limitations discussed regarding the cost components, data assumptions and methods?	Were the results presented at the appropriate level of detail to answer the study question
Bartsch 2017[59]											
Canton 2020[74]											
CCA 2019[60]											
De Kraker 2011[61]											
ECDC 2009[62]											
Johnston 2019[63]											
Klein 2019[64]											
Lee 2020[73]											
Lemos 2014[65]											
Naylor 2019[66]											
Nelson 2016[67]											
Nguyen 2019[68]											
OECD 2018[10]											
Public Health Sweden											

2018[58]*											
Resch 2009[69]											
Stewardson 2016[70]											
Touat 2019[71]											
Wozniak 2019[72]											

Key: CCA – Council of Canadian Academies; ECDC – European Centre for Disease Prevention and Control; OECD – Organisation for Economic Co-operation and Development.
Green box means yes. Red box means no. Yellow box means unclear.
*Public Health Sweden 2018 presented both population & modelling and outbreak data separately, this report has therefore been included in both sets of tables

2.4.4 Antimicrobial resistance

Each included study estimated the economic cost of AMR based on a select number of antimicrobial-resistant pathogens (Table 2.3). These antimicrobial-resistant pathogens were categorised differently across the studies, both in terms of the biological taxonomy and the pattern of antimicrobial resistance, making exact comparisons difficult. In other words, the study may have focussed on specific pathogens at a family (such as *Enterobacteriaceae*), genus (such as *Enterococcus)* or species (such as *E. coli*) level, while pathogens may have been resistant to one specific antimicrobial agent (such as meticillin-resistance) or to multiple antimicrobial (such as multidrug resistance). The most commonly included antimicrobial-resistant species were *S. aureus* (n=15),[10, 51, 57, 58, 60-64, 68-73] *K. pneumoniae* (n=8),[10, 55, 56, 62, 72-74] *A. baumannii* (n=7),[49, 53, 54, 57, 65, 67, 74] *E. coli* (n=7),[10, 61, 62, 66, 71-73] *P. aeruginosa* (n=6)[10, 57, 62, 72-74], *S. pneumoniae* (n=2),[10, 58] *E. faecium* (n=2),[10, 62] and *E. faecalis* (n=1).[10] Eight studies examined antimicrobial-resistant *Enterococcus,*[51, 52, 57, 58, 60, 71-73] and four studies examined antimicrobial-resistant *Enterobacteriaceae*. The most commonly studied resistant antimicrobials (either individual drug or class) were meticillin (n=13),[51, 57, 58, 60-64, 68-70, 72, 73] carbapenem (n=9),[50, 53, 55-57, 59, 62, 65, 74] vancomycin (n=8),[51, 52, 57, 58, 60, 62, 72, 73] cephalosporins (n=5),[61, 62, 70, 72, 73] beta-lactams (n=4)[51, 57, 58, 60, 68] penicillin (n=2)[58, 62] and quinolones (n=1).[68] Five studies examined multidrug resistance.[49, 54, 57, 67, 68] The most commonly examined antimicrobial resistance-pathogen combinations were MRSA (n=13),[51, 57, 58, 60-64, 68-70, 72, 73] vancomycin-resistant enterococci (VRE) (n=8),[51, 52, 57, 58, 60, 62, 72, 73] and CPE/CRE (n=6).[50, 55-57, 59, 74]

2.4.5 Economic methods

2.4.5.1 Outbreak studies

The costing methodologies used in the 10 outbreak studies were broadly consistent in that they primarily used a combination of bottom-up (by using disaggregated costs, for example unit cost per swab) and top-down approaches (by using aggregated costs, for example, average cost per bed day), though the exact cost inputs varied from study to study.[49, 51-53, 55-58] Two of the ten outbreak studies only used bottom-up approaches.[50, 54] None of the outbreak studies used econometric approaches. Additionally, all 10 outbreak studies adopted a healthcare system/hospital perspective.[49-58] In general, for these studies, the actual hospital expenditure to contain the outbreak (in terms of additional bed days, staff costs, treatment costs and surveillance etc.) was combined with the opportunity costs associated with bed closures and elective surgery cancellations. These studies required detailed resource utilisation and cost data from the affected units, in order to estimate the costs of the outbreaks. Two of the outbreak studies obtained these data through survey methodology,[57, 58] while the remainder collected these data

on-site.[49-56]

Seven of the 10 outbreak studies had no cost comparator group.[49, 51, 52, 55-57] Three outbreak studies included comparator groups; two studies used a pre-outbreak period as a comparator,[50, 54] while one study compared costs during an outbreak period with the costs simulated in a hypothetical unit.[53]

The direct costs measured varied between studies, but generally included costs due to additional LOS,[51, 56, 58] testing, screening and surveillance,[49-53, 55-58] cleaning,[49, 51, 53, 54, 58] personal protective equipment (PPE),[52, 54] staffing,[50-56, 58] antimicrobial agents[53, 54, 56] and administrative support.[54, 58] The indirect costs measured primarily related to productivity losses from the hospital's perspective due to bed closures or cancelled surgeries.[51-53, 56-58]

2.4.5.2 Population & modelling studies

The costing methodologies used in the 18 population & modelling studies varied substantially. Fifteen of the population & modelling studies adopted a healthcare system/hospital perspective,[10, 58-64, 66-71, 73] five adopted a societal perspective,[58-60, 62, 74] three adopted a third-party payer perspective,[59, 65, 67] and one adopted a public health insurance perspective.[71] Eight studies used primarily top-down approaches (in that aggregate costs were used),[10, 58, 60, 61, 66, 67, 70, 74] seven studies used primarily econometric approaches (in that antimicrobial-resistant and antimicrobial-sensitive cohorts were compared to estimate differences in costs),[63-65, 68, 69, 71, 73] and three used a combination of top-down and bottom-up approaches (in that both aggregated and disaggregated costs were used).[59, 62, 72] None of the population & modelling studies used solely bottom-up approaches. Fourteen of the population & modelling studies used a prevalence-based approach to analyse the epidemiological data, where the economic burden due to AMR was estimated over a specific time frame.[60-66, 68-74] Four studies used an incidence-based approach, where the costs per infection were estimated from the onset of infection to cure or death.[10, 58, 59, 67] The analytical methods used varied also. Six studies used modelling approaches (by modelling transitions between various phases in the infection);[10, 58, 59, 66, 70, 72] three studies used matching (by comparing outcomes from similar patient cohorts with and without antimicrobial-resistant infections);[64, 69, 71] three studies used regression analysis (by adjusting for confounders);[63, 65, 68] three studies performed burden of disease or cost-of-illness analysis (by estimating the mortality, morbidity and the associated costs due to AMR);[61, 62, 74] two studies used a combination of matching and modelling;[67, 73] and one study used a combination of evidence synthesis and expert opinion.[60]

Sixteen of the 18 population & modelling studies had cost comparator groups.[10, 58, 60-73] These comparator groups comprised hospitalised patients that were not

infected with an antimicrobial-resistant pathogen. Eleven of these studies used patients infected with susceptible pathogens as the comparator group,[10, 58, 61-65, 68, 70-72] two studies used patients that had no infection as the comparator group,[60, 67] two studies used three different comparator groups (resistant infection, susceptible infection and uninfected),[66, 73] and one study compared a cohort of patients without MRSA (regardless of whether they had an infection or not) with a cohort with MRSA specifically.[69]

The direct costs considered in all 18 population & modelling studies centred on the cost per bed day. In most studies, the cost per bed day used was assumed to capture all costs associated with an episode of hospitalisation.[10, 60, 61, 63, 64, 66-68, 70, 73, 74] However, some studies additionally considered other costs such as intensive care unit (ICU) admission or mechanical ventilation,[59, 65, 69, 71] drug therapies,[59, 65, 71, 72] microbiology tests,[59, 65] procedures and examinations,[59, 65, 71] staffing,[59, 65, 71] outpatient and GP visits,[58, 62] and contact tracing.[58] Indirect costs were measured in five of the population & modelling studies and included productivity[58, 59, 62, 74] or general domestic product (GDP) losses,[60] due to illness or mortality, from a societal perspective.

2.4.6 Author-reported economic costs

Given the substantial variation in terms of study design, population, methodology, approach, perspective, pathogens, comparators, and cost inputs, the author-reported economic costs of these studies are not directly comparable. This is further complicated by how the study authors reported cost outcomes, with some studies focussing on the cost of AMR per infection,[51, 55, 58-60, 63-68, 70, 73] with other studies focussing on the cost of AMR on the healthcare system or society more broadly.[10, 49, 50, 52-63, 69-72, 74] Additionally some studies reported additional costs (that is, the costs due to AMR over and above those associated with a relevant comparator group),[10, 50, 54, 58, 59, 61-73] whereas others reported the total costs associated with AMR (that is, the costs due to AMR without taking into consideration any relevant comparator group).[49, 51-53, 55-57, 60, 74] These costs are presented in Table 2.6 for information.

Table 2.6: Author reported economic costs

First author (year) Country	Year of cost valuation (currency)	Costs included	Author reported economic costs
Outbreak studies			
Ayraud-Thevenot (2012)[49] **France**	2009 (€)	Direct costs: Rectal swabs, surface swabs, hygiene measures, bed closures, ICU closures. Indirect costs: None.	**Total costs**: 2006 outbreak: **€539,325**. 2009 outbreak: **€202,214** Direct costs (2006: €23,485 and 2009 outbreak: €6,441) Bed Closures (2006) €515,840, (2009) €195,773
Daroukh (2014)[50] **France**	2012-2013 (€)	Direct costs: Activity of wards during periods, overtime hours of staff and screening tests. Indirect costs: None.	Loss of activity due to ward closures = €547,303. Costs due to extra screening = €30,931. Costs due to overtime paid to staff = €63,870. **Total costs = €642,104**
Dik (2016)[51] **The Netherlands**	2015 (€)	Direct costs: Microbiological diagnostics/ surveillance costs; additional cleaning costs; additional personnel; costs made for contact or strict isolation of patients and other costs (e.g. purchase of extra materials, possible prolonged length of stay, extra medication). Indirect costs: Missed revenue due to closed beds.	**MRSA** outbreak **€657.08** (cost per patient per outbreak day **ESBL** outbreak #1 **€1,368.92** (cost per patient per outbreak day; ESBL outbreak #2 **€980.51** (per patient per outbreak day, **VRE** outbreak **€197.26** (per patient per outbreak day) **Pantoea spp**. outbreak **€88.11** per patient per outbreak day, **Norovirus** outbreak **€10.40** per patient per outbreak day, **S. marcescens** outbreak **€518.54** per patient per outbreak day.
Escaut (2013)[52] **France**	2008 (€)	Direct costs: Cost of staffing, disposable materials, hygiene procedures, and surveillance cultures. Indirect costs: Loss of income due to reduced availability of isolation rooms.	**Total cost €171,439.** The direct cost of the outbreak (2008 Euros) due to infection control measures was €60 524 and the loss of income from reduced activity of isolation beds was €110 915.

First author (year) Country	Year of cost valuation (currency)	Costs included	Author reported economic costs
Gagnaire (2017)[53] **France**	2012 (USD)	Direct costs: Staff costs, environmental sampling costs, screening costs, carbapenemase identification and routine examination costs, drug costs, environmental disinfection. Indirect costs: Loss of ward activity, DRG-related loss of income.	Observed outbreak cost: **$474,474**. Simulated dedicated unit estimate: $190,265
Jiang (2015)[54] **US**	2011 (USD)	Direct costs: Nursing costs, respiratory therapy, deep cleaning labour and supply, transport, supplies, admin time, environmental testing. Indirect costs: None.	**Overall excess cost $371,079**
Mollers (2017)[55] **The Netherlands**	2015 (USD and €)	Direct costs: Diagnostics, ward-related costs, and other outbreak control costs (infection prevention experts, patients in isolation, staff meetings, communication, costs for mailings). Indirect costs: None.	**Total outbreak costs $804,263 or €653,801**, corresponding to a cost of $27,700 per patient.
Morii (2020)[57] **Japan**	2015 (USD)	Direct costs: Costs for containment (including surveillance, screening, cleaning and decontamination, disposal and repurchase) Indirect costs: Productivity loss.	The maximum observed productivity loss was 4.62 million USD. The minimum observed productivity loss resulted in an increase of 587,000 USD. Across 23 included studies, **the median estimated productivity loss was 674,000 USD per hospital**. The maximum and minimum observed total cost for containment was 678,000 USD and 1,110 USD respectively. Across 23 included studies the **median estimated containment cost was 43,900 USD per hospital**.

First author (year) Country	Year of cost valuation (currency)	Costs included	Author reported economic costs
Otter (2017)[56] UK	2016 (€)	Direct costs: Additional bed-days for infected patients, anti-infective costs, lab/screening costs, IPC team time, staff time outside of IPC, isolation, ward based monitors, environment/equipment. Indirect costs: Elective surgical missed revenue, closed beds.	The outbreak cost **a total of €1,133,000** (range €943,000 - €1,424,000) over 10 months, comprising €312,000 of actual expenditure and €822,000 (range €631,000 - €1,112,000) in opportunity cost. An additional €153,000 was spent on Estates renovations prompted by the outbreak.
Public Health Sweden (2018)[58]* Sweden	2016 (SEK)	Direct costs: Cleaning, laundry, Screening, sampling (patients, staff, environment), staff costs, longer care period, reduction of care places, administration education, information. Indirect costs: Lost production.	An average cost of approximately SEK 73,000 (SEK 14,000-137,000) per case in an outbreak was estimated. According to estimates, approximately 30–40 outbreaks per year occurred between 2013 and 2015 with 8–14 cases per outbreak on average. **Outbreaks in** Sweden are estimated to **cost SEK 29 million per year**, based on average cost per case.
Population & modelling studies			
Bartsch (2017)[59] US	2016 (USD)	Direct Costs: ICU bed days, General ward bed days, Hospitalisation costs (for bacteraemia/intra-abdominal infection/pneumonia/VAP/UTI), Drug treatments per day, PICC line insertion, urine analysis, urine culture, abdominal CT, Bronchoscopy, wound culture, CXR, sputum culture, blood culture, nurse hourly wage. Indirect costs: Productivity losses.	Depending on the infection type, the median cost of a **single CRE infection can range from $22,484 to $66,031 for hospitals**. An infection incidence of 2.93 per 100,000 population in the USA (9418 infections) would cost hospitals $275 million (95% CR $217-334 million), with a 25% attributable mortality. An incidence of 15 per 100,000 (48,213 infections) would cost hospitals $1.4 billion (95% CR $1.1-1.7 billion).
Canton (2020)[74] Spain	2017 (€)	Direct costs: Hospitalisation costs. Indirect costs: Productivity losses.	Direct costs total €389,843,161. (break down A. baumannii €71,330,596 (18% of total); K. pneumoniae €15,007,790 (4% of total); P. aeruginosa €303,504,775 (78% of total)). **Total cost overall €471,591,266** - consisting of €81,748,104 in indirect costs and €389,843,161 in direct costs.

First author (year) Country	Year of cost valuation (currency)	Costs included	Author reported economic costs
CCA (2019)[60] **Canada**	2018 (CAD)	Direct Costs: Hospital costs (no details on what these comprised). Indirect costs: Gross Domestic Product Loss.	$18000 CAD per patient = average cost of a resistant bacterial infection in the hospital in 2018. **$1.4 Billion CAD** = cost to the Canadian healthcare system in 2018
de Kraker (2011)[61] **31 European countries**	2007 (€ and international dollars)	Direct Costs: Bed days. Indirect costs: None.	**Total costs: MRSA: €44.0 million** (95% CI €23.8 million-67.8 million) (63.1 million international dollars), **3GC-resistant *E. coli*: €18.1 million** (95% CI €7.5 million-32.2 million) (29.7 million international dollars).
ECDC (2009)[62] **30 EU/EEA countries**	2007 (€)	Direct Costs: Bed days, outpatient (GP) consultations. Indirect costs: Productivity losses.	**Total overall costs €1.534 billion** (including €927.8 million for in-hospital bed days, €10 million for extra out-patient visits and €150.4 million for productivity losses due to absence from work and €445.9 million for productivity losses due to mortality).
Johnston (2019)[63] **US**	2017 (USD)	Direct Costs: Cost-to-charge estimates per hospital stay. Indirect costs: None.	The **national cost of infections associated with MDROs** is **at least $2.39 billion** (95% CI: $2.25-$2.52 billion) and **as high as $3.38 billion** (95% CI: $3.13-$3.62 billion) if undercoded infections are accounted for. MRSA, C. difficile, another MDRO, and the presence of more than one MDRO are associated with $1718 (95% CI: $1609-$1826), $4617 (95% CI: $4407-$4827), $2302 (95% CI: $2044-$2560), and $3570 (95% CI: $3019-$4122) in additional costs per hospital stay, respectively. The mean cost per hospital stay for stays with any diagnosis of bacterial infection was $19 037.
Klein (2019)[64] **US**	2014 (USD)	Direct Costs: Cost-to-charge estimates per hospital stay. Indirect costs: None.	Propensity score–adjusted costs for MSSA pneumonia- and other S.aureus–related hospitalisations were 5.5% ($40,725 vs $38,561; P = .045) and 5.2% ($15,578 vs $14,792; P < .001) higher than for MRSA related hospitalisations, respectively. **MSSA–related septicaemia hospitalisation costs were not significantly different from MRSA-related hospitalisation costs** ($34 526 vs $34 175; P = .69). However, among pneumonia-related hospitalisations, patients with MRSA infections had a higher rate of mortality than patients with MSSA infections (P < .001)

First author (year) Country	Year of cost valuation (currency)	Costs included	Author reported economic costs
Lee (2020)[73] **Australia**	2020 (AUD)	Direct costs: Length of stay and value of a bed day. Calculated as an opportunity cost (defined as "willingness to pay" to release a bed day from some infection-reducing intervention, 250.40 AUD) and an accounting cost (obtained by dividing the total annual hospital budget by the number of bed days supplied during the same period, 2721.8 AUS $ in 2020 prices). Indirect costs: None.	Data are the cost of resistance calculated as the difference in cost between resistant and sensitive infection, represented as opportunity (*OC*) and accounting costs (*AC*) associated with health care-associated infections in Queensland in AUD (SD) (2012-2016). BSI: S. aureus *OC*: 503.2 (172.9); *AC*: 5422.9 (1744.2) E. faecium *OC:* −442.3 (90.8); *AC*: −4805.0 (916.7) E. coli *OC*: 2.7 (62.7); *AC*: 51.8 (634.2) K. pneumoniae *OC*: 753.5 (147.9). *AC*: 8206.1 (1516.8) P. aeruginosa *OC*: 342.6 (123.1). *AC*: 3718.9 (1262.2) UTI: S. aureus *OC*: 180.5 (59.6). *AC:* 1953.1 (608.5) E. faecium *OC*: 92.6 (36). *AC*: 1010.0 (370.6) E. coli *OC*: 83.2 (27.3). *AC:* 905.5 (283.5) K. pneumoniae *OC*: 381.8 (55.7). *AC*: 4160.3 (588.9) P. aeruginosa *OC:* 209.5 (44). *AC*: 2273.3 (457.8) RTI: P. aeruginosa *OC:* −86.4 (71.6). *AC*: −946 (734.2)
Lemos (2013)[65] **Colombia**	2011 (USD)	Direct Costs: Hospital costs (days of stay in the ICU, fees for health professionals, surgical procedures, laboratory, tests, microbiological cultures and radiological examinations) and antimicrobial therapy and other drugs. Indirect costs: None.	The average total cost of hospitalisation among patients with **CRAB** was significantly higher than that among patients with **CSAB** in both the univariate and multivariate analyses (adjusted **US$ 11,359 versus US$ 7049**; p <0.01; Table 4). **Carbapenem resistance** was associated with an additional treatment cost of **US$ 4309** (95% CI US$ 2819–5645; p <0.01) after adjusting for age, gender, APACHE II score and site of infection. Patients with CRAB had significantly higher costs for hospital-related cost and for cost of antimicrobial drugs than patients with CSAB (both p <0.01 and p <0.01).
Naylor (2019)[66] **UK**	2012 (£)	Direct Costs: Bed days. Indirect costs: None.	Cost per spell (per in-patient) with E. coli bacteraemia = £1,020 (95% CI; £970 –£1,070). Utilising this cost per spell and number of spells, the estimated annual cost burden to hospitals due to E. coli bacteraemia in 2011/12 was £14,346,400. Adjusting only for time dependency bias, **excess annual costs** associated **with third generation cephalosporin resistance and piperacillin/tazobactam** (comparative to if these had been susceptible infections) **were £366,600** (95% CI; £194,927 –£550,000) and **£275,400** (95% CI; £105,200 - £436,600) respectively. That is to say, if all third generation cephalosporin resistant infections had been susceptible it was estimated that £366,600 would not have been spent on those infections (based on reduced LoS). **Third-generation cephalosporin resistance associated with excess costs per infection of £420** (95% CI: 220–630).

First author (year) Country	Year of cost valuation (currency)	Costs included	Author reported economic costs
Nelson (2016)[67] **US**	2014 (USD)	Direct Costs: Bed day. Indirect costs: None.	This study generated costs per HAI using 3 methods: (1) overall cost estimates, (2) multiplying LOS estimates by a cost per inpatient-day ($4,350) from the payer perspective, and (3) multiplying LOS estimates by a cost per inpatient-day from the hospital ($2,030) perspective. **The cost per infection were $129,917 (method 1), $72,025 (method 2), and $33,510 (method 3).** Adjusting for the timing of infection, the cost per infection were $68,359 (method 1), $37,916 (method 2), and $17,646 (method 3). Using a multistate mode, the cost per infection were $38,423 (method 1), $21,294 (method 2), and $9,906 (method 3)
Nguyen (2019)[68] **US**	2016 (USD)	Direct Costs: Cost-to-charge estimates per hospital stay. Indirect costs: None.	Unadjusted costs associated with hospitalisation with AMR were 2730 USD (95%CI, 2596–2864) higher than non-AMR group (p<0.001). In the multivariable regression, **admissions with AMR, on average, consumed 1259 USD** (95%:1178–1340) **more than those without AMR**, though distinct patterns were observed in different types of AMR.
OECD (2018)[10] **33 OECD and EU/EEA countries**	2017 (USD PPP)	Direct Costs: Length of stay. Indirect costs: None.	AMR cost the health systems of the **countries included in the analysis around USD PPP 3.5 billion per year**. For EU/EEA countries this amounts to USD PPP 1.5 billion per year which means that in less than 10 years, the impact of AMR on healthcare expenditure has increased by 60%. 2015-2050 - AMR will have cost the health systems of EU/EEA countries a total of USD PPP 60 billion, while USA, Canada and Australia, this amount will reach a combined total of approx USD PPP 74 billion. In absence of antimicrobial treatments, cost to different health systems a total of USD PPP 16.3 billion annually.
Public Health Sweden (2018)[58]* Sweden	2016 (SEK)	Direct Costs: Inpatient care days, outpatient care visits, primary care visits, contact tracing. Indirect costs: Productivity losses.	**Overall cost for Swedish society** of at approximately **SEK 4.3 billion up to 2030** (which includes 4 billion of healthcare costs) and SEK 15.8 billion by 2050 (which includes 14.9 billion of healthcare costs). The cost of the final year 2030 was roughly SEK 400 million and for 2050 SEK 600 million.
Resch (2009)[69] **Germany**	2004 (€)	Direct Costs: Length of stay, mechanical ventilation. Indirect costs: None.	The total burden for **German hospitals** can be estimated at around **€ 761.5 million annually**. Incremental cost per MRSA case € 8,198

First author (year) Country	Year of cost valuation (currency)	Costs included	Author reported economic costs
Stewardson (2016)[70] **6 European countries**	2011-2012 (€)	Direct Costs: Length of stay. Indirect costs: None.	Estimated cost per infection EUR (95% CrI): MSSA BSI: economic cost 760 (190–3,000), Accounting cost 9,500 (5,800-16,000). MRSA BSI: economic cost 890 (220-3,600), accounting cost (11,000 (6,600-19,000). Meticillin resistance: economic costing 120 (-60-740), accounting cost 1,600 (-700 to 5000). 3GCSE BSI: economic cost: 320 (80-1,300), accounting cost 4,000 (2,400-6,700). 3GCRE BSI: economic cost 560 (140-2,300), accounting cost 7,300 (4,300-12,000). 3GC resistance: economic cost 250 (60-1,100), accounting cost 3,200 (1,600-6,000). Estimated cost per hospital year EUR 1,000 (95% CrI): MSSA BSI: economic cost 77 (19-300), accounting cost 970 (590-1,600). MRSA BSI: economic cost 17(4.1-67), accounting cost 210 (130-360). 3GCSE BSI: economic cost 77 (19-300), accounting cost 970 (590-1,600). 3GCRE BSI: economic cost 24 (5-94), accounting cost 300 (180-510).
Touat (2019)[71] **France**	2015 (€)	Direct Costs: Medical procedures, nursing care, administration, routine drug consumption, and room service. Cost from expenses of innovative drugs for the National Health Insurance Funds and expenditure from transfer in ICU were added to DRG. Indirect costs: None.	For **2015 AMR overall cost reached EUR 109.3 million in France** with a mean of EUR 1103 per stay; extrapolation to the entire database shows that the overall cost could potentially reach EUR 287.1 million if all cases would be identified. The mean excess length of hospital stay attributable to AMR was estimated at 1.6 days

First author (year) Country	Year of cost valuation (currency)	Costs included	Author reported economic costs
Wozniak (2019)[72] **Australia**	2014 (AUD)	Direct Costs: Length of stay, treatment costs. Indirect costs: None.	For the five AMR pathogens included in the analysis, Australian hospitals spent an **estimated additional AUD $16.8 million per year.** Ceftriaxone-resistant E.coli BSI total cost $5.8 million (95% uncertainty interval, $2.2–$11.2 million) per year. Ceftriaxone-resistant KP BSI $1,351,360 (358,717–3,158,370) per year. Ceftazidime-resistant PA BSI $108,581 (48,551–202,756) per year. Ceftazidime-resistant PA RTI $1,296,324 (456,198–2,577,397) per year. VRE BSI $1,404,064 (415,766–3,287,542) per year. MRSA BSI $5.5 million per year (339,633–22.7 million) MRSA RTI $1,525,552 (726,903–2,791,453)

Key – AC – accounting cost; AMR – antimicrobial resistance; AUD – Australian dollars; BSI – bloodstream infection; CAD- Canadian dollars; CDI – *Clostridioides/Clostridium difficile* infection; CP-AB - Carbapenemase-producing Acinetobacter baumannii; CPE - carbapenemase-producing Enterobacteriales (Enterobacteriaceae); CSAB - carbapenem-sensitive *Acinetobacter baumannii*; CRAB - carbapenem-resistant *Acinetobacter baumannii*; CRE - carbapenem-resistant *Enterobacteriaceae;* CT - computerized tomography; CXR – chest x-ray; DRG - Diagnosis-related Group; ESBL - extended-spectrum beta-lactamases; GNB – gram negative bacilli; GP – general practitioner; ICU – intensive care unit; IPC – infection prevention and control; KP - *Klebsiella pneumoniae*; LOS – length of stay; MDRAB – multidrug resistant *Acinetobacter Baumannii*; MDRO – multi-drug resistant organism; MSSA – meticillin-sensitive *Staphylococcus aureus*; MRSA – meticillin-resistant *Staphylococcus aureus*; NDM - New Delhi metallo-beta-lactamase 1; OC – opportunity cost; PA - *Pseudomonas aeruginosa;* PICC - Peripherally inserted central catheter; PNSP - penicillin-non-susceptible pneumococci; PPP –purchasing power parity; (U)/(L)/RTI – (upper)/(lower) respiratory tract infection; SD – standard deviation, SEK – Swedish Krona; SSTI – skin and soft tissue infection; UK – United Kingdom; US – United States; USD – United States Dollars; UTI – urinary tract infection; VAP – ventilator-associated pneumonia; VRE - vancomycin-resistant enterococci; 3GC - third-generation cephalosporin; 3GCSE - third-generation cephalosporin-sensitive Enterobacteriaceae; 3GCRE - third-generation cephalosporin-resistant Enterobacteriaceae.

2.5 Discussion

2.5.1 Overall summary

This review identified a broad range of methodologies, of varying quality and complexity, which have been used to estimate the cost of AMR in acute hospital settings. In general, outbreak studies adopted a healthcare system/hospital perspective, and used predominantly a combination of top-down and bottom-up approaches to costing. Outbreak studies were mostly conducted in single wards or hospitals, and required in-depth data on unit cost and resource utilisation, as well as data on the organisational disruption that occurred as a result of the outbreak. These studies tended to combine the actual expenditure of the hospital with the opportunity costs associated with bed closures and elective surgery cancellations. Conversely, population & modelling studies varied much more substantially in terms of perspective, epidemiological approach and methodology. The analytical methods used in population & modelling studies also varied and included modelling,[10, 58, 59, 66, 70, 72] matching,[64, 69, 71] regression,[63, 65, 68] burden of disease/cost-of-illness,[61, 62, 74] evidence synthesis and expert opinion,[60] and various combinations of the above.[67, 73] All studies considered the direct costs to the hospital due to AMR, in particular, the cost of hospital care (that is, bed days, ICU, staffing, antimicrobials, testing and screening etc.). Some studies also considered indirect patient costs, in particular productivity losses (due to mortality and morbidity)[58-60, 62, 74] and hospital revenue losses (due to ward closures and cancelled elective procedures).[51-53, 56-58] Importantly, none of these studies (outbreak or population & modelling) estimated the costs associated with the governance systems for AMR at a national or regional level.

2.5.2 Challenges with conducting outbreak costing studies

The two included studies that conducted surveys of hospitals where outbreaks occurred discussed challenges they encountered, and limitations with their findings.[57, 58] The Public Health Agency of Sweden stated that it was difficult to quantify activities and costs directly related to a given outbreak as these may have been handled differently in different units, depending on the size of the outbreak, resistance patterns, and resources that were available locally.[58] Morii et al. discussed how only 25 of the 104 hospitals contacted (24%), agreed to share their outbreak information and financial performance.[57] Of these 25 hospitals, two were subsequently excluded due to insufficient data, resulting in data from only 23 hospitals (22%) being included in the final analysis. This has implications for the generalisability of the cost estimates, with the authors concluding that the 23 included hospitals were unlikely to be representative of all Japanese hospitals, as university hospitals were found to be over-represented in the final sample. The

authors further discussed issues with potential over- and underestimation of costs. For example, the authors acknowledged that the study did not estimate costs due to staff overtime, lawsuits, or compensation associated with outbreaks, hence there is likely underestimation of these costs. However, the authors also discussed how hospitals can implement coping strategies to mitigate financial damage, by transferring patients who test negative for the antimicrobial-resistant pathogen, to another ward to continue receiving care. Therefore, if patients are transferred from one ward to another and services are continued, the overall revenue loss may be negligible from the hospital's perspective, in spite of ward closures. The economic impact of AMR may also be mitigated by planning elective surgery in such a way as to minimise disruptions to an operating theatre. For example, by scheduling an operation involving a person with a resistant infection for a Friday, so that the theatre is closed for two days afterwards regardless, this means that any required decontamination measures do not result in any unplanned cancellations. As the study by Morri et al. focused on opportunity costs at the ward-level and did not take into consideration the potential transfer of services into other parts of the hospital, or the rescheduling of elective surgery, these opportunity costs may have been overestimated.[57]

Only one study estimated the cost of AMR in both outbreak and population/modelling situations. However, different approaches were required; a survey of infection control units to estimate the costs of outbreaks, and a microsimulation modelling study based on national epidemiological data to estimate the costs of AMR in general.[58] It is unclear how much of an overlap there might be when estimating AMR in general, from a predominantly top-down as opposed to estimating outbreak costs from a predominantly bottom-up approach. It is likely that the former approach may greatly underestimate the total cost of AMR in hospitals, given the substantial organisational disruption and the subsequent knock-on effect that outbreaks can have on hospital operations. This organisational impact is rarely recorded on national epidemiological or administrative databases and so directly obtaining this information from the affected units is necessary.

2.5.3 Strengths and limitations

A limitation of this review is that a pragmatic targeted search as opposed to a systematic search was undertaken, and so there is a possibility that some studies were missed. In the interest of time, a pragmatic approach to searching the literature was adopted which focussed on studies linked to four seminal systematic reviews.[9, 29, 35, 36] This was supplemented by a comprehensive grey literature search, along with a targeted search of PubMed. This pragmatic, but comprehensive approach is a strength of this review. This is highlighted by the fact that a total of 1,233 records were identified and screened, despite the restricted nature of the

search, resulting in a finalised list of 27 studies included in this review. These studies provided detailed information to inform the development of an appropriate methodology to address the second research question. Though the current review identified a comprehensive range of different methodological approaches to estimate the economic burden of AMR on hospitals, it is possible that other unidentified approaches are available, given the recent proliferation of literature in this area along with a drive to develop more innovative methods.[75]

Another important limitation of this review, is that many of the included studies were assessed to be of low methodological quality.[49, 50, 52-55, 58, 60, 67, 69, 74] In particular, most studies faired poorly in terms of reporting uncertainties[49, 50, 52-56, 58, 60, 63-66, 68-71, 74] and conducting sensitivity analysis.[49-58, 60, 61, 64-67, 73, 74] The consistently poor reporting of these domains among included studies, highlights important areas for improvement in future AMR costing studies.

A third limitation of this review is that none of the included studies were conducted since the onset of the COVID-19 pandemic in December 2019. COVID-19 is having a devastating impact on health and social care systems, economies and societies across the world,[76] with over 185 million COVID-19 cases reported globally, as of July 2021.[77] It is as yet unclear what impact, if any, COVID-19 will have on AMR, with early studies reporting conflicting findings.[78] An editorial by Monnet and Harbarth discussed the potential factors that may increase or decrease the risk of AMR in the context of COVID-19.[78] For instance, the authors suggested that the increased use of antibiotics among COVID-19 patients, in particular broad spectrum antibiotics and azithromycin, may contribute to greater levels of AMR.[78] A rapid review article by Langford et al. estimated that about 70% of hospitalised COVID-19 patients receive antibiotics, despite low levels (approximately 3.5%) of bacterial co-infection on admission.[79] Conversely, Monnet and Harbarth suggested that fewer patient consultations for self-limiting infections may result in fewer antibiotic prescriptions and hence lower levels of AMR. Additionally, compliance with public health measures such as hand hygiene, face mask use and physical distancing, along with reduced international travel, may reduce the levels of circulating respiratory illnesses and hence reduce the need for antibiotics.[78] However, the true impact of COVID-19 on AMR is still unknown.

2.5.4 Information to inform development of appropriate methodology

Based on this review of international literature, there does not appear to be a universally accepted, or gold standard, approach to costing AMR. This reflects both the diverse models of health and social care delivery systems internationally, as well as the differing ways in which cost and resource utilisation data are collected. It was evident that the accurate costing of outbreaks is particularly challenging. From

the included studies, it was apparent that the only way to effectively ascertain these costs was to survey and or interview individual hospitals directly. As discussed, this is further complicated by the fact that outbreaks can often be contained within wards, and so patients may be transferred from an affected ward to an unaffected ward, and hence in order to get an accurate picture of the impact of an outbreak, data may be required from multiple wards within a hospital. Though potentially feasible to conduct such a survey in Ireland at the individual hospital level, or even at the hospital group level, issues relating to reporting bias, incomplete data and heterogeneity due to differences in the infrastructure, practices and casemix between hospitals, present significant challenges to the conduct of such a survey. Development of relevant key performance indicators (KPIs) in this area, may enable better monitoring of the national impact of outbreaks in acute hospitals along with better estimation of the costs associated with these outbreaks.

There were a number of important similarities in the way population & modelling studies estimated and reported costs. For instance, most studies estimated the additional costs associated with treating resistant infections relative to susceptible infections [10, 58, 61-65, 68, 70-72] with outcomes commonly reported as the additional cost per excess bed day.[10, 50, 54, 58, 59, 61-73] Additionally, all of the population & modelling studies used predominantly top-down or econometric approaches,[10, 58-74] with some studies also incorporating bottom-up approaches.[59, 62, 72] Hence, using predominantly top-down or econometric approaches with the aim of estimating the additional costs associated with treating AMR, relative to susceptible infections, would appear to be broadly consistent with international research.

A broad range of methodological approaches to estimate the population & modelling costs of AMR were reviewed. These included modelling, matching, regression, burden of disease/cost-of-illness, evidence synthesis, and expert opinion. The three population & modelling studies that were assessed as having the highest quality overall were those by the OECD,[10] Bartsch et al.[59] and Wozniak et al.,[72] all of which used simulation modelling approaches. The OECD approach has the advantage of using European AMR surveillance data, uses an evidence-based burden of disease analysis that was developed by the European Centre for Disease Prevention and Control (ECDC), and allows for cross-country comparisons.[28] This methodological approach formed the basis for the second research question.

All models require good quality data. In adopting a simulation model, there is a need for access to nationally representative data. Hospital In-Patient Enquiry (HIPE) is the principal source of national data on discharges from public acute hospitals in Ireland. HIPE collects demographic, clinical and administrative data on discharges from, and deaths in, public acute hospitals nationally.[40] Data from the HIPE database were considered to be useful for the simulation model in the second research question.

2.6 Conclusion

The economic burden of AMR on acute hospital settings can be estimated using a broad range of methodologies.

Outbreak studies, tend to focus on single wards or hospitals, and use a combination of top-down and bottom-down approaches. Population & modelling studies tend to be population-based, often involving data from multiple countries, and use predominantly top-down or econometric approaches. While outbreak studies tend to use similar costing methods, a diverse range of methods can be used in population & modelling studies.

The choice of costing methodology selected by researchers to estimate the cost of AMR in acute hospital settings will largely be influenced by the quality and type of data available. The methodological approach adopted from the OECD formed the basis for the second research question, and was used to estimate the additional cost associated with treating resistant infections relative to susceptible infections. The cost of managing outbreaks associated with specific antimicrobial-resistant pathogens was not estimated due to lack of appropriate data and timing constraints.

3 Research question 2: Economic analysis

3.1 Key points

- The aim of this research question was to estimate the costs associated with antimicrobial resistance (AMR) with respect to public acute hospital care in Ireland. This research question comprised two parts:
    1. estimate the burden of disease due to AMR
    2. estimate the additional cost of treating resistant relative to susceptible infections in the public acute hospital system in Ireland.
- AMR surveillance data, as collated by the Health Protection Surveillance Centre (HPSC) and reported to the European Antimicrobial Resistance Surveillance (EARS-Net) system, were used as the primary data source.
- Based on the Irish EARS-Net data, 814 of the 6,117 blood stream infections (BSIs) of the eight bacterial pathogens of concern were resistant to at least one of the antimicrobials examined, representing an AMR rate of 13.31%.
- The burden of disease is specifically concerned with the measurement of health loss. The disability-adjusted life year (DALY), is a utility measure, commonly used in burden of disease studies that refers to the loss of one year of full health. A DALY is equal to the sum of the years of life lost (YLL) due to premature mortality plus the years lost due to disability (YLD) for people living with a health condition or its consequences.
- Part 1 used a step-wise approach to estimate the burden of disease due to AMR in all 50 public acute hospitals in Ireland in 2019. This population-modelling methodology developed by the European Centre for Disease Prevention and Control (ECDC) focusses exclusively on 16 antibiotic resistance-bacterium combinations that are considered to be of public health concern within the European Union and European Economic Area (EU/EEA).
- Part 2 used a simulation model to estimate the additional costs associated with treating these selected resistant infections relative to susceptible infections, with outcomes reported as the additional cost per excess bed day.
- The total number of resistant infections (BSI and non-BSI) in all 50 public acute hospitals in Ireland in 2019 was estimated to be 4,787 (95% confidence interval (CI), 2,432-14,764), which resulted in an expected total additional cost, relating to excess length of stay (LOS), of €12,020,068 (95% CI: €4,879,603 - €23,267,352), relative to susceptible infections. These estimates were found to be broadly similar to those previously reported by the Organisation for

Economic Co-operation and Development (OECD) for Ireland.

- These resistant infections accounted for an estimated 215 attributable deaths (95% uncertainty interval (UI): 208-222) and 4,961 DALYs (95% UI: 4,861-5,062). The burden of disease was found to be highest in males, and in infants (<1 year) and older adults (≥65 years).
- The base case analysis assumed an average cost per inpatient bed day of €737 for excess LOS, which might underestimate the true economic burden on public acute hospitals, due to more costly intensive care unit (ICU) admissions. The number of ICU admissions and the excess LOS spent in ICU due to AMR, are currently unknown.
- Scenario analyses were undertaken to assess the impact of potential ICU admission, as well as different durations of stay in ICU, on expected hospital costs. Three scenarios were considered (1) risk of ICU admission by pathogen-infection type combinations with 100% of excess LOS spent in ICU (for admitted cases); (2) different durations of stay in ICU as a proportion of excess LOS (for all cases); and (3) risk of ICU admission by infection type with different durations of stay as a proportion of excess LOS (for admitted cases).
- In the first scenario, where the difference in the proportion of individuals with resistant relative to susceptible infections that experienced complications was used as a proxy for ICU admission, the total additional cost was estimated to be €11,561,842 (95% CI: €4,574,594-€22,528,949). Where the difference in the proportion of individuals with resistant relative to susceptible infections that experienced complications, or who died, was used as a proxy for ICU admission, the total additional cost was estimated to be €11,848,838 (95% CI: €4,810,681-€22,302,611).
- In the second scenario, when 100% of the excess LOS was spent in ICU for all cases, representing a worst-case scenario, the total additional cost was estimated to be €33,949,931 (95% CI: €14,060,290-€64,224,879).
- In the third scenario, when 100% of the excess LOS was spent in ICU for admitted cases, which varied by infection type, the total additional cost was estimated to be €15,515,044 (95% CI: €6,594,222-€28,723,702).
- Models are simplifications of complex systems and rely heavily on the underpinning data and assumptions. AMR is a complex phenomenon that can affect individuals differently, resulting in very different outcomes and costs, and models may not be able to accurately reflect these complexities. It is important to consider these inherent limitations when interpreting the findings

of this study.

- This study was restricted in terms of the included pathogens and only considered costs relating to excess length of stay. Therefore the costs estimated in this report are acknowledged to be an underestimate of the total costs of AMR to public acute hospitals.

3.2 Introduction

As discussed in Chapter 2, a diverse range of methodologies can potentially be used to estimate the economic cost of antimicrobial resistance (AMR) in acute hospital settings. While the costing of outbreaks requires in-depth data from individual wards and hospitals, particularly in relation to the organisational disruption that occurs as a result of the outbreak, other studies that cost AMR more generally, tend to use large epidemiological datasets as the primary source of information. Therefore, at a national level, estimating the cost of AMR in general may be more feasible than estimating the cost of pathogen-specific AMR outbreaks.

For the purpose of this current study, AMR surveillance data, as collated by the Health Protection Surveillance Centre (HPSC) and reported to the European Antimicrobial Resistance Surveillance (EARS-Net) system, were used as the primary data source.[80] EARS-Net is the largest publicly funded system for AMR surveillance in Europe, and is the main European surveillance system for AMR in bacteria that cause serious infections. It is managed and coordinated by the European Centre for Disease Prevention and Control (ECDC), and is supported by a coordination committee composed of disease-specific experts. The data collected in EARS-NET are limited to invasive isolates (blood and cerebrospinal fluid (CSF)) and serve as important indicators of the occurrence and spread of AMR in Europe.[23]

Hospital In-Patient Enquiry (HIPE) is the principal source of national data on discharges from public acute hospitals in Ireland. HIPE collects demographic, clinical and administrative data on discharges from, and deaths in, public acute hospitals nationally.[40] Though antimicrobial-resistant infections are coded on HIPE, scoping work done by the evaluation team, in conjunction with EAG input, identified some limitations to using HIPE data for the purpose of estimating the burden of AMR in Ireland. These issues included an apparent under-reporting of AMR on HIPE and the mutually non-exclusive nature of some of the AMR codes. Therefore, HIPE data were not used as the primary data source for this question, but these data did inform some of the model input parameters.

The HPSC is the statutory organisation in Ireland responsible for the collation, analysis and dissemination of notifiable disease data.[80] All medical practitioners, including clinical directors of diagnostic laboratories, are required to notify the Medical Officer of Health or the Director of Public Health of certain infectious diseases. The list of diseases (and their respective causative pathogens) that are notifiable is contained in the Infectious Diseases Regulations 1981 and subsequent amendments. Included on this list of notifiable diseases are invasive infections (that is, infections of the blood or CSF) caused by *Enterococcus* species *(spp.), Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus* and *Streptococcus pneumoniae.*[81]

EARS-Net data are collected and analysed in accordance with a reporting protocol,[82] using European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines on clinical breakpoints, in order to standardise definitions of clinical antimicrobial susceptibility across laboratories.[83] EARS-Net facilitates surveillance of antimicrobial susceptibility of eight bacterial pathogens commonly causing infections in humans: *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter spp., Streptococcus pneumoniae, Staphylococcus aureus, Enterococcus faecium* and *Enterococcus faecalis*. All of these pathogens, with the exception of *Acinetobacter spp.*, are notifiable pathogens in Ireland, in accordance with the Infectious Diseases Regulations 1981, as amended.[81] All public and private acute hospitals in Ireland, comprising a total of 61 hospitals, contributed to EARS-Net in 2019 (the most recently available full year of data), with data being provided by 39 microbiology laboratories.[84] In addition, 84% of Irish laboratories that contributed data in 2019 to EARS-Net participated in an External Quality Assessment (EQA) to assess the reliability of the laboratory test results.[85] The national coverage and representativeness of populations, hospitals and isolates included in the Irish EARS-Net data is notably high by European standards.[23] The use of EARS-Net as the primary epidemiological data source for estimating the economic cost of AMR in all public acute hospitals in Ireland, is therefore justified by the mandatory and standardised reporting of these data, the national coverage of contributing laboratories, the high participation rate in an EQA programme, and the high level of sample representiveness.

The burden of disease is specifically concerned with the measurement of health loss, as opposed to income or productivity loss, and is an important way of comparing the impact of different diseases and conditions on populations.[86] The disability-adjusted life year (DALY), is a utility measure, commonly used in burden of disease studies, that refers to the loss of one year of full health.[47] The DALY utility measure takes into account the burden of both fatal and non-fatal disease states. A DALY is equal to the sum of the years of life lost (YLL) due to premature mortality plus the years lost due to disability (YLD) for people living with a health condition or its consequences.[87] Estimation of the burden of disease, using DALYs, enables policy-makers to compare diseases and to understand their relative contributions to health loss.[86]

The aim of this research question was to estimate the costs associated with AMR with respect to public acute hospital care in Ireland.

3.3 Methods

3.3.1 Review question

With respect to public acute hospital care in Ireland, what are the costs associated

with AMR?

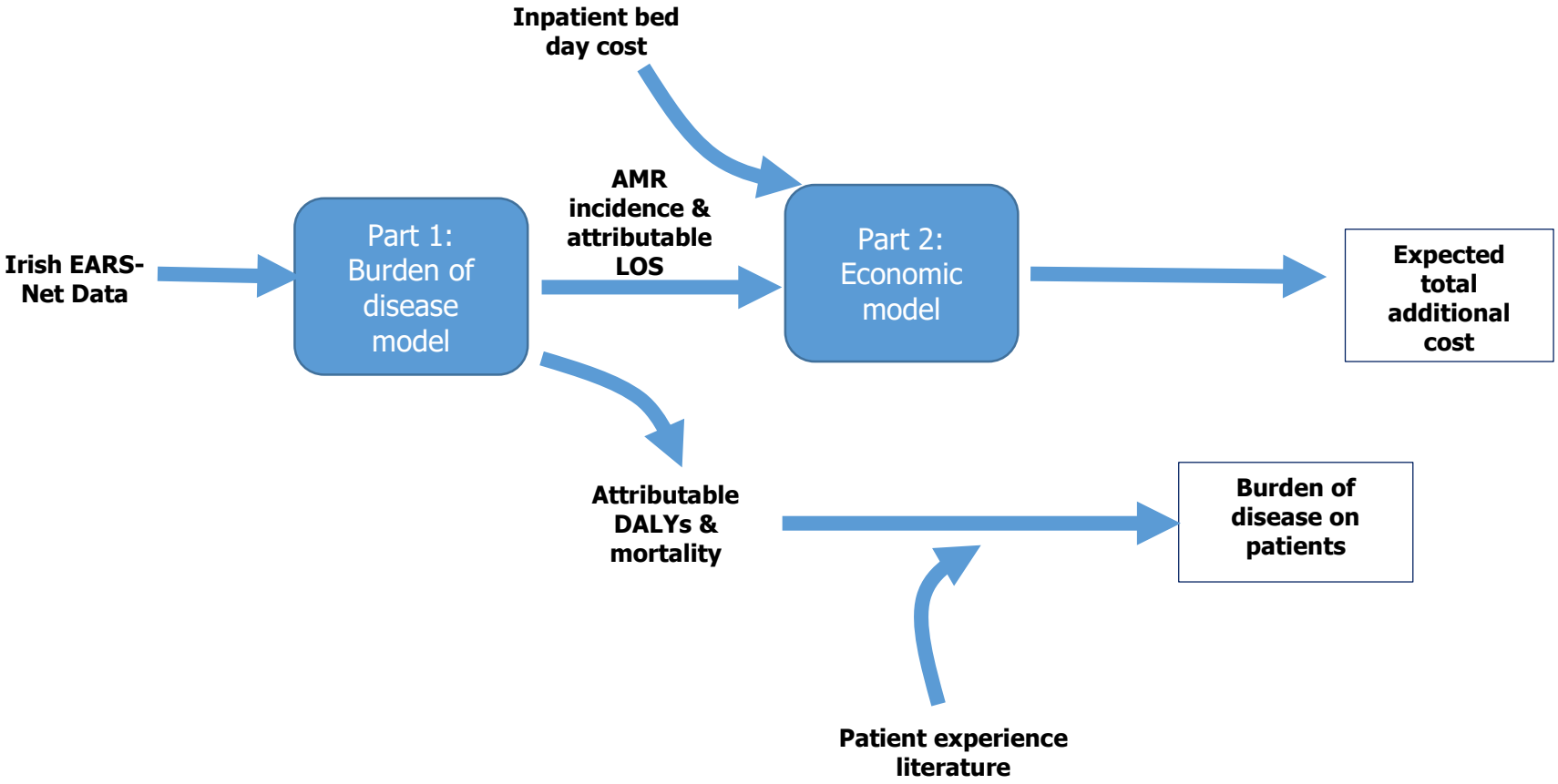
3.3.2 Overall approach

There were two main parts to this research question as outlined in Figure 3.1:

- Part 1: Estimation of the burden of disease
- Part 2: Estimation of the additional cost due to AMR.

The inputs to Part 1 were the EARS-Net data collected from public acute hospitals in Ireland in 2019. The outputs of Part 1 were the incidence of AMR, the attributable length of stay (LOS), DALYs and mortality. The attributable DALYs and mortality were combined with a brief overview of patient experience literature to describe the burden of disease on patients. The inputs to Part 2 were the incidence of AMR, the attributable LOS and cost per inpatient bed day. The outputs of Part 2 were the additional cost associated with treating resistant infections relative to susceptible infections. Four analysts worked on individual sections of this research question. Quality assurance was undertaken by a second analyst in each case to ensure accuracy of findings.

Figure 3.1: Overview of methodological approach for review question 2



Key – AMR – antimicrobial resistance; DALYs –disability-adjusted life years; EARS-Net - European Antimicrobial Resistance Surveillance Network; LOS – length of stay.

3.3.3 Part 1: Estimation of the burden of disease due to AMR

Part 1 of this research question used a step-wise approach as developed the ECDC (henceforth called the ECDC study), to estimate the burden of disease due to AMR in all 50 public acute hospitals in Ireland.[28] This population-modelling methodology focusses exclusively on 16 antibiotic resistance-bacterium combinations that are considered to be of public health concern within the European Union and European Economic Area (EU/EEA) (Table 3.1). The approach used by the ECDC had been adapted from a previous ECDC-funded project (Burden of Communicable Disease in Europe (BCoDE)), that developed a new methodology to estimate the burden of infectious diseases.[88] The BCoDE methodology uses a pathogen-based incidence approach to estimate the burden of disease, taking into account chronic sequelae that can be causally linked to the pathogen.[88]

Table 3.1: The 16 included antibiotic resistance bacterium combinations

Antibiotic resistance-bacterium combinations considered to be of public health concern within the EU/EEA
1. *Acinetobacter* spp., Colistin-resistant
2. *Acinetobacter* spp., Carbapenem-resistant (excluding isolates also resistant to colistin)
3. *Acinetobacter* spp., Aminoglycoside- and fluoroquinolone-resistant (excluding isolates also resistant to colistin and/or carbapenem)
4. *E. faecalis* and *E. faecium*, Vancomycin-resistant
5. *E. coli* , Colistin-resistant
6. *E. coli*, Carbapenem-resistant (excluding isolates also resistant to colistin)
7. *E. coli,* Third-generation cephalosporin-resistant (excluding isolates also resistant to colistin and/or carbapenem)
8. *K. pneumoniae*, Colistin-resistant
9. *K. pneumoniae*, Carbapenem-resistant (excluding isolates also resistant to colistin)
10. *K. pneumoniae*, Third-generation cephalosporin-resistant (excluding isolates also resistant to colistin and/or carbapenem)
11. *P. aeruginosa*, Colistin-resistant

12. *P. aeruginosa*, Carbapenem-resistant (excluding isolates also resistant to colistin)
13. *P. aeruginosa,* Resistance to three or more antibiotic groups (excluding isolates also resistant to colistin and/or carbapenem)
14. *S. aureus*, Meticillin-resistant
15. *S. pneumoniae*, Penicillin-resistant (excluding isolates also resistant to macrolides)†
16. S. pneumoniae, Penicillin- and macrolide-resistant (excluding isolates only resistant to penicillin)†

Key – *Escherichia coli – E. coli; E. faecalis* and *E. faecium - Enterococcus faecalis* and *Enterococcus faecium; Klebsiella pneumoniae – K. pneumoniae; Pseudomonas aeruginosa - P. aeruginosa; Staphylococcus aureus – S. aureus; Streptococcus pneumoniae – S. pneumoniae.*
† Penicillin-resistant *S. pneumoniae* did not include those that are defined as "Susceptible, increased exposure" as defined by EUCAST 2019 guidelines.

Within Part 1, there are three steps involved in estimating the burden of disease in accordance with the methodology developed by the ECDC:[28]

1. using established disease models and estimating attributable mortality and LOS
2. estimating the incidence of AMR for the 16 specific AMR-pathogen combinations outlined in Table 3.1.
3. calculating burden of disease using the BCoDE toolkit.[89]

3.3.3.1 Using established disease models and estimating attributable mortality and LOS

The ECDC developed disease outcome trees for five main categories of infections:

- blood stream infections (BSIs)
- respiratory tract infections (RTIs)
- urinary tract infections (UTIs)
- surgical site infections (SSIs)
- other infections (including digestive tract infections, skin and soft tissue infections, eye, ear, nose or mouth infections, bone and joint infections, cardiovascular infections, reproductive tract infections and other less frequent infections)).[28]

A disease outcome tree describes the course of a disease over time, starting at the initial infection followed by all subsequent relevant health outcomes and ending with persistent health outcomes (for example, death) or recovery.[90] The baseline model

structures in the ECDC model were adapted from previous literature reviews[90] and modelling work.[91] Disability weights were derived from the European disability weight study by Haagsma et al.[92] This resulted in the creation of baseline models for the five types of infections, without incorporating the impact of AMR (Appendix 5).

As part of their study, the ECDC conducted a series of systematic reviews to determine the attributable mortality, as well as the attributable LOS, for each of the 16 antibiotic resistance-bacterium combinations within each of the five main infection categories.[28] For these 16 systematic reviews, the attributable risk was calculated by comparing the absolute risks between patients with the respective resistant infection and matched patients without the infection or infected with a susceptible strain. A total of 281 papers were included and these informed the estimation of attributable mortality and LOS for each of the 16 antibiotic resistance-bacterium combinations. The authors of this study discussed and agreed on the best summary estimates for each of the disease models. A summary of the final disease health outcome parameters, along with the baseline parameters are provided in Appendix 6.

For the purpose of the current study, we used the disease models, and the attributable mortality and LOS, as estimated in the ECDC study.[28]

3.3.3.2 Estimating incidence of AMR

The 2019 EARS-Net dataset containing all susceptible and resistant invasive (blood or CSF) infections with the eight bacterial pathogens of interest, limited to public acute hospitals in Ireland, was provided by the HPSC to the evaluation team. Stata software version 16 (StataCorp, Texas, USA) was used by the evaluation team to clean these raw data and code according to resistance pattern, sex and age group. No data imputation was required given the completeness of the 2019 dataset.

The ECDC study herein describes a three step process for estimating the incidence of AMR once the resistant cases have been extracted from the EARS-Net dataset, and re-organised according to sex and age groups.[28]

Step 1: Correct for under ascertainment of cases

Population coverage (with regards to the proportion of laboratories and hospitals within a country that report data to EARS-Net) is an important factor when interpreting the number of isolates reported to EARS-Net. This national population coverage varies from country to country but in general, Ireland has very high levels of coverage, reported as being 96-100% since 2015, with participating laboratories considered to have high levels of geographical representativeness.[23] Additionally, all public and private acute hospitals in Ireland, comprising of a total of 61 hospitals, contributed to EARS-Net in 2019, with data being provided by 39 microbiology laboratories.[84] At a pathogen-level, the estimated population coverage also varies

substantially from country to country, however Ireland tends to have very high levels of coverage, by European standards. Given the high degree of coverage and representativeness of population, hospitals and isolates in the Irish EARS-Net data, no under ascertainment correction was performed by the evaluation team.

Step 2: Apply correction factors to account for non-BSIs

EARS-Net data are exclusively based on invasive isolates from blood or CSF. This restriction prevents some of the inconsistencies that arise from differences in clinical case definitions, different sampling frames or heterogeneous healthcare utilisation that would otherwise confound the data analysis if isolates from all anatomical sites were accepted. However, invasive isolates may not be representative of isolates of the same bacterial species from other type of infections (for example, UTIs, SSIs and RTIs).[93] Importantly, the ECDC study treated all invasive isolates as BSIs, as it is assumed that the number of CSF isolates were negligible. In order to account for non-BSIs, a correction factor was applied to each BSI from EARS-Net. This was a multiplier to reflect the ratio of BSIs to non-BSIs for each antibiotic-resistance-bacterium combination. These correction factors were derived from a European-wide point prevalence survey (PPS) of health-care-associated infections (HCAIs) in acute care hospitals conducted in 2016/2017.[94]

The PPS 2016/2017 study did not collect data with respect to *S. pneumoniae.* Therefore, the ECDC undertook a comprehensive literature review followed by expert opinion to estimate the conversion factors for this pathogen.[28] The infection site conversion factors were provided by the ECDC to the evaluation team and are outlined in Appendix 7. For each antibiotic-resistant bacterium, the conversion factors along with the 95% confidence intervals (95% CIs) were applied to the age group and sex data, to estimate the number of UTIs, RTIs, SSIs, and other infections in Ireland.

Step 3: Apply reduction factors to correct for secondary BSIs

The percentage of secondary BSIs were then subtracted from each of the non-BSIs,[28] due to the fact that any infection leading to a secondary BSI retrieved through the ECDC point prevalence study is is expected to be reported as BSI in EARS-Net, which may lead to double-counting of infections. Therefore, the percentage of secondary BSIs from each of the other infection sites[95, 96] were deducted from infections in other sites. This deduction was applied to the number of cases for each non-BSI infection site. The reducing factors calculated from the 2016/2017 ECDC PPS are outlined in Appendix 7. [95] The reducing factors were applied to age group and sex adjusted cases obtained from step 2, in order to estimate the number of all infections for each antibiotic-resistant bacterium combination. When the initial number of cases is low, the resulting lower uncertainty

bound after Step 3 can be negative. In these cases it was assumed that in those cases the lower uncertainty bound is 0.

The ECDC did not apply a reducing factor for *S. pneumoniae* due to the lack of evidence from the literature.[28] Given this lack of evidence, the current study did not apply a reducing factor for *S. pneumoniae.*

At the end of this process, the incidence of each of the 80 resistant pathogen-infection type combinations (comprising the five different infection types for each of the 16 antibiotic resistance-bacterium combinations) were estimated with medians and 95% CIs, and reported according to age group and sex.

Of note, 27 of these 80 possible resistant pathogen-infection type combinations were estimated to have 0 cases in Ireland in 2019. That is, the 2019 Irish EARS-Net dataset included no reports of:

- colistin-resistant invasive cases in any of the four included gram-negative bacilli pathogens (*E. coli, P. aeruginosa, Acinetobacter spp.* and *K. pneumoniae*)
- combined penicillin- and macrolide-resistant invasive cases of *S. pneumoniae*.

If there are no BSI cases reported, the ECDC conversion factors assume that there are no non-BSI cases of that antibiotic resistance-bacterium combination in the population (Appendix 7). Collectively, these account for 25 of the 80 pathogen-infection type combinations. Additionally, the ECDC conversion factors assume that UTIs and SSIs of *S. pneumoniae* are clinically rare, and so penicillin-resistant *S. pneumoniae* BSIs were not converted to UTIs or SSIs (Appendix 7), thus accounting for another two of the 80 resistant pathogen-infection type combinations. As a result of these assumptions, a total of 53 resistant pathogen-infection type combinations had at least one reported case.

Descriptive statistics were used to summarise the population and incidence estimates, using both Stata software version 16 (StataCorp, Texas, USA) and Excel 2013 (Microsoft, Washington, USA).

3.3.3.3 Calculating burden of disease using the BCoDE toolkit

Computational and uncertainty analysis were conducted using the bespoke BCoDE software toolkit created by the ECDC.[89] Using the BCoDE toolkit, DALYs were estimated by inputting the age group- and sex-specific number of cases for each of the 16 antibiotic-resistance-bacterium combinations divided according to each of the five main types of infections (BSI, RTI, UTI, SSI and other). Therefore, a total of 80 disease models were included in the estimation of the burden of disease for this study.

The disease progression models within this toolkit are based on the comprehensive systematic review and analysis of health outcome parameters by the ECDC described above.[28] The BCoDE burden of disease model was run for 10,000 Monte Carlo simulations of the input parameters and provided results specific to each of the 80 disease models, including 95% uncertainty intervals (UI)[97] Necessary input data were the number of annual cases (calculated from above) and 2019 demographic data from the Central Statistics Office (CSO) in Ireland.[98] Outputs included detailed information on incidence, attributable mortality, YLL, YLD and DALYs, for each of the 80 disease models, as well as aggregated results. Estimates were calculated in absolute terms as well as per 100,000 population. Medians are reported alongside their 95% UI on the basis of the input uncertainties. To reflect the broad range of uncertainty in the estimates of the burden of disease, arising from the coimbination of multiple data sources, for example, the BCoDE reports outcomes using UIs.

3.3.3.4 Describing the health and economic burden of AMR on patients

To describe the health and economic burden of AMR on patients, the findings from this study were examined in conjunction with a brief literature review of the impact of AMR on patients, which includes those who are infected or colonised with a resistant pathogen, as well as their carers and family members. To structure this brief literature review, the Health Technology Assessment (HTA) Core Model® developed by the European Network for HTA (EUnetHTA) (specifically, the 'Patients and Social aspects' domain)[99] and a framework developed by Krahn et al. for use in HTA were used.[100] Patients' perspectives on their illnesses provide a unique insight, and are central to any discussion on the burden of disease. Both qualitative and quantitative research of relevance to the current study were included.

3.3.4 Part 2: Estimation of the additional cost due to AMR

Part 2 of this research question centred on estimating the additional costs associated with treating resistant relative to susceptible infections, with outcomes reported as the additional cost per excess bed day. Excess bed days refers specifically to the time spent in hospital by one group (that is, those with resistant infections) over and above the time spent in hospital by the other group (that is, those with suspectible infections). This outcome relates specifically to the incremental time spent in hospital by those with resistant relative to susceptible infections, and so does not refer to the total time spent in hospital.

Based upon the findings of Chapter 2, in conjunction with EAG advice and awareness of the available Irish data, a simulation model was decided as the most appropriate method of analysis. The study estimated the additional cost of treating a resistant compared with a susceptible infection, as a means of understanding the economic burden that is specifically attributable to AMR, as opposed to that attributable to all

infections.[29] The model was similar to those used by the Organisation for Economic Co-operation and Development (OECD),[10] Wozniak et al.,[72] and Bartsch et al.[59] as identified in the first research question.

3.3.4.1 Overview of the economic analysis

The economic analysis was undertaken from the perspective of the public acute hospital system in Ireland. The time horizon for the economic analysis was one year. A retrospective, prevalence-based approach was adopted to estimate annual costs. The reference year was 2019. Since the analysis was retrospective and all costs accrued in the same year, discounting was not applied. A top-down costing approach was used to estimate the cost associated with an inpatient hospital bed day using data from the Healthcare Pricing Office (HPO) in Ireland.[41, 101]

The model estimated the additional cost to the health system of treating 16 antibiotic-resistance bacterium combinations (outlined in Table 3.1). As illustrated in Figure 3.1, the input parameters of the model were the:

- AMR incidence based on the EARS-Net data collected from all 50 public acute hospitals in Ireland
- attributable LOS estimates for each antibiotic-resistance bacterium combinations
- average inpatient bed day cost for public acute hospitals.

As discussed in Part 1, the incidence for each of the 16 antibiotic-resistance bacterium combinations according to the five main types of infections (BSI, SSI, UTI, RTI and other types) were estimated in line with the population-modelling methodology developed by the ECDC.[28] Hence, a total of 80 AMR incidence parameters were used in the model.

Data in relation to LOS were taken from the ECDC study.[28] In this paper, the range in LOS for each infection type (including resistant and susceptible infections) was presented. In some cases, the median length of stay was reported, as well as the range; in cases where the median was not reported, for the purposes of this analysis, the average LOS was calculated. To calculate excess LOS associated with a resistant infection, the LOS of an individual with a susceptible infection was subtracted from the LOS of an individual with a resistant infection in accordance with the approach taken by the OECD.[10] The model also assumed that the LOS of resistant infections was at least the same duration as that of susceptible infections. The LOS data are presented in Appendix 8.

The model only included direct costs to public acute hospitals in Ireland, in line with HIQA guidelines for economic evaluations.[102] Specifically, an average cost per in patient bed day was applied in the base case analysis. Though the first research

question identified a number of studies with cost data pertaining to inpatient bed days,[10, 56, 58, 59, 61-63, 65-67, 70-74] none were applicable to the Irish healthcare system. Currently, there are no agreed Irish cost models available.[102] As a result, estimation of the value of an average inpatient bed day was required. The research team assumed that the daycase base price of €737, as outlined in the Activity Based Funding (ABF) 2019 Admitted Price List, was equivalent to the average inpatient bed day cost in public acute hospitals in Ireland in 2019.[41] It was assumed that this cost incorporated all relevant costs associated with inpatient care, for example, accommodation, staffing, treatment, cleaning etc.

Since an average cost per inpatient bed day might not reflect the true cost of treating resistant infections in Irish hospitals, for example, due to the need for more critical care in severe cases, a higher cost specific to intensive care was considered in scenario analyses. Costs specific to non-intensive care, such as care in a general ward, were also considered. Based on personal communications with the HPO,[101] along with an estimation of total bed capacity and utilisation across all public acute hospitals,[103, 104] costs for an ICU and non-ICU bed day were estimated by the evaluation team. The cost for an ICU bed day was provided by the HPO in confidence as an indicative, rather than authoritative, price. The estimated bed day cost was for an available bed (that is, it assumed capacity was available within the system to facilitate intensive care at no additional cost).

3.3.4.2 Base case analysis

To estimate the additional costs to the public acute hospital system of treating resistant relative to susceptible infections in Ireland in 2019, a probabilistic analysis was undertaken in Excel 2013 (Microsoft, Washington, USA). Ten thousand Monte Carlo simulations were performed, with point-estimates randomly sampled from predefined probability distributions. The expected costs were computed as an average over the 10,000 simulations.

A gamma distribution was assumed for count parameters, including LOS and the incidence of resistant infections. Given the lack of uncertainty around the incidence estimates for BSIs, fixed values were applied in the model, in accordance with the ECDC conversion factors. Since a gamma distribution samples from the mean rather than the median of a probability distribution, it was important to convert the EARS-Net data, which were reported as median values; use of median values may under- or over-estimate the incidence of resistant infections depending on whether the data are positively or negatively skewed. A method developed by Wan et al. was used to estimate the mean from the median, range, and sample size for each antibiotic resistant bacterium.[105] There was insufficient information for the LOS data to estimate the mean LOS for each parameter. In scenarios where median values were

reported by the ECDC, an assumption was made that these were the same as the mean.[28] A lognormal distribution was used for costs with a standard deviation of 0.1 (or 10% of the baseline value) assumed.

3.3.4.3 Scenario analyses

Scenario analyses were undertaken to investigate the influence of key parameter inputs and assumptions used in the base case analysis on expected costs.[102] For the purposes of these analyses, 10,000 Monte Carlo simulations were performed.

The scenarios assessed the influence of higher hospital costs arising from potential ICU admission and different durations of stay in ICU on expected costs. In particular, three scenarios were considered to assess the impact of (1) risk of ICU admission by pathogen-infection type combinations with 100% of excess LOS spent in ICU (for admitted cases); (2) different durations of stay in ICU as a proportion of excess LOS (for all cases); and (3) risk of ICU admission by infection type with different durations of stay in ICU as a proportion of excess LOS (for admitted cases).

1. To assess the impact of the risk of ICU admission for each of the 80 pathogen-infection combinations on expected costs, where 100% of the excess LOS was spent in ICU for any admitted cases, the BCoDE simulation model was used to estimate the proportion of patients that experienced complications or deaths; the absolute difference in proportions between resistant and susceptible infections was used as a proxy for ICU admission in the simulation model, with two scenarios considered. In scenario A, the proportion of patients with resistant infections that experienced complications was used as a proxy for ICU admission, while in scenario B, the proportion of patients with resistant infections that experienced complications, or who died, was used as a proxy for ICU admission. In both scenarios, it was assumed that the excess LOS was spent in ICU.

2. To assess the impact of different durations of stay in ICU as a proportion of excess LOS on expected costs for all cases, a threshold analysis was conducted. The threshold analysis varied the duration of stay in ICU between 0 and 100% for all resistant cases. The analysis presents an extreme worst case scenario, whereby up to 100% of all excess LOS is spent in ICU (assuming there is ICU capacity for the resistant cases).

3. To assess the impact of the risk of ICU admission by infection type with different durations of stay in ICU as a proportion of excess LOS for admitted cases on expected costs, a weighted probability of admission to ICU was estimated for the different infections and a threshold analysis on duration of stay was applied for cases admitted to ICU. For the purposes of this analysis,

it was assumed that the mortality rate, as per the baseline disease outcome tree (Appendix 5) (that is, 14.85% in BSIs, 3.6% in RTIs, 2.7% in SSIs and 0% in UTIs and in other infections), was indicative of the proportion of each of the five main infection types that get admitted to ICU. Importantly, for all of these analyses, it is assumed that the risk of death or complications in non-BSIs excludes the risk attributable to secondary BSIs, as this latter risk is already accounted for in BSIs. A continuity factor of 0.5% was added to all infection types to account for cases that get admitted to ICU but do not result in death. These data were used to estimate a weighted probability of admission to ICU for the different infections. As per these data, 65% of those with a resistant BSI were admitted to ICU, as well as 17% of those with a resistant RTI, 14% of those with a resistant SSI, and 2% of those with a resistant UTI or other infection type. The threshold analysis was conducted for cases admitted to ICU only, with the duration of stay in ICU as a proportion of excess LOS varied between 0 and 100% (as in scenario 2). For cases that were not admitted to ICU, it was assumed that the excess LOS in hospital was spent in a general ward (that is, a general ward bed day cost was applied, rather than an average inpatient bed day cost).

When interpreting the findings of the scenario analyses, it is important to remember that the outcome relates specifically to the incremental time spent in hospital by those with resistant relative to susceptible infections. The assumptions underpinning the economic model are that those with resistant infection spend at least the same amount of time in hospital as those with equivalent susceptible infections, based on evidence syntheses conducted by Cassini et al.,[28] the evidence tables for which are replicated in Appendix 6. While there are evidence-based estimates for the excess LOS for each of the 16 antibiotic resistance bacterium combinations, the evidence base is relatively poor with regards to excess ICU duration. It is possible that none, some, or the entirety of excess time in hospital, for a patient with a resistant infection, may be spent in ICU. It is also possible that patients with certain resistant infections are more likely to get admitted to ICU than patients with other resistant infections. Hence the need for these scenario analyses, which explores these interacting possibilities.

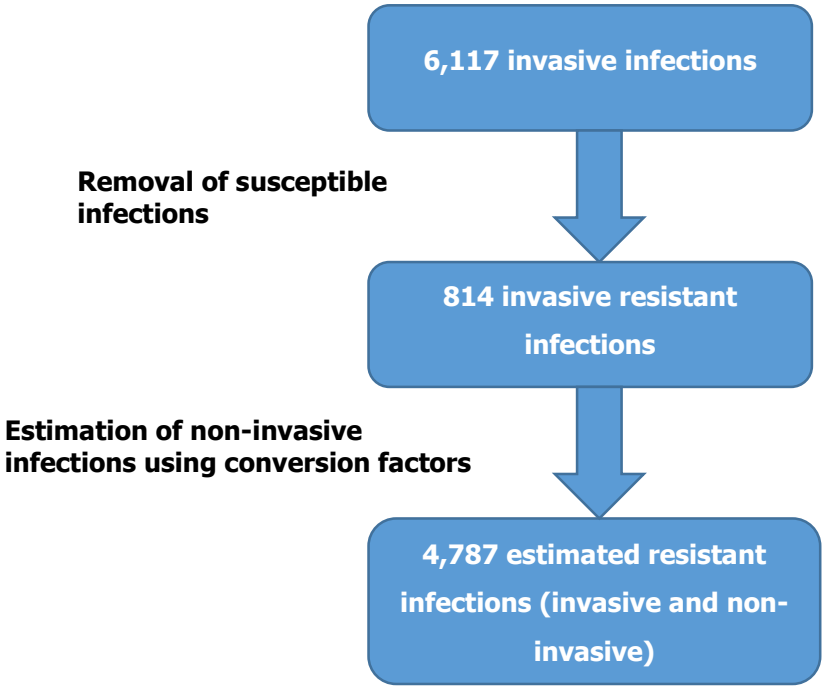
3.4 Results

3.4.1 Incidence of AMR

Of 6,117 invasive infections with the eight pathogens of interest reported to the EARS-Net system in 2019 from all 50 public acute Irish hospitals, 814 (13.31%) were resistant, in line with the definitions in Table 3.1. Using the ECDC conversion factors,[28] the total estimated number of resistant cases of all infection types was

4,787 (95% CI: 2,432-14,764) (Figure 3.2).

Figure 3.2: Epidemiological data flow

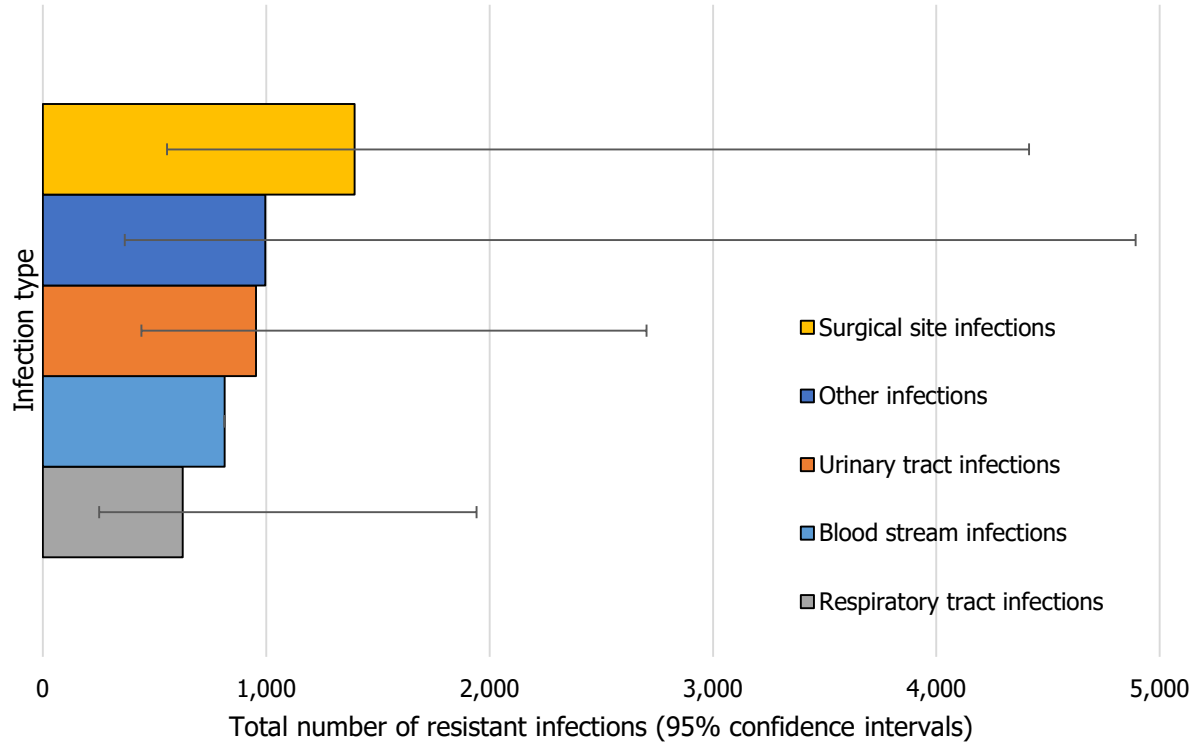


As illustrated in Figure 3.3, of all 4,787 resistant cases, it was estimated that:

- 29.2% (n=1,396; 95% CI: 556-4,414) were SSIs
- 19.9% (n=954; 95% CI: 442-2,703) were UTIs
- 17% (n=814; 95% CI: 814-814) were BSIs
- 13.1% (n=627; 95% CI: 253-1,941) were RTIs
- 20.8% (n=996; 95% CI: 367-4,892) were other infection types.

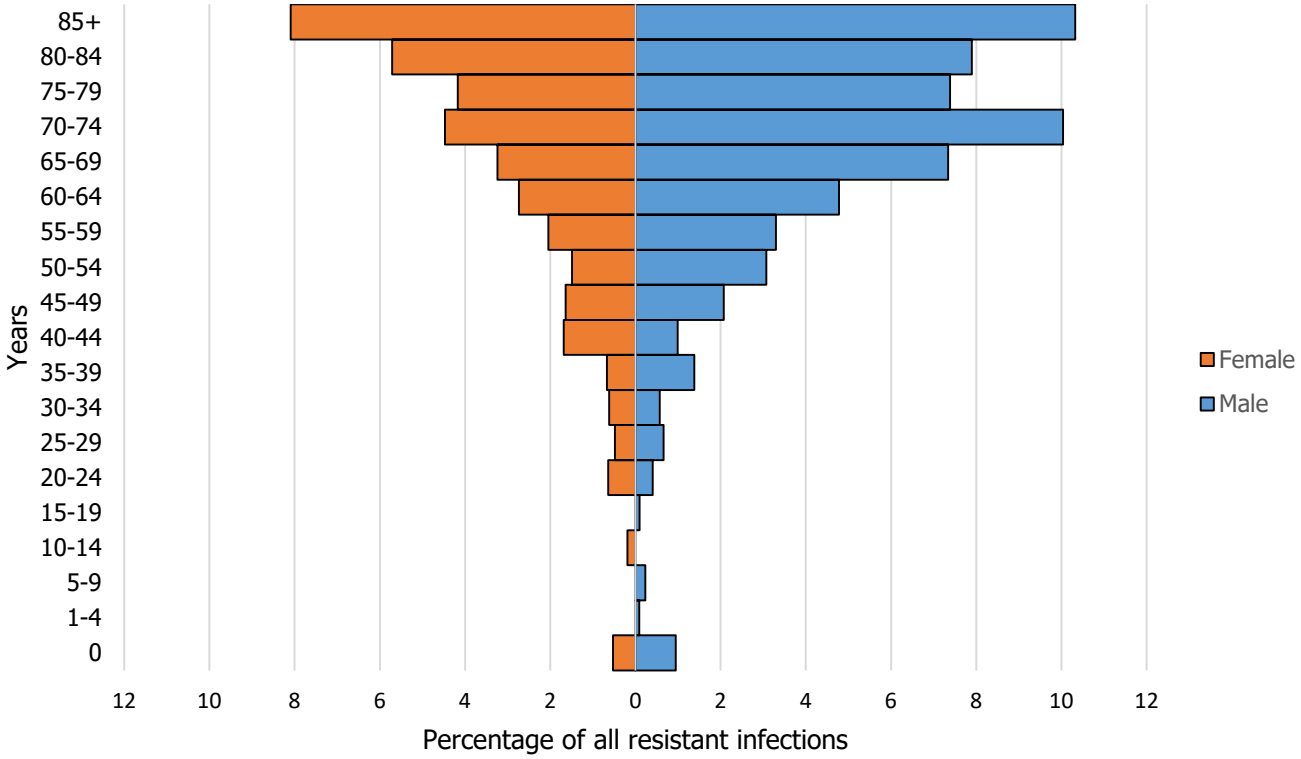
As a result of the methods used for converting BSIs to non-BSIs, there is substantial uncertainty around each of the incidence estimates for the non-BSIs.

Figure 3.3: Total number of resistant infections per infection type



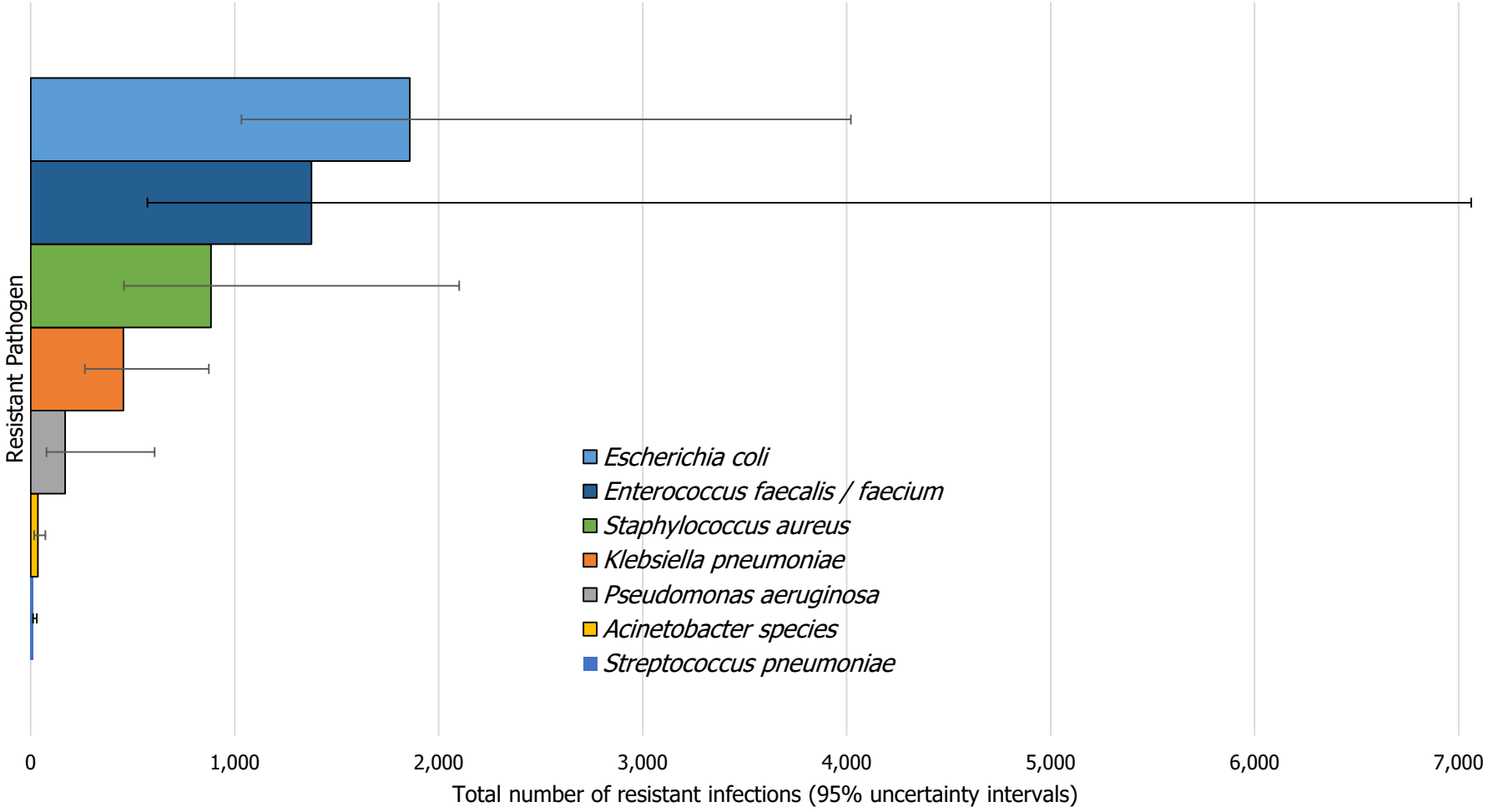
The majority (61.6%), of all resistant infections occurred in males (n=2,949; 95% CI: 1,501-9,014) and in individuals aged 65 years and older (68.7%) (n=3,287; 95% CI: 1,675-9,957) (Figure 3.4). According to CSO population estimates for Ireland in 2019, males accounted for just under half (49.5%) (n=2,438,006) and individuals aged 65 years and older accounted for just under a seventh (14.2%) of the total population (n=696,284).[98] Therefore, males and individuals aged 65 years and older are over-represented in the population experiencing resistant infections. The age-sex pyramids for each of the eight resistant pathogens are available in Appendix 9.

Figure 3.4: All resistant infections by age group and sex



The most prevalent resistant pathogen was *E. coli*, which accounted for 38.7% of all resistant infections (n=1,858; 95% CI: 1,033-4,020) (Figure 3.5). This was followed by *E. faecalis* and *E. faecium* (28.7%) (n=1,376; 95% CI: 572-7,061), *S. aureus* (18.5%) (n=883; 95% CI: 456-2,101), *K. pneumoniae* (9.5%) (n=454; 95% CI: 265-873), *P. aeruginosa* (3.5%) (n=168; 95% CI: 77-608), *Acinetobacter spp.* (0.7%) (n= 34; 95% CI: 16-72) and *S. pneumoniae* (0.3%) (n=13; 95% CI: 12-30).

Figure 3.5: Total number of resistant infections per pathogen



Third-generation cephalosporin resistant *E. coli* (3GCREC) infections were the most prevalent (38.7%) of the 16 antibiotic resistance-bacterium combinations examined (n= 1,853; 95% CI: 1,030-4,010) (Figure 3.6). This was followed by vancomycin-resistant *Enterococci* (VRE) infections (28.7%), specifically *E. faecalis* and *E. faecium* (n=1,376; 95 CI, 572-7,061), meticillin-resistant *S. aureus* (MRSA) infections (18.5%) (n=883, 95% CI: 456-2,101) and third-generation cephalosporin-resistant *K. pneumoniae* (3GCRKP) infections (9.1%) (n=437; 95% CI: 256-836). All remaining combinations each accounted for 2% or less of all resistant infections, and are reported in Table 3.2.

Figure 3.6: Proportion of resistant infections attributable to each antibiotic resistance-bacterium combination

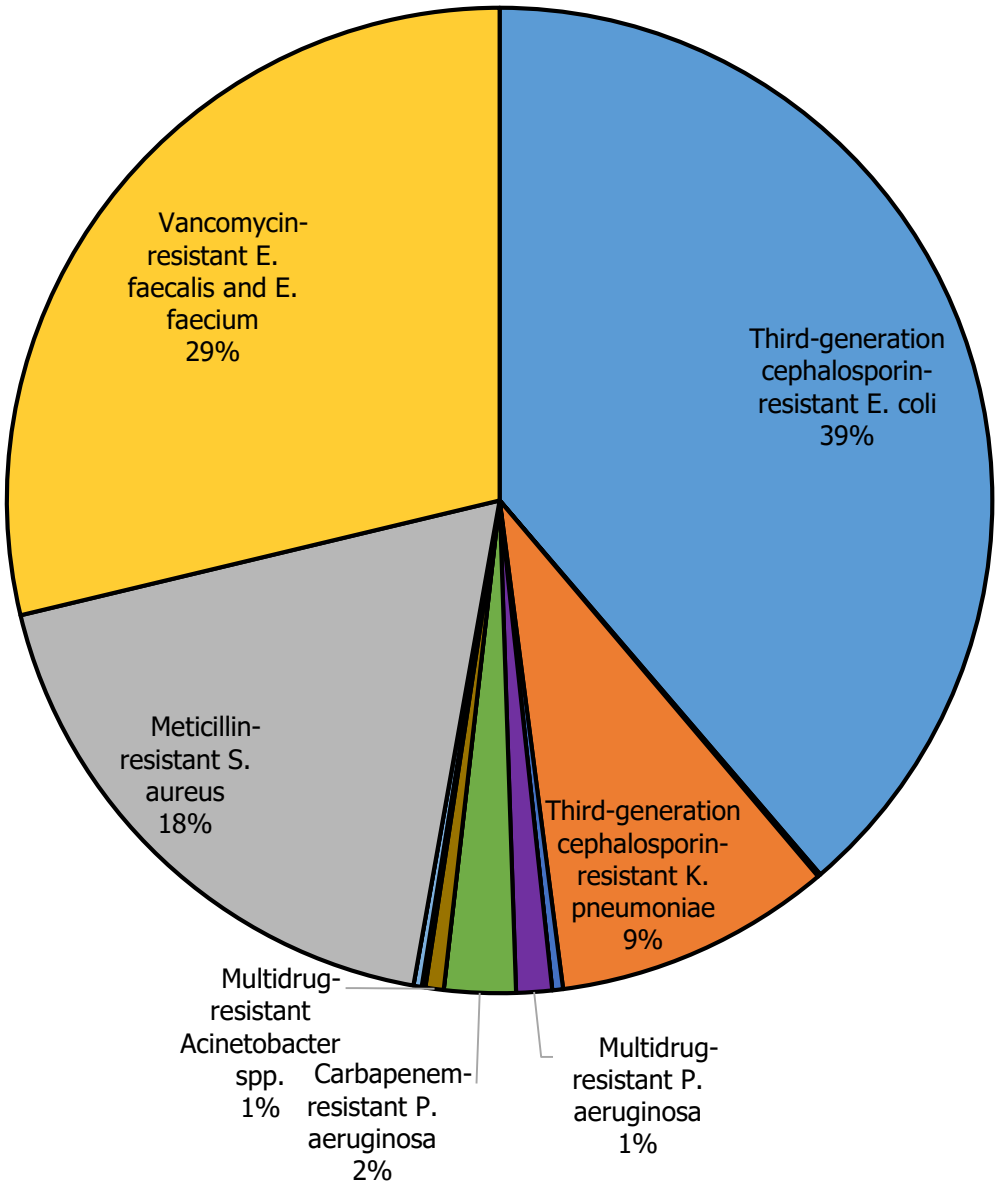


Table 3.2: Incidence of AMR according to each antibiotic resistance-bacterium combination

Pathogen	Total number of infections (95% CI)	Incidence per 100,000 population (95% CI)	Proportion of all resistant infections (%)
Escherichia coli	**1,858.12 (1,033.03-4,020.44)**	**37.76 (20.99-81.69)**	**38.82**
Third-generation cephalosporin-resistant *E. coli*	1,853.43 (1,030.43-4,010.29)	37.66 (20.94-81.49)	38.72
Carbapenem-resistant *E. coli*	4.69 (2.61-10.15)	0.10 (0.05-0.21)	0.10
Colistin-resistant *E. coli*	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0
Klebsiella pneumoniae	**453.84 (265.33-873.10)**	**9.22 (5.39-17.74)**	**9.48**
Third-generation cephalosporin-resistant *K. pneumoniae*	436.91 (256.23-836.20)	8.88 (5.21-16.99)	9.13
Carbapenem-resistant *K. pneumoniae*	16.93 (9.10-36.90)	0.34 (0.18-0.75)	0.35
Colistin-resistant *K. pneumoniae*	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0
Pseudomonas aeruginosa	**168.32 (77.21-607.85)**	**3.42 (1.57-12.35)**	**3.52**
Multidrug-resistant *P. aeruginosa*	56.11 (25.74-202.62)	1.14 (0.52-4.12)	1.17
Carbapenem-resistant *P. aeruginosa*	112.21 (51.47-405.23)	2.28 (1.05-8.23)	2.34
Colistin-resistant *P. aeruginosa*	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0
Acinetobacter species	**34.44 (16.38-71.56)**	**0.70 (0.33-1.45)**	**0.72**
Multidrug-resistant *Acinetobacter spp.*	28.70 (13.65-59.63)	0.58 (0.28-1.21)	0.60
Carbapenem-resistant *Acinetobacter spp.*	5.74 (2.73-11.93)	0.12 (0.06-0.24)	0.12
Colistin-resistant *Acinetobacter spp.*	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0
Streptococcus pneumoniae	**12.90 (11.94-29.61)**	**0.26 (0.24-0.60)**	**0.27**

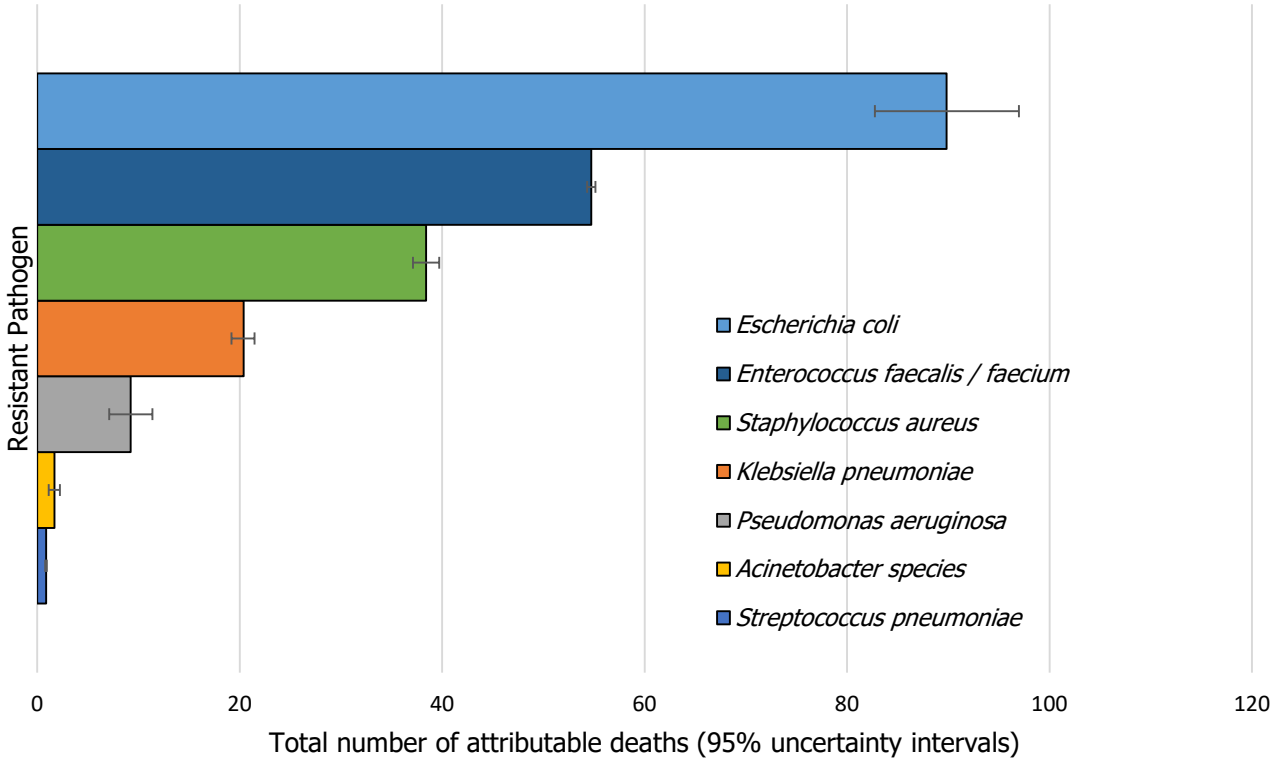
Penicillin-resistant *S. pneumoniae*	12.90 (11.94-29.61)	0.26 (0.24-0.60)	0.27
Penicillin- and macrolide-resistant *S. pneumoniae*	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0
Staphylococcus aureus	**883.48 (456.26-2,100.51)**	**17.95 (9.27-42.68)**	**18.46**
Meticillin-resistant *S. aureus*	883.48 (456.26-2,100.51)	17.95 (9.27-42.68)	18.46
Enterococcus faecalis / faecium	**1375.96 (571.76-7,061.25)**	**27.96 (11.62-143.48)**	**28.74**
Vancomycin-resistant *E. faecalis and E. faecium*	1375.96 (571.76-7,061.25)	27.96 (11.62-143.48)	28.74
Overall	**4787.05 (2,431.91-14,764.32)**	**97.27 (49.41-300.00)**	**100%**

Key – CI - Confidence Interval.

3.4.2 Attributable mortality and DALYs

The total number of deaths attributable to the 16 antibiotic resistance-bacterium combinations in public acute hospitals in Ireland in 2019 was estimated to be 215 (95% uncertainty interval (UI), 208-222) (Table 3.3). It was estimated that resistant strains of *E. coli* contributed the most to these deaths (41.8%) (n=90; 95% UI: 83-97) followed by resistant strains of *E. faecalis* and *E. faecium* (25.5%) (n=55; 95% UI: 54-55), *S. aureus* (17.9%) (n=38; 95% UI: 37-40), *K. pneumoniae* (9.5%) (n=20; 95% UI: 19-21), *P. aeruginosa* (4.3%) (n=9; 95% UI: 7-11), *Acinetobacter spp.* (0.8%) (n=2; 95% UI: 1-2) and *S. pneumoniae* (0.4%) (n=1; 95% UI: 1-1) (Figure 3.7).

Figure 3.7: Total number of attributable deaths per resistant pathogen



Of the 16 antibiotic resistance-bacterium combinations examined, third-generation cephalosporin resistant *E. coli* (3GCREC) infections were associated with the highest proportion (41.6%) of deaths (n= 89; 95% UI: 82-96) (Figure 3.8) (Table 3.3). This was followed by VRE infections (25.5%), specifically *E. faecalis* and *E. faecium* (n=55; 95% UI: 54-55), MRSA infections (17.9%) (n=38; 95% UI: 37-40) and third-generation cephalosporin-resistant *K. pneumoniae* (3GCRKP) infections (8.6%) (n=18; 95% UI: 18-19). All remaining combinations are reported in Table 3.3.

Figure 3.8: Proportion of deaths attributable to each antibiotic resistance-bacterium combination

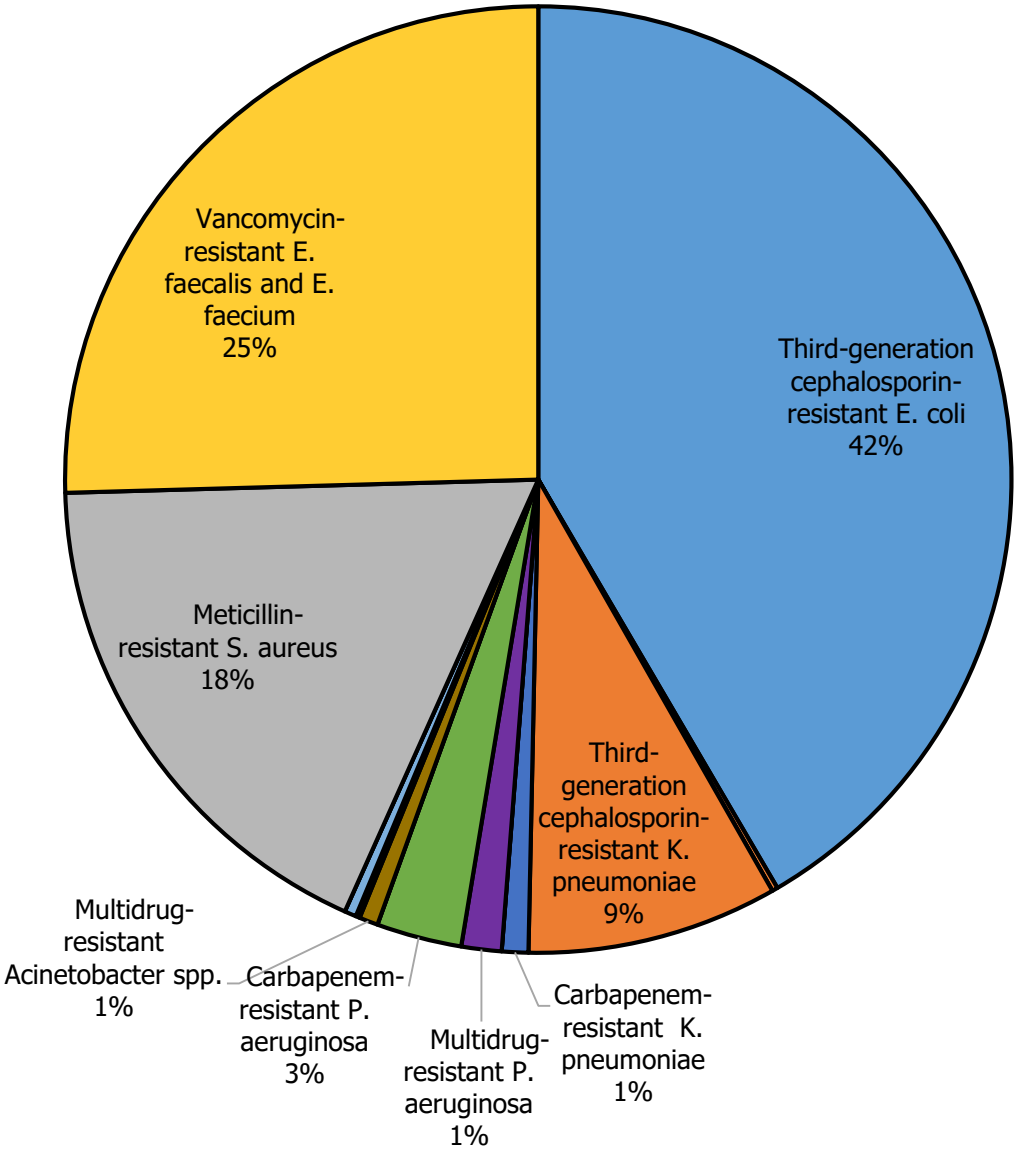


Table 3.3: Burden of disease due to AMR according to each antibiotic resistance-bacterium combination

Pathogen	Total number of attributable deaths (95% UI)	Mortality rate per 100,000 population (95% UI)	Proportion of all attributable deaths (%)	Total number of DALYs (95% UI)	DALYs per 100,000 population (95% UI)	Proportion of all DALYs (%)
Escherichia coli	**89.84 (82.74-96.99)**	**1.83 (1.68-1.97)**	**41.76**	**1,863.71 (1,763.11-1,965.13)**	**37.87 (35.82-39.93)**	**37.57**
Third-generation cephalosporin-resistant *E. coli*	89.42 (82.48-96.42)	1.82 (1.68-1.96)	41.57	1,856.07 (1,758.05-1,954.94)	37.71 (35.72-39.72)	37.42
Carbapenem-resistant *E. coli*	0.42 (0.26-0.57)	0.01 (0.01-0.01)	0.19	7.64 (5.05-10.20)	0.16 (0.10-0.21)	0.15
Colistin-resistant *E. coli*	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0
Klebsiella pneumoniae	**20.38 (19.20-21.47)**	**0.41 (0.39-0.44)**	**9.47**	**599.80 (568.15-631.00)**	**12.19 (11.54-12.82)**	**12.09**
Third-generation cephalosporin-resistant *K. pneumoniae*	18.43 (17.67-19.14)	0.37 (0.36-0.39)	8.57	545.19 (524.84-565.32)	11.08 (10.66-11.49)	10.99
Carbapenem-resistant *K. pneumoniae*	1.94 (1.53-2.34)	0.04 (0.03-0.05)	0.90	54.60 (43.31-65.67)	1.11 (0.88-1.33)	1.10
Colistin-resistant *K. pneumoniae*	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0
Pseudomonas aeruginosa	**9.22 (7.12-11.36)**	**0.19 (0.14-0.23)**	**4.29**	**229.29 (181.33-276.93)**	**4.66 (3.68-5.63)**	**4.62**
Multidrug-resistant *P. aeruginosa*	2.95 (2.21-3.72)	0.06 (0.04-0.08)	1.37	66.17 (50.76-81.89	1.34 (1.03-1.66)	1.33
Carbapenem-resistant *P. aeruginosa*	6.27 (4.91-7.65)	0.13 (0.10-0.16)	2.91	163.13 (130.57-195.03)	3.31 (2.65-3.96)	3.29
Colistin-resistant *P. aeruginosa*	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0
Acinetobacter species	**1.68 (1.14-2.23)**	**0.03 (0.02-0.05)**	**0.78**	**70.75 (51.67-89.65)**	**1.44 (1.05-1.82)**	**1.43**
Multidrug-resistant *Acinetobacter spp.*	1.38 (0.98-1.78)	0.03 (0.02-0.04)	0.64	64.68 (47.95-81.19)	1.31 (0.97-1.65)	1.30

Pathogen	Total number of attributable deaths (95% UI)	Mortality rate per 100,000 population (95% UI)	Proportion of all attributable deaths (%)	Total number of DALYs (95% UI)	DALYs per 100,000 population (95% UI)	Proportion of all DALYs (%)
Carbapenem-resistant *Acinetobacter spp.*	0.30 (0.17-0.44)	0.01 (0.00-0.01)	0.14	6.07 (3.72-8.45	0.12 (0.08-0.17)	0.12
Colistin-resistant *Acinetobacter spp.*	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0
Streptococcus pneumoniae	**0.86 (0.78-0.94)**	**0.02 (0.02-0.02)**	**0.40**	**67.25 (61.59-72.98)**	**1.37 (1.25-1.48)**	**1.36**
Penicillin-resistant *S. pneumoniae*	0.86 (0.78-0.94)	0.02 (0.02-0.02)	0.40	67.25 (61.59-72.98)	1.37 (1.25-1.48)	1.36
Penicillin- and macrolide-resistant *S. pneumoniae*	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0
Staphylococcus aureus	**38.40 (37.13-39.70)**	**0.78 (0.75-0.81)**	**17.85**	**864.92 (841.09-888.86)**	**17.57 (17.09-18.06)**	**17.44**
Meticillin-resistant *S. aureus*	38.40 (37.13-39.70)	0.78 (0.75-0.81)	17.85	864.92 (841.09-888.86)	17.57 (17.09-18.06)	17.44
Enterococcus faecalis / faecium	**54.74 (54.32-55.15)**	**1.11 (1.10-1.12)**	**25.45**	**1,264.91 (1,252.59-1,277.59)**	**25.70 (25.45-25.96)**	**25.50**
Vancomycin-resistant *E. faecalis and E. faecium*	54.74 (54.32-55.15)	1.11(1.10-1.12)	25.45	1,264.91 (1,252.59-1,277.59)	25.70 (25.45-25.96)	25.50
Overall	**215.11 (208.38-221.90)**	**4.37 (4.23-4.51)**	**100**	**4,960.60 (4,860.70-5,061.70)**	**100.80 (98.75-102.83)**	**100**

Key – DALYs – disability-adjusted life years; UI – uncertainty interval.

The total number of DALYs attributable to the 16 antibiotic resistance-bacterium combinations in public acute hospitals in Ireland in 2019 was estimated to be 4,961 (95% UI: 4,861-5,062) (Table 3.3). Resistant strains of *E. coli* (37.6%) were associated with the most DALYs (n=1,864; 95% UI: 1,763-1,965), followed by resistant strains of *E. faecalis* and *E. faecium* (25.5%) (n=1,265; 95% UI: 1,253-1,278), *S. aureus* (17.4%) (n=865; 95% UI: 841-889), *K. pneumoniae* (12.1%) (n=600; 95% UI: 568-631), *P. aeruginosa* (4.6%) (n=229; 95% UI: 181-277), *Acinetobacter spp.* (1.4%) (n=71; 95% UI: 52-90) and *S. pneumoniae* (1.36%) (n=67; 95% UI: 62-73) (Figure 3.9).

Figure 3.9: Total DALYs per resistant pathogen

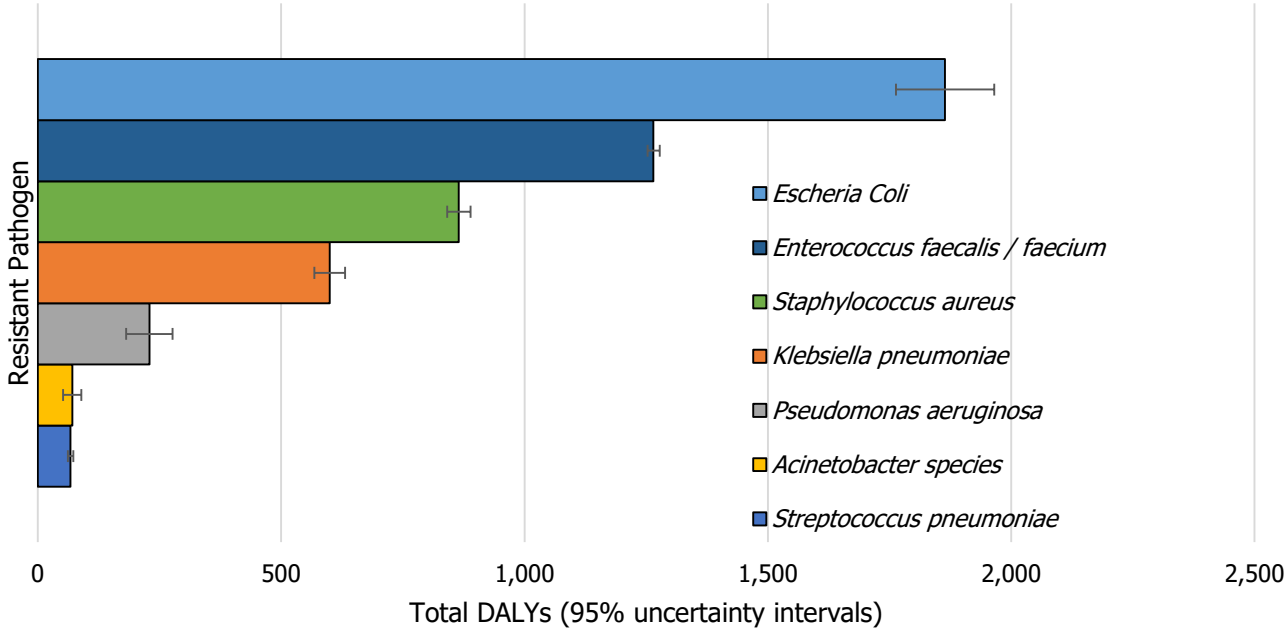
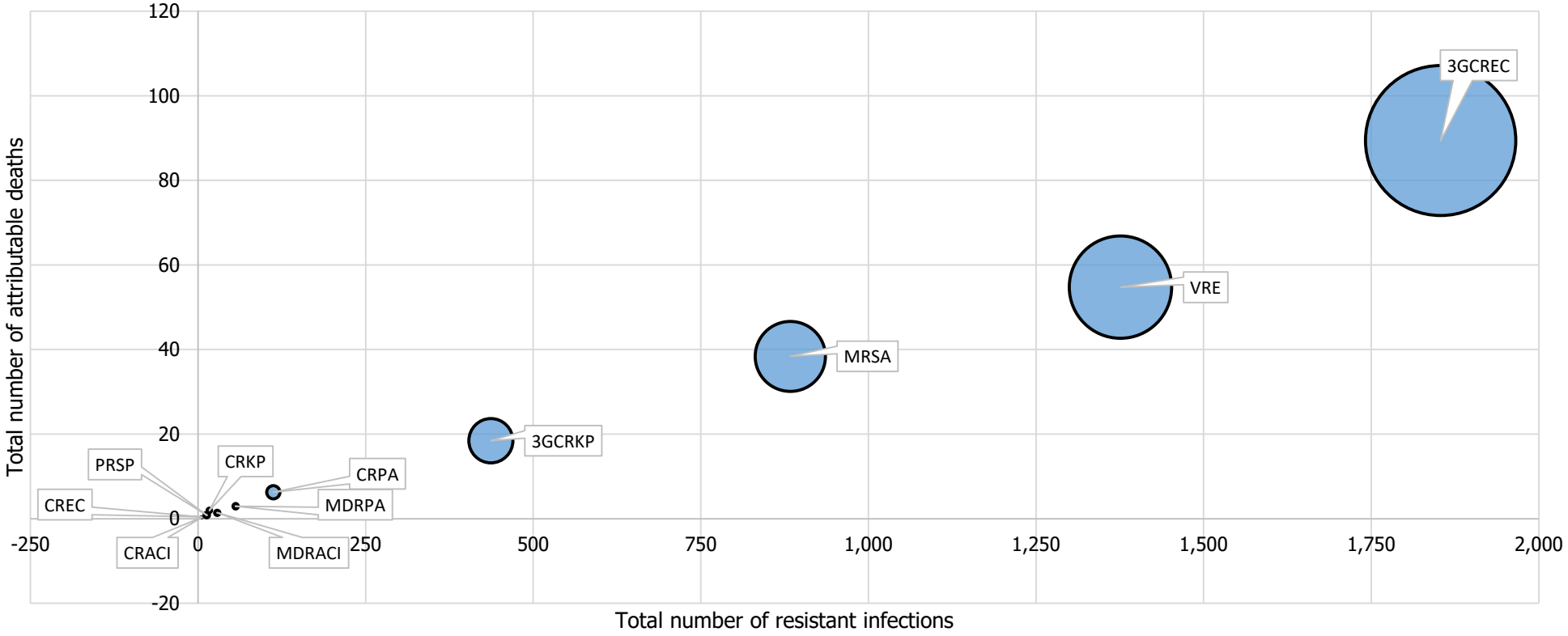


Figure 3.10 shows the relationship between the total number of infections, attributable deaths and DALYS for each antibiotic resistance-bacteria combination, in Irish public acute hospitals in 2019. This graph illustrates the relatively high burden of disease associated with third-generation cephalosporin-resistant bacteria (3GCREC and 3GCRKP), VRE and MRSA. By contrast, there was a relatively low burden of disease associated with carbapenem- or colistin-resistant bacteria, multidrug-resistant bacteria, and *S. pneumoniae* that is fully resistant to penicillin.

Figure 3.10: Total number of infections vs. total number of attributable deaths vs. total number of DALYs per antibiotic resistance–bacterium combination

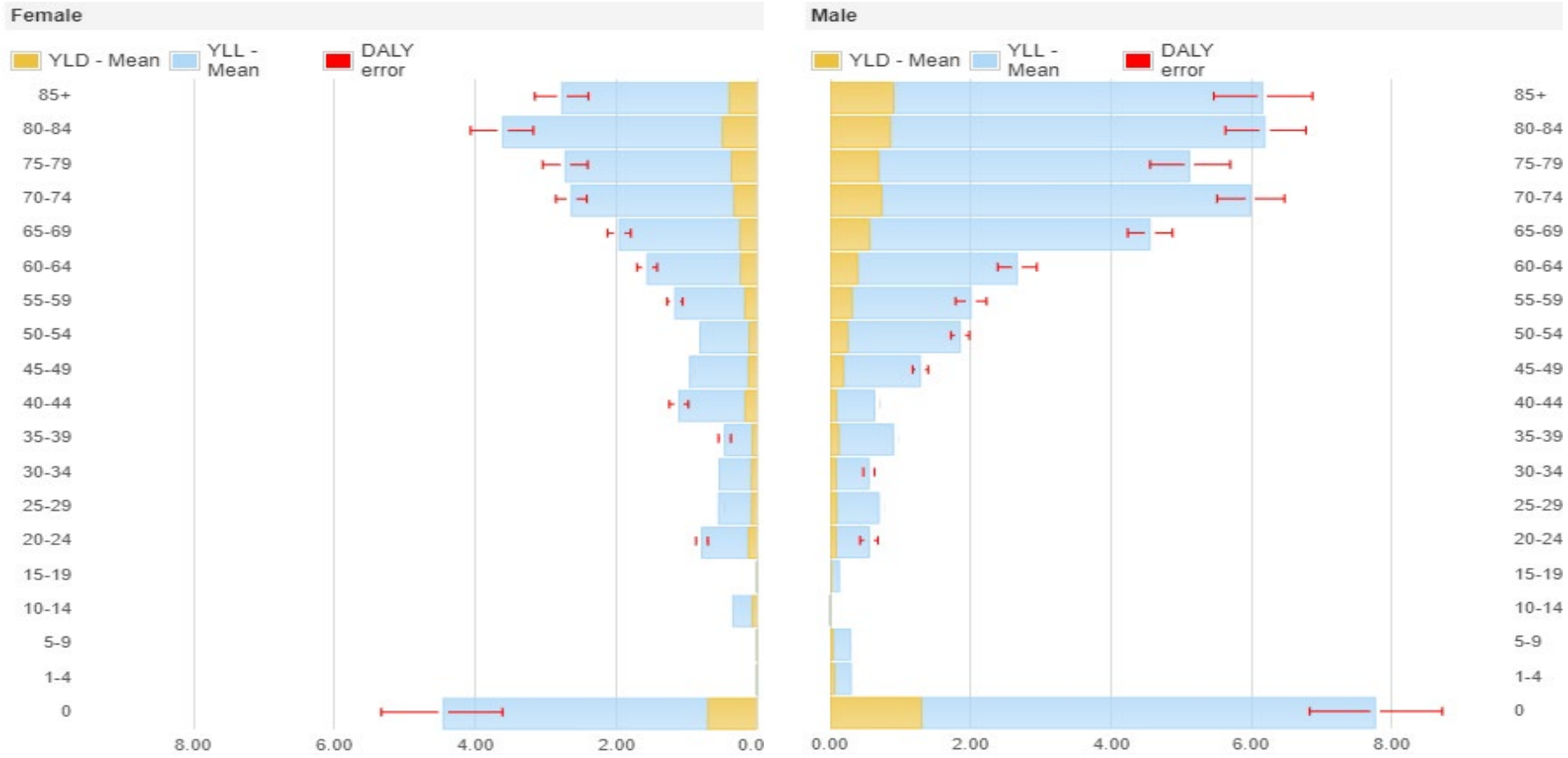


Key: **Diameter of bubbles represents the total number of DALYs**. **Note that combinations with no incidence are not displayed**. 3GCREC - Third-generation cephalosporin-resistant Escherichia coli; 3GCRKP - Third-generation cephalosporin-resistant Klebsiella pneumoniae; ColRACI - Colistin-resistant Acinetobacter species; ColREC - Colistin-resistant Escherichia coli; ColRKP - Colistin-resistant Klebsiella pneumoniae; ColRPA - Colistin-resistant Pseudomonas aeruginosa; CRACI - Carbapenem-resistant Acinetobacter species; CREC - Carbapenem-resistant Escherichia coli; CRKP - Carbapenem-resistant Klebsiella pneumoniae; CRPA - Carbapenem-resistant Pseudomonas aeruginosa; MDRACI - Multidrug-resistant Acinetobacter species; MDRPA - Multidrug-resistant Pseudomonas aeruginosa; MRSA - Meticillin-resistant Staphylococcus aureus; PMRSP - Penicillin- and macrolide-resistant Streptococcus pneumoniae; PRSP - Penicillin-resistant Streptococcus pneumoniae; VRE - Vancomycin-resistant Enterococci.

Figure 3.11 illustrates the number of DALYs per 100,000 stratum population. In other words, the number of DALYs associated with each stratum of age group and sex, from 100,000 population of that same stratum of age group and sex. This figure highlights the high burden of disease due to AMR, in males, in those aged 65 years and older, and also in those under the age of one year. Notably, the highest number of DALYs per 100,000 stratum population was associated with males under the age of one year (n=7.76; 95% UI: 6.83-8.72). This finding indicates the significant burden of disease, driven largely by years of life lost (YLL) that is associated with deaths caused by resistant infections in infants (<1 year old). Resistant *E. coli, K. pneumoniae, S. aureus* and *S. pneumoniae* infections occurred in infants (Appendix 9). Other age-sex pyramids reporting DALY outcomes are located in Appendix 9.

As evident from Figure 3.11, the majority of all DALYs (n=4,961; 95% UI: 4,861-5,062) can be attributed to YLL (n=4,256; 95% UI: 4,157-4,356) rather than to years lost due to disability (YLD) (n=704; 95% UI: 689-721). Overall, YLL accounted for 85.8% of total DALYs, indicative of the predominantly acute nature of infectious diseases and the significant mortality associated with AMR. However, a sizeable proportion (14.2%) of total DALYs were due to YLD, indicative of the long term effects that resistant infections can have on individuals.

Figure 3.11: Total DALYs per 100,000 stratum population, according to age group and sex



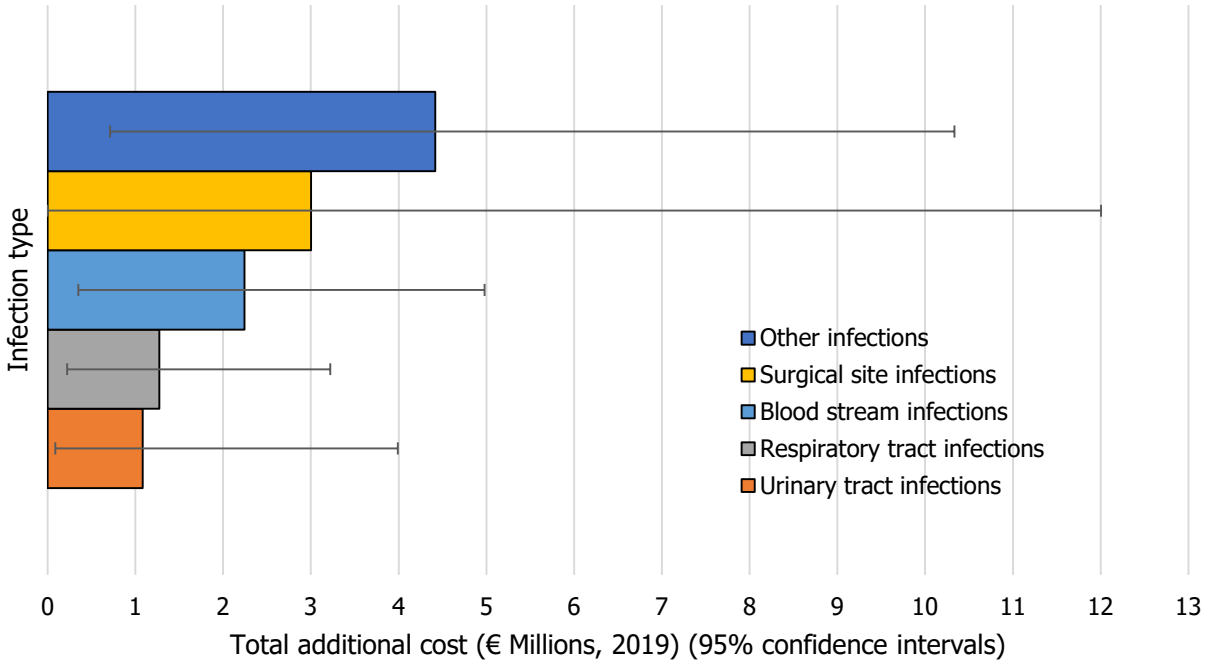
Key - DALY – disability-adjusted life year; YLD – years lost due to disability; YLL – years of life lost. This is an output from BCoDE Version 2.0 Software.

3.4.3 Additional cost due to AMR

3.4.3.1 Base case analysis

The expected total additional cost to public acute hospitals in Ireland in 2019 arising from excess LOS associated with AMR was estimated to be €12,020,068 (95% CI: €4,879,603 - €23,267,352) (Table 3.4). Resistant infections categorised as 'other infections' contributed the most (36.7%) of all five infection types, to this additional cost (€4,416,543; 95% CI: €712,084 - €10,333,077) (Figure 3.12) (Table 3.4). The 'other infections' category includes digestive tract infections, skin and soft tissue infections, eye, ear, nose or mouth infections, bone and joint infections, cardiovascular infections, reproductive tract infections and other less frequent infections. This was followed by resistant SSIs (25%), resistant BSIs (18.7%), resistant RTIs (10.6%) and resistant UTIs (9.02%) (Table 3.4). Of note, there was substantial uncertainty observed in the cost estimates as indicated by the wide confidence intervals; this was driven largely by the uncertainty in the incidence estimates.

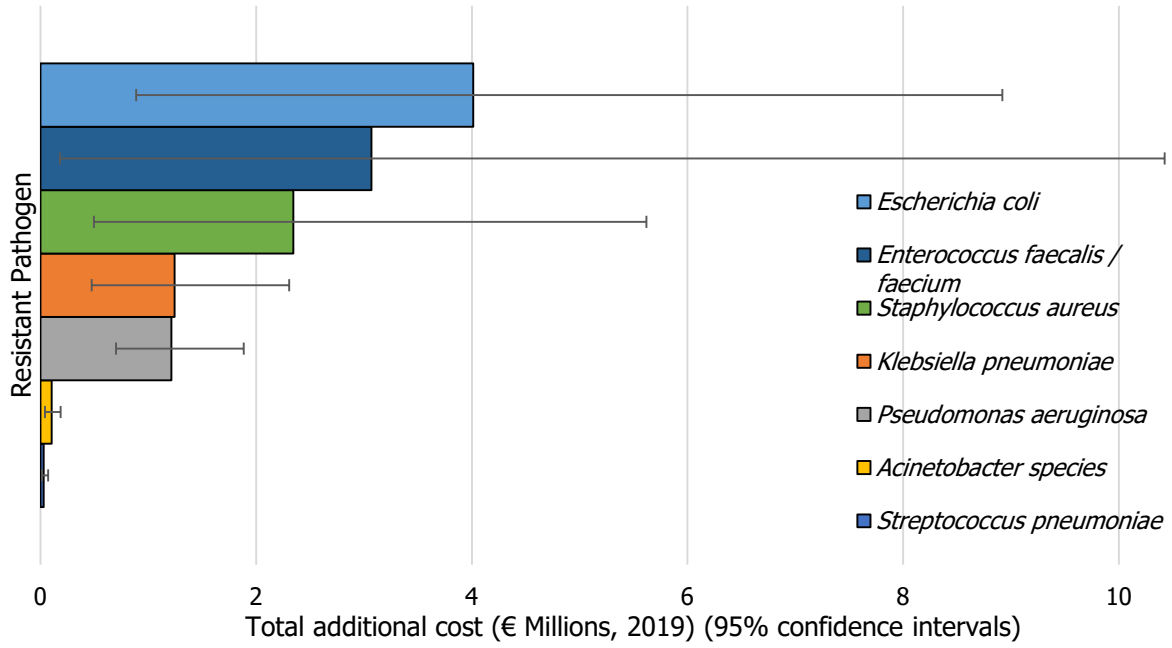
Figure 3.12: Total additional cost per resistant infection type



In terms of pathogens, the largest contribution to the expected total additional cost (relating to excess LOS) were infections from resistant strains of *E. coli* (€4,014,738; 95% CI: €888,268 - €8,921,653) which accounted for a third of the estimated additional costs (Figure 3.13) (Table 3.4). This was followed by resistant strains of *E. faecalis* and *E. faecium* (25.5%), *S. aureus* (19.5%), *K. pneumoniae* (10.4%), *P. aeruginosa* (10.1%), *Acinetobacter spp.* (0.9%), and *S. pneumoniae* (0.3%). There was substantial

uncertainty associated with these estimates as indicated by the wide confidence intervals.

Figure 3.13: Total additional cost per resistant pathogen



Of the 16 antibiotic resistance-bacterium combinations examined, 3GCREC infections (33.2%) contributed the most to the expected total additional cost, relating to excess LOS, (€3,992,444; 95% CI: €868,525 - €8,899,795). This was followed by VRE infections (25.5%), MRSA infections (19.5%), 3GCRKP infections (9.5%), and carbapenem-resistant *P. aeruginosa* (CRPA) infections (7.6%) (Table 3.4). There was substantial uncertainty associated with these estimates as indicated by the wide confidence intervals.

Table 3.4: Cost findings: base case analysis

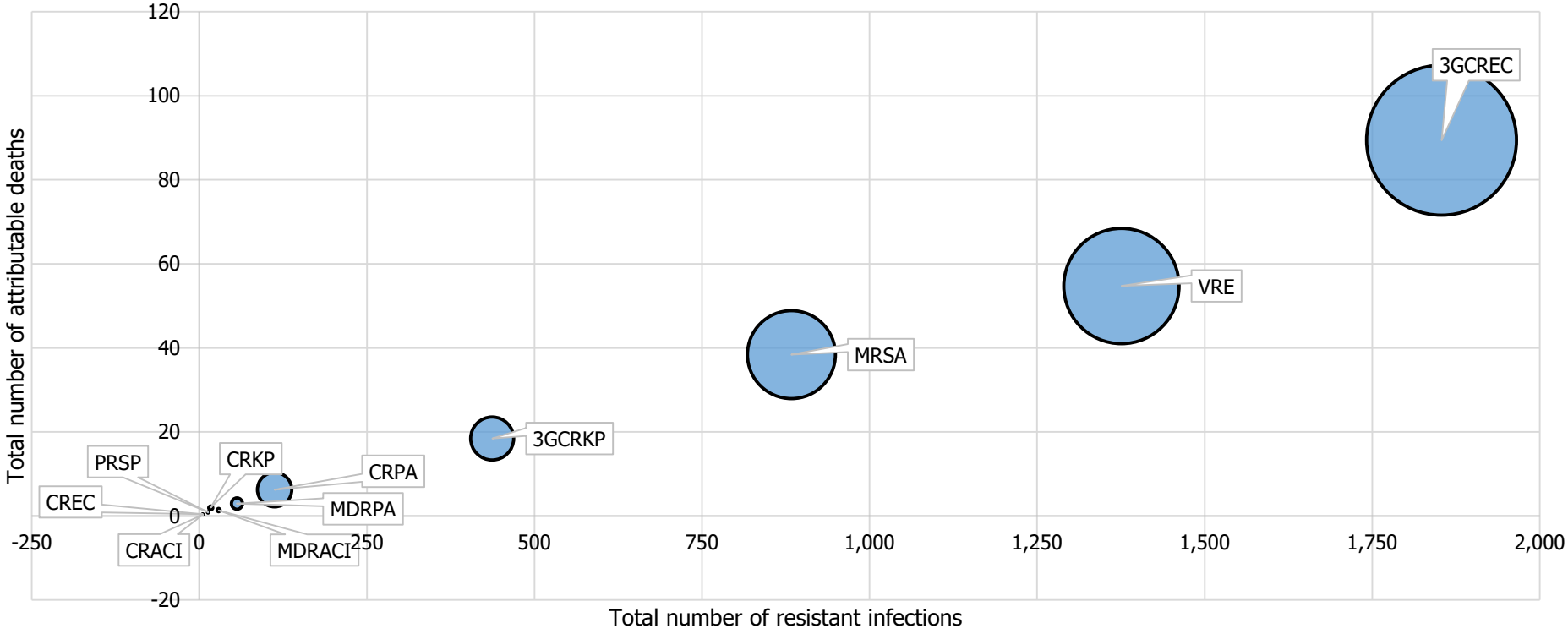
Pathogen	BSI Mean (95% CI)	RTI Mean (95% CI)	UTI Mean (95% CI)	SSI Mean (95% CI)	OTHER Mean (95% CI)	Total cost (pathogen) Mean (95% CI)
Escherichia coli						
Third-generation cephalosporin-resistant	€1,099,825 (€0 - €3,278,650)	€207,459 (€0 - €1,111,253)	€504,590 (€0 - €2,676,437)	€815,109 (€0 - €4,531,593)	€1,365,461 (€0 - €3,800,270)	€3,992,444 (€868,525 - €8,899,795)
Carbapenem-resistant	€11,972 (€4,912 - €20,800)	€2,790 (€471 - €6,012)	€1,895 (€0 - €9,653)	€2,053 (€0 - €11212)	€3,585 (€0 - €12,674)	€22,294 (€10,511 - €39,027)
Colistin-resistant	*No data*					
Total	***€1,111,797 (€7,159 - €3,291,004)***	***€210,249 (€493 - €1,115,395)***	***€506,485 (€0 - €2,679,614)***	***€817,162 (€0 - €4,531,935)***	***€1,369,046 (€654 - €3,801,443)***	***€4,014,738 (€888,268 - €8,921,653)***
Klebsiella pneumoniae						
Third-generation cephalosporin-resistant	€55,722 (€0 - €193,071)	€384,241 (€64,868 - €770,770)	€869,92 (€0 - €454,512)	€129,157 (€0 - €709,202)	€485,149 (€0 - €1,273,285)	€1,141,260 (€390,661 - €2,189,499)
Carbapenem-resistant	€60,172 (€24,693 - €105,372)	€16,373 (€2,354 - €38,117)	€4,127 (€0 - €21,136)	€5,167 (€0 - €28,636)	€16,988 (€0 - €57,543)	€102,827 (€50,907 - €170,218)
Colistin-resistant	*No data*					
Total	***€115,894 (€27,325 - €270,326)***	***€400,614 (€68,718 - €793,972)***	***€91,119 (€0 - €461,600)***	***€134,323 (€0 - €716,711)***	***€502,136 (€2,419 - €1,288,589)***	***€1,244,087 (€474,325 - €2,305,700)***
Pseudomonas aeruginosa						
Multidrug-resistant	€56,058 (€29,211 - €85,141)	€58,160 (€0 - €179,610)	€16,503 (€0 - €74,638)	€22,558 (€0 - €129,749)	€146,637 (€26,666 - €333,914)	€299,916 (€128,308 - €547,860)
Carbapenem-resistant	€112,074 (€58,911 - €171,566)	€297,941 (€80,538 - €654,394)	€165,991 (€53,108 - €356,327)	€45,670 (€0 - €251,699)	€291,854 (€5,7261 - €667,985)	€913,529 (€499,572 - €1,493,088)
Colistin-resistant	*No data*					
Total	***€168,132 (€96,497 - €245,291)***	***€356,101 (€94,673 - €742,657)***	***€182,494 (€62,517 - €379,475)***	***€682,27 (€0 - €310,492)***	***€438,491 (€120,685 - €868,024)***	***€1,213,445 (€701,095 - €1,884,586)***
Acinetobacter species						
Multidrug-resistant	€16,463 (€0 - €48,054)	€7,505 (€0 - €39,835)	€4,441 (€0 - €18,617)	€9,748 (€0 - €5,3791)	€47,384 (€9,877 - €10,0917)	€85,541 (€30,394 - €163,544)
Carbapenem-resistant	€3,329 (€0 - €9,451)	€1,543 (€0 - €7,993)	€889 (€0 - €3,620)	€1,961 (€0 - €10,549)	€9,475 (€1,872 - €20,040)	€17,197 (€5,931 - €32,825)
Colistin-resistant	*No data*					
Total	***€19,792 (€0 - €52,573)***	***€9,048 (€0 - €44,234)***	***€5,329 (€0 - €20,610)***	***€11,709 (€0 - €57,564)***	***€56,859 (€1,4595 - €112,720)***	***€102,738 (€42,394 - €186,245)***
Streptococcus pneumoniae						
Penicillin-resistant	€19,196 (€12,773 - €27,418)	€9,504 (€0 - €49,452)	-	-	€1544 (€0 - €4,931)	€30,245 (€14,532 - €71,376)

Pathogen	BSI Mean (95% CI)	RTI Mean (95% CI)	UTI Mean (95% CI)	SSI Mean (95% CI)	OTHER Mean (95% CI)	Total cost (pathogen) Mean (95% CI)
Penicillin- and macrolide-resistant	€0 (€0 - €0)	€0 (€0 - €0)	-	-	€0 (€0 - €0)	€0 (€0 - €0)
Total	***€19,196 (€12,773 - €27,418)***	***€9,504 (€0 - €49,452)***	**-**	**-**	***€1,544 (€0 - €4,931)***	***€30,245 (€14,532 - €71,376)***
Staphylococcus aureus						
Meticillin-resistant	**€314,895 (€0 - €717,233)**	**€15,5250 (€0 - €812,000)**	**€63,519 (€0 - €349,783)**	**€614,988 (€0 - €3,449,317)**	**€1,195,963 (€0 - €2,986,134)**	**€2,344,614 (€495,992 - €5,619,760)**
Enterococcus faecalis / faecium						
Vancomycin-resistant	**€493,124 (€0 - €1,337,199)**	**€133,167 (€0 - €776,675)**	**€235,065 (€0 - €1,310,674)**	**€1,356,342 (€0 - €7,757,646)**	**€852,503 (€0 - €5,033,893)**	**€3,070,201 (€181,342 - €10,426,009)**
Total cost (infection)	**€2,242,831 (€350,476 - €4,978,502)**	**€1,273,932 (€223,798 - €3,222,046)**	**€1,084,010 (€86,468 - €3,992,488)**	**€3,002,751 (€0 - €12,006,711)**	**€4,416,543 (€712,084 - €10,333,077)**	**€12,020,068 (€4,879,603 - €23,267,352)**

Key – BSI – blood stream infection; CI – confidence interval; RTI – respiratory tract infection; SSI – surgical site infection; UTI – urinary tract infection.

Figure 3.14 shows the relationship between the total number of infections, attributable deaths, and total additional cost for each antibiotic resistance-bacteria combination, in Irish public acute hospitals in 2019. This graph illustrates the relatively high additional costs associated with 3GCREC, 3GCRKP, VRE and MRSA infections. Of note, despite the relatively low absolute number of infections and deaths associated with carbapenem- and multidrug-resistant *P. aeruginosa* infections, these pathogens were still associated with substantial additional costs, as evident by the diameter of the bubbles (Figure 3.14).

Figure 3.14: Total number of infections vs. total number of attributable deaths vs. total additional cost per antibiotic resistance–bacterium combination



Key: **Diameter of bubbles represents the total additional cost**. **Note that combinations with no incidence are not displayed**. 3GCREC - Third-generation cephalosporin-resistant Escherichia coli; 3GCRKP - Third-generation cephalosporin-resistant Klebsiella pneumoniae; ColRACI - Colistin-resistant Acinetobacter species; ColREC - Colistin-resistant Escherichia coli; ColRKP - Colistin-resistant Klebsiella pneumoniae; ColRPA - Colistin-resistant Pseudomonas aeruginosa; CRACI - Carbapenem-resistant Acinetobacter species; CREC - Carbapenem-resistant Escherichia coli; CRKP - Carbapenem-resistant Klebsiella pneumoniae; CRPA - Carbapenem-resistant Pseudomonas aeruginosa; MDRACI - Multidrug-resistant Acinetobacter species; MDRPA - Multidrug-resistant Pseudomonas aeruginosa; MRSA - Meticillin-resistant Staphylococcus aureus; PMRSP - Penicillin- and macrolide-resistant Streptococcus pneumoniae; PRSP - Penicillin-resistant Streptococcus pneumoniae; VRE - Vancomycin-resistant Enterococci.

3.4.3.2 Scenario analyses

Three scenarios were considered to assess the impact on expected costs arising from (1) the risk of ICU admission by pathogen-infection type combinations with 100% of excess LOS spent in ICU (for admitted cases); (2) different durations of stay in ICU as a proportion of excess LOS (for all cases); and (3) the risk of ICU admission by infection type with different durations of stay in ICU as a proportion of excess LOS (for admitted cases).

(1) Risk of ICU admission by pathogen-infection combinations with 100% of excess LOS spent in ICU (for admitted cases)

In the first scenario analysis, where the difference in the proportion of individuals with resistant relative to susceptible infections that experienced complications was used as a proxy for ICU admission, the total additional cost was estimated to be €11,561,842 (95% CI: €4,574,594 - €22,528,949). In a variation of this first scenario, where the difference in the proportion of individuals with resistant relative to susceptible infections that experienced complications, or who died, was used as a proxy for ICU admission, the total additional cost was estimated to be €11,848,838 (95% CI: €4,810,681 - €22,302,611). This compares with the base case analysis, where the total additional cost was estimated to be €12,020,068 (95% CI: €4,879,603 - €23,267,352). The results of the scenario analyses are located in Appendix 9.

(2) Different durations of stay in ICU as a proportion of excess LOS (for all cases)

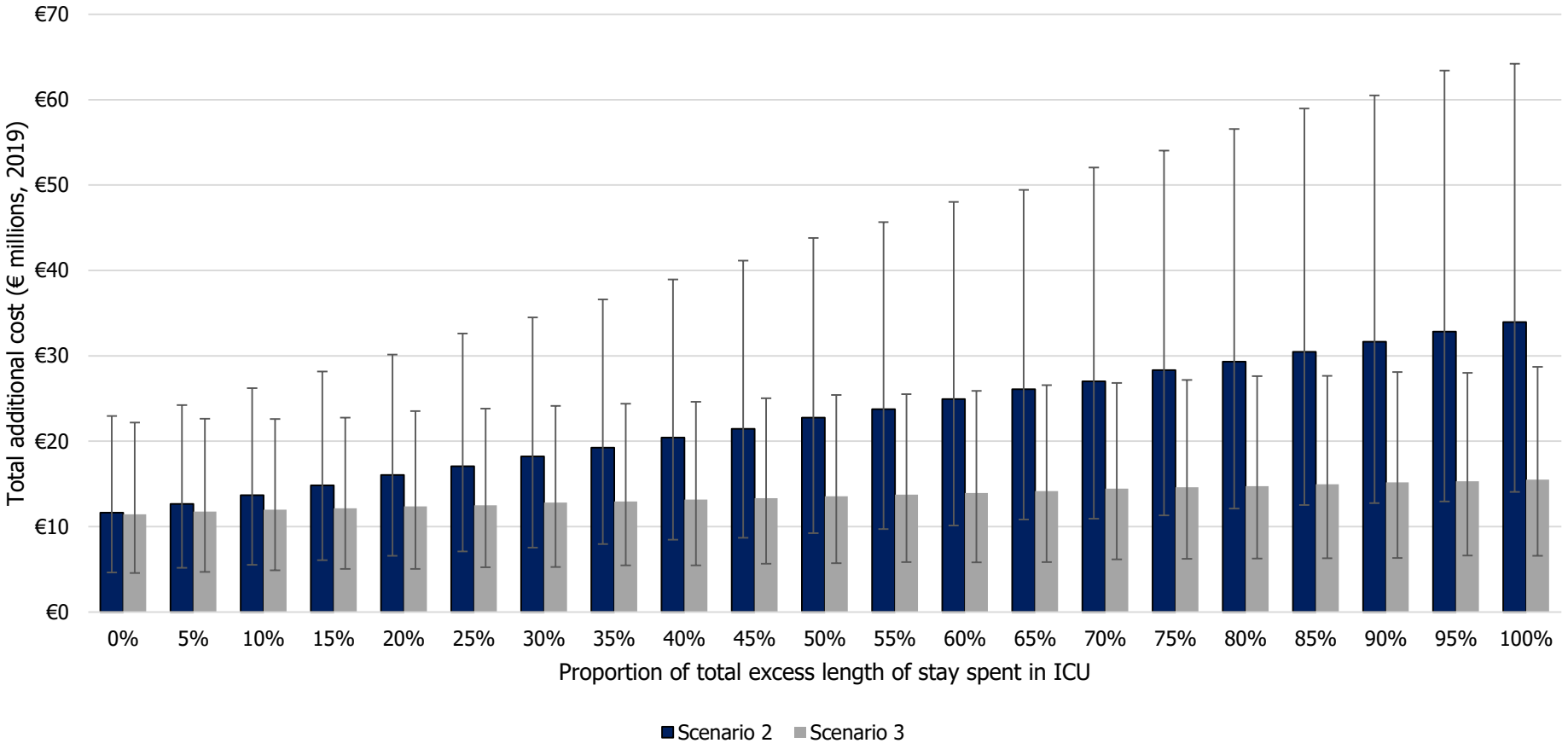
A threshold analysis was undertaken to assess the impact on expected total costs of different durations of stay in ICU as a proportion of excess LOS. The results of this analysis are graphically represented in Figure 3.15 (navy bars). The threshold analysis started at 0%, that is, when none of those with resistant infections spent any of their excess LOS in ICU, and increased in 5% increments up until 100%, that is, when all of those with resistant infections spent all of their excess LOS in ICU. When 0% of the excess LOS was spent in ICU, the total additional cost was estimated to be €11,637,513 (95% CI: €4,621,228-€22,957,975), when 50% of the excess LOS was spent in ICU, the total additional cost was estimated to be €22,757,940 (95% CI: €9,237,732-€43,822,291), and when 100% of the excess LOS was spent in ICU, representing a worst-case scenario, the total additional cost was estimated to be €33,949,931 (95% CI: €14,060,290-€64,224,879).

(3) Risk of ICU admission by infection type with different durations of stay in ICU as a proportion of excess LOS (for admitted cases)

Although the above threshold analysis (scenario 2) is useful in describing a worst-case scenario, it is highly unlikely that all cases would require intensive care. In scenario 3, a weighted probability of admission to ICU was conservatively estimated for the different infection types with a threshold analysis on duration of stay in ICU as a proportion of excess LOS applied for admitted cases. The results are presented in Figure 3.15 (grey bars). When 0% of the excess LOS was spent in ICU, the total additional cost was estimated to be €11,440,096 (95% CI: €4,560,465-€22,188,549), when 50% of the excess LOS was spent in ICU for a fixed proportion of cases (comprising 65% of BSIs, 17% of RTIs, 14% of SSI and 2% or UTIs or other infection), the total additional cost was estimated to be €13,542,385 (95% CI: €5,720,697-€25,411,593), and when 100% of the excess LOS was spent in ICU, assuming the same fixed proportion of cases in ICU, the total additional cost was estimated to be €15,515,044 (95% CI: €6,594,222-€28,723,702).

Unlike what was observed in the second scenario analysis, as the duration of excess LOS spent in ICU transitioned from 0% to 100%, assuming different risks for ICU admission among the infection types, the total additional costs only increased by about 30% in this scenario analysis. The gap between the two scenarios is explained by the fact that in the latter, a sizeable proportion of each resistant infection type were not in ICU (35% of BSIs, 83% of RTIs, 86% of SSIs, and 98% of UTIs and other infections). The disparity in costs is most apparent at the higher thresholds, whereby the second scenario (in navy bars) modelled the impact of 100% of those with resistant infections spending 100% of their excess LOS in ICU, compared with the third scenario (in grey bars) that modelled the impact of a fixed proportion of individuals with resistant infections spending 100% of their excess LOS in ICU (Figure 3.15). The third scenario analysis that jointly considers the probability of ICU admission and different durations of stay in ICU (for admitted cases) is likely to be a more realistic representation of the additional costs associated with AMR than the second scenario, however uncertainty remains regarding the risk for ICU admission. In the absence of any evidence of the risk of ICU admission by resistant relative to susceptible infections, different proxy indicators were used in the scenario analyses to reflect the risk of ICU admission by pathogen-infection type combinations (scenario 1) and infection types (scenario 3).

Figure 3.15: Scenario analysis: Total additional cost due to antimicrobial resistance, at different durations of stay in ICU as a proportion of excess length of stay



Key – CI – confidence interval; ICU – intensive care unit.

Scenario 2: The total cost at different durations of stay in ICU (as a proportion of excess length of stay). **Scenario 3:** The total cost at different durations of stay in ICU (as a proportion of excess length of stay), assuming a ratio of 65% (BSI): 17% (RESP): 2% (UTI): 14% (SSI): 2% (OTH) admission to ICU at each threshold.

3.4.4 The health and economic burden of AMR on patients: literature review findings

This section describes the health and economic burden of AMR on patients, and their carers and family members, based on the findings of a brief literature review in conjunction with the findings of the main study.

Patient burden and harm

AMR has important consequences for patients in terms of morbidity and mortality. Friedman et al. found that infections caused by resistant bacterial strains can cause up to two fold higher rates of adverse outcomes compared with similar infections caused by susceptible strains.[106] These adverse outcomes may be clinical in nature such as death or treatment failure, or economic such as the cost of care and length of stay in hospital.[106]

In terms of mortality, the OECD has estimated that around 2.4 million people could die in Europe, North America and Australia between 2015-2050, due to AMR.[10] A seminal United Kingdom (UK) government report, chaired by the economist Lord Jim O'Neill, estimated that globally by 2050, 10 million lives a year are at risk due to the rise of drug-resistant infections.[11] The ECDC study estimated that antimicrobial resistant infections accounted for 33,100 (95% UI: 28,480–38,430) attributable deaths across all European Union (EU) and European Economic Area (EEA) countries in 2015.[28] The current study estimated that 215 deaths (95% UI: 208-222) occurred in all public acute hospitals in Ireland in 2019 that were attributable to the 16 included antibiotic resistance-bacterium combinations.

The morbidity caused by AMR is more difficult to quantify than mortality. Morbidity related outcomes of AMR include increased hospital LOS, increased length of mechanical ventilation, increased admission and length of stay in ICU, excess surgery, functional decline and need for post-acute care.[106, 107]

DALYs are outcome measures used in this report to describe the burden of AMR. These are a combination of years lost due to disease (that is, premature mortality) and time spent disabled by the disease (that is, morbidity), with one DALY being equal to one year of full health lost. Overall, the current study estimated that 4,961 DALYs (95% UI: 4,861-5,062) were attributable to the 16 antibiotic resistant-pathogen combinations in 2019. The groups experiencing the highest burden of AMR were males, especially infants (under one year old) and older adults (65 years and older). To put this in context, this is similar to the burden reported in Ireland for certain cancers (malignant melanoma and bladder cancer) and rheumatoid arthritis.[108]

Due to AMR, there has been a requirement to use older antibiotics that had been replaced in treatment algorithms due to the availability of less toxic or more efficacious alternatives.[106] For example, polymyxins, such as colistin, are now used in ICU patients with otherwise untreatable gram negative bacterial infections, despite the unfavourable characteristics of these antibiotics. This can have consequences for patients in terms of nephrotoxicity (that is, damage to the kidneys) and neurotoxicity (that is, damage to the brain or peripheral nervous system).[109] There were no reports of colistin-resistant invasive infections in Ireland in 2019,[23] however these infections have been reported in other European countries in recent years,[91] with several outbreaks of these highly virulent and resistant strains observed in Germany and Finland.[110]

In addition, AMR can undermine the safety of many medical procedures (for example, total hip replacement surgery) whose success relies on the existence of effective antimicrobial prophylaxis.[10, 111] This may cause people to choose not to undergo recommended procedures due to the higher risk of infection and death, which can lead to a reduction in quality of life for those individuals as well as increased healthcare expenditure dealing with the complications of non-treatment (for example, anxiety/depression or pain).[111]

Patient experience and preferences

Qualitative studies can offer rich insights into the first hand experiences of the negative effects of AMR. Although each patient's experience is unique, common themes can be found through these experiences. One report described the experience of a 59 year old woman with MRSA: "*It has destroyed my life. I cannot use my pool, maintain my house, earn a living, go anywhere for more than a few hours, and I've had to give away 4 of my beloved birds. It is devastating! I can only stand for a few minutes at a time (I had a hip replacement that got infected and I currently have no left hip). I no longer go anywhere and have become a burden on my family. I hate my life."*[112]

A systematic review of qualitative evidence on patients' experiences of healthcare associate infections (HCAIs) identified 17 studies, with seven studies on patients with MRSA, four studies on patients with SSIs, one study on patients with *S. aureus* BSIs and one study on patients infected with extended-spectrum beta lactamase (ESBL)-producing bacteria.[113] Four main themes were identified from the review. The first theme was the continuum of emotional and physical responses to HCAIs. The authors reported that patients who were colonised by MRSA and experiencing no physical symptoms sometimes found it hard to accept the need to manage the MRSA colonisation especially after discharge from hospital, and these individuals sometimes felt socially isolated and emotionally upset. Whereas other patients with

ESBL infections experience pain and symptoms and worry about possible transmission as well as anger and irritation over the lack of information regarding their situation. The second theme was the response of healthcare providers to HCAIs, with patients often reporting that they had a limited understanding of their illness and even those who felt the information provided by their healthcare provider was adequate, often sought additional information from the internet. The third theme was around adapting to life with a HCAI. Some patients with MRSA reported that being colonised or infected with a HCAI had little effect in their day-to-day lives, while others had a fear of transmission of infection and felt a need to protect others. This fear had an impact on patients' daily lives, how they interacted with family and friends and had implications for work and finances. The fourth theme was related to the complex cultural context of HCAIs. Some patients reported *"feeling dirty"* and were worried about being contagious and a risk to others. Patients reported that they faced many challenges in terms of concerns regarding transmission of their infection while interacting with others, including healthcare providers, family and friends as well as in work situations. Patients reported feeling stigmatised or *"like a leper",* and there was limited understanding of risk and appropriate risk-reducing behaviour due to lack of knowledge and information about the condition. The authors concluded that regardless of the HCAI and type of resistance, daily living was often significantly affected.[113]

Carbapenemase-producing *Enterobacteriaceae* (CPE) are emerging pathogens of concern with very limited antimicrobial treatment options.[14] CPE screening in hospitalised individuals occurs in a number of countries, including Ireland, which can lead to some individuals being identified as being colonised with CPE upon admission to hospital. A qualitative study that used semi-structured interviews to explore patients' experiences in this area found two main themes:

1. a lack of understanding by patients as to what CPE was and why they were being screened for it

2. if they screened positive, then a sense of blame and responsibility often ensued in that they believed it was in some way their fault and their responsibility to make sure they didn't pass it on to others.[114]

The study concluded that enabling healthcare professionals to engage sensitively with patients being managed for colonisation with CPE is paramount to providing patient-centred care.[114]

Additional costs to patients, carers or family members

The analysis presented in this study is from the perspective of the public acute hospital system in Ireland. Although it serves the scope and purpose of the study,

one of the limitations of the analysis is that it does not include costs from the perspective of the patient, carer or family member. Patients with an AMR infection are more likely to have poorer health, experience higher levels of disability which will last for longer, and die, than those with susceptible infections, and this leads to an economic burden on patients, carers and their families.[10, 112] The exact value of the economic burden depends on many factors, and is often hard to quantify. Depending on the healthcare system, a patient with a resistant infection may incur significant out-of-pocket expenditure.[112]

The direct cost to a patient could include costs associated with the long term consequences of an AMR infection, for example additional hospital admissions or additional care for recurrent infections, addressing the psychological impact of the illness as well as other costs resulting from side effects of AMR infections (for example a prosthesis or wheel chair for amputees).[115] Other out-of-pocket expenditure may include transport to and from hospital, child care, parking, accommodation, food and funerals (in the case of deaths that are attributable to AMR).[47, 116] For those who are colonised with a resistant pathogen, there may be other costs in terms of additional tests and isolation rooms.[112] There may also be additional insurance costs to cover issues specifically relating to resistance and legal costs in the case of litigation.[115] In terms of indirect costs, these relate to the loss of earnings and opportunity when the patient is seeking treatment for, or dying from, the resistant infection, and this may also affect carers and family members while visting or providing care. These indirect costs include the loss of work earnings and leisure time for both patients and carers/family members, which may be substantial.[115]

3.5 Discussion

3.5.1 Overall summary

This study estimated the burden of disease and additional costs due to eight antimicrobial-resistant micro-organisms of public health concern, in all 50 public acute hospitals in Ireland in 2019. Based on the EARS-Net data, 814 of the 6,117 BSIs of the eight bacterial pathogens of concern were resistant to antimicrobials, representing an AMR rate of 13.31%. The total number of resistant infections was estimated to be 4,787 (95% CI: 2,432-14,764), with an expected total additional cost, relating to excess LOS, of €12,020,068 (95% CI: €4,879,603-€23,267,352), relative to the treatment of susceptible infections. These resistant infections accounted for an estimated 215 (95% UI: 208-222) attributable deaths and 4,961 (95% UI: 4,861-5,062) DALYs. While the majority of all resistant infections occurred in males (n=2,949; 95% CI: 1,501-9,014; 61.6%), and in individuals aged 65 years and older (n=3,287; 95% CI: 1,675-9,957; 68.67%), the highest number of DALYs

per 100,000 stratum population was associated with males under the age of one year (n=7.76; 95% UI: 6.83-8.72), indicating the high burden of disease in males, in infants (< 1 year) and in older adults (≥ 65 years). The most prevalent resistant pathogen was *E. coli*, (n=1,858; 95% CI: 1,033-4,020) and specifically 3GCREC (n= 1,853; 95% CI: 1,030-4,010). Relatively high additional costs were associated with 3GCREC, 3GCRKP, VRE and MRSA infections. Despite the relatively low absolute number of cases and deaths associated with carbapenem- and multidrug-resistant *P. aeruginosa* infections in Ireland, collectively these pathogens were still associated with substantial total additional costs of €1,213,445 (95% CI: €701,095 - €1,884,586) in 2019. These costs are conservative estimates, are restricted to costs associated with excess length of stay, and are likely to increase over time.

3.5.2 Comparison with extant literature

The population-modelling used in this study to estimate the burden of disease was adopted from a methodology developed by the ECDC.[28] The authors of the ECDC study applied this methodology to 2015 EARS-Net data from 30 EU/EEA countries, and estimated that in Ireland in 2015, across public and private hospitals, there were 4,893 (95% UI: 4,322-5,486) resistant infections that accounted for 219 (95% UI: 192-249) attributable deaths and 5,463 (95% UI: 4,830-6,180) attributable DALYs.[28] These estimates are similar to the estimates generated in the current study. While the absolute number of resistant isolates in Ireland reported to EARS-Net has generally increased across most pathogens, between 2015 and 2019,[23] and so an increase in case numbers, disease burden and deaths may be anticipated, the current study specifically excluded data from all 11 private hospitals. This may explain why the estimates from 2015 and 2019 are similar despite the increasing incidence of AMR nationally. Though the absolute number of resistant isolates in Ireland has generally increased across most pathogens between 2015 and 2019, no significant trend in the rate of resistance has been observed. In fact, a significantly decreasing trend was observed specifically for MRSA and *E. faecium* during this time period, potentially highlighting the impact of the additional IPC measures that were adopted.[23] Similarly, a 2019 report by the US Centers for Disease Control and Prevention (CDC) found that while the burden of disease due to AMR in the US had increased relative to 2013 estimates, the estimated number of AMR-related deaths had decreased. The authors of the report suggested that IPC measures that have been put in place were effective at preventing deaths due to AMR.[117] Therefore, the broadly similar estimates for case numbers, disease burden and deaths between 2015 and 2019 found in the current study may also be partially explained by widespread implementation of effective IPC measures during this period. While rates of AMR may be stable or even in decline for some pathogens at the moment in Ireland, it is important to acknowledge that at a global level, resistance rates are growing.[10] Across all OECD countries, it is estimated that average resistance

proportions across eight antibiotic-bacterium combinations may increase from 17% to 18%, between 2015 and 2030, if current trends in resistance continue and no policy actions are taken.[10]

The OECD developed a simulation model to estimate the clinical and economic impact of AMR across 33 OECD and EU countries, called the strategic public health planning for AMR (SPHeP-AMR) model.[10] The model used the same input parameters developed by the ECDC regarding mortality and LOS associated with different resistant pathogens relative to susceptible pathogens.[28] The epidemiological input parameters for the model came from the 2015 EARS-Net data and considered the same eight pathogens of public health concern. The hospital costs were based on the World Health Organization-Choosing Interventions that are Cost-Effective (WHO-CHOICE) project.[118] The OECD estimated 9,794 cumulative deaths in Ireland between 2015 and 2050 due to AMR, which equates to an average of 280 deaths per year. The OECD also estimated average annual healthcare costs associated with AMR, to be US $375,530 per 100,000 population in Ireland (2017 US $ prices). This equates to an estimated average cost of US $18,481,710 per year.[10] After adjustment for purchasing power parity (PPP) and inflation, this converts to a 2019 price of €14,820,956. These estimates of deaths and costs are broadly similar to those reported in the current study despite some differences in methods used.

The WHO estimated that the highest cause of DALYs in Ireland in 2019, was ischaemic heart disease, which contributed 74,800 DALYs (6.7%) of all 1,109,600 DALYs experienced.[108] The current study estimated that 4,961 DALYs were attributable to the 16 antibiotic resistance-bacterium combinations in public acute hospitals in Ireland in 2019. While acknowledging that the current study does not represent a complete picture of the total burden of AMR, and that only resistant infections in public acute hospitals were included, the total number of DALYs attributable to these 16 antibiotic resistance-bacterium combinations in public acute hospitals still accounted for 0.5% of all DALYs experienced in Ireland in 2019. This is similar to the estimated total number of DALYs attributable to rheumatoid arthritis (5,000 DALYs) in Ireland in 2019.[108, 119] Furthermore, the total DALYs attributable to AMR in Ireland is more than double those attributable to acute viral hepatitis (1,100 DALYs), human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) (600 DALYs) and tuberculosis (TB) (500 DALYs) combined.[119] These findings indicate the significant burden of disease associated with AMR. Not only is AMR associated with substantial mortality during the acute phase of the infection, particularly in BSIs,[120, 121] but there can also be long lasting complications for some affected individuals, both physical and psychological, which can negatively impact upon their quality of life.[28, 91]

3.5.3 Interpretation of scenario analyses

The expected total additional cost estimate produced in the base case analysis, relating to excess LOS (€12,020,068 (95% CI: €4,879,603 - €23,267,352), are supported by the comparable estimates produced in the first scenario analysis (€11,561,842 (€4,574,594 - €22,528,949), where the difference in the proportion of individuals with resistant relative to susceptible infections that experienced complications was used as a proxy for ICU admission. In a variation of this first scenario, where the difference in the proportion of individuals with resistant relative to susceptible infections that experienced complications, or who died, was used as a proxy for ICU admission, the total additional cost was estimated to be €11,848,838 (95% CI: €4,810,681 - €22,302,611), which is also comparable to the base case. The reasons why these scenario analyses are associated with slightly lower costs than the base case are two-fold. Firstly, the assumed incidence of ICU admission based on the proxy data was low. Secondly, a general ward bed day cost was applied for cases not admitted to ICU (that is, the majority of cases), which is cheaper than the average inpatient bed day cost used in the base case analysis.

In the second scenario analysis, which assumed a hypothetical worst-case scenario, where 100% of the excess LOS was spent in ICU for all resistant cases, the total additional cost of treating resistant infections was estimated to be €33,949,931 (95% CI: €14,060,290-€64,224,879). However, it is unlikely that all cases would require intensive care and that all of the excess LOS would be spent in ICU. It is more likely that the risk of ICU admission varies by infection type and that the time spent in ICU as a proportion of excess LOS is variable across cases. When the risk of ICU admission for different infection types is considered and a threshold analysis is applied for cases admitted to ICU, even when 100% of the excess LOS was spent in ICU for admitted cases, the total additional cost was estimated to be €15,515,044 (95% CI: €6,594,222-€28,723,702). The second and third scenario analyses highlight how the total additional cost is driven by the number of patients in ICU as well as the duration of stay in ICU. The role of ICU is particularly central to the management of AMR, and in theory, the total additional cost could have reached almost €34 million had all the excess LOS been spent in ICU. However, the reality of the situation in Ireland, is that ICU capacity is particularly constrained.[104] Insufficient ICU capacity may limit the clinicians capacity to escalate care when necessary with potential consequences for patient outcomes.[122] There are other important knock-on effects arising from AMR-related ICU admissions, such as the displacement of other services and associated opportunity costs; for example, the cancellation of high-risk elective surgeries due to a lack of appropriate postoperative intensive care, and the subsequent loss in revenue for the hospital.[123]

3.5.4 Strengths and limitations

Models are simplifications of complex systems and rely heavily on the underpinning

data and assumptions. AMR is a complex phenomenon that can affect individuals differently, resulting in very different outcomes and costs, and models may not be able to accurately reflect these complexities.[107] Though the modelling approach developed by the ECDC is based on systematic reviews of attributable outcomes, and comprehensive, standardised surveillance data, there are some limitations with this approach.[28] Firstly, the conversion factors for estimating non-BSIs from BSIs were based solely on the 2016/2017 ECDC point prevalence survey.[94] As this survey did not measure infections with *S. pneumoniae*, expert opinion was ultimately used by the ECDC to determine appropriate conversion factors for these infections, which may have introduced bias into these resulting incidence estimates. Secondly, given that the 95% CIs around incidence estimates were produced by the simple addition of the 95% CIs for each of the contributing sub-parts, in line with the ECDC methodology, this generated very wide 95% CIs that infer very high degrees of uncertainty, which may be unfounded.[28] Thirdly, when no BSI for a particular antibiotic resistance-bacterium combination was recorded in the EARS-Net data, the ECDC conversion factors assumed that no non-BSI of that combination occurred either. For a country with a relatively small population such as Ireland, this may be problematic for some of the less common pathogen combinations such as those resistant to colistin. For example, no colistin-resistant BSI of any pathogen was recorded in the Irish EARS-Net data in 2019, and accordingly it was assumed that there were no colistin-resistant UTIs, RTIs, SSIs or other infection types either. This is in spite of the fact that the ECDC conversion factors infer that some of these infection types may be more likely to occur than BSIs, depending on the pathogen. Given that only invasive isolates of BSI and CSF are routinely collected and reported to EARS-Net, it is unclear whether this assumption holds true or not. In addition, there are certain groups of patients who are prone to acquiring resistant respiratory tract infections (for example, those with cystic fibrosis), but who would almost never get BSIs, and so these patients may be under-represented in this study due to the model assumptions.[124] This further highlights the complex relationship between BSI and non-BSIs. Finally, given the dearth of data regarding ICU admissions and LOS for people with resistant infections, certain assumptions were made. It is important to acknowledge that not all patients with resistant infections will necessarily get admitted to ICU (for example, patients receiving palliative care), that the association between AMR and ICU admission is unclear, and that populations with and without AMR are not necessarily directly comparable. However, despite the limitations outlined, there was still merit in using this standardised methodology, which is used by both the ECDC and OECD, as it allows for comparisons to be made over time and between countries.[28] There is potential for the methodology to be improved upon, which could result in more accurate estimates of AMR incidence and burden going forward.

Another limitation of this study was its restricted scope in terms of the included pathogens and costs considered. In order to ensure the successful completion of the study within the available time and resource constraints, a select number of pathogens with good data availability, were used as the basis for estimating the economic burden of AMR on public acute hospitals in Ireland. The EARS-Net surveillance data currently provides the most comprehensive and nationally representative data for conducting AMR research, and is linked to the established ECDC methodology.[28] Therefore, the evaluation team opted to use this approach although it was restricted to 16 specific antibiotic resistance-bacterium combinations, which importantly do not represent the entire spectrum of AMR in Ireland. Based on information publicly available on the HPSC website (www.hpsc.ie) the evaluation team crudely estimated that, in absolute terms, the number of BSIs for the 16 included antibiotic resistance-bacterium resistant combinations accounted for approximately half of all pathogens that have resistance data (for example, tuberculosis (TB), *Shigella, Salmonella, Neisseria gonorrhoea* etc). However, the true burden and costs associated with these additional pathogens cannot be inferred or extrapolated from the current study due to substantial differences in how resistance in these infections is treated compared with the 16 included combinations. For example, while multidrug resistant (MDR) or extensively drug-resistant (XDR) TB are relatively rare in Ireland,[24] the healthcare costs for these patients are substantial, as treatment may involve prolonged periods of hospitalisation.[25]

Currently, there are no agreed Irish cost models available and this presents challenges when undertaking a health economic analysis.[102] There are some important caveats with the cost data used in this study. Firstly, the ABF price list relates to the entire episode of care from admission to discharge from hospital, and the HPO advise that these prices cannot be used to infer either a cost or price for the treatment of a particular diagnosis, or the provision of a particular intervention or procedure in isolation of the entire episode of care.[41] Secondly, individual hospitals cost items differently, due to local behaviour, the presence or absence of information systems and the particular technologies adopted. Thirdly, there is no definition of an 'average ward' and given that hospitals differ in how they record their own costs, estimation of the 'average' may be skewed by certain hospitals.[101] However, despite these caveats, the ABF price lists are the most representative national cost data available.

Estimating the significant costs associated with implementing infection prevention and control (IPC) measures and the organisational disruption associated with outbreaks would require the collation of detailed information from individual hospitals, as there are currently no national information systems in existence that would routinely collect these data. There are considerable costs associated with screening for AMR, and Carbapenase-producing *Enterobacteriaceae* (CPE) in

particular.[56] While screening hospitalised patients for CPE may be appropriate depending on the local prevalence of colonisation,[125] uncertainty remains regarding the most cost-effective approach and when and how screening can be stepped down. It is evident that screening practices also vary between hospitals with implications for costs.[126] There are substantial costs associated with CPE outbreaks in hospital settings including additional costs for surface swabbing, screening, isolating, contact tracing, cleaning, PPE, ward closures, theatre closures and healthcare professional time.[56] These IPC measures accrue as part of patient care (for example, screening on admission and isolation pending a negative result), irrespective of whether a patient is ultimately identified as having CPE or not. As noted, no micro-costing was undertaken as part of this study, rather, the additional costs for AMR were limited to costs associated with excess bed days. The costs relating to outbreaks contribute to overall hospital costs and are therefore included in the average cost of a bed day; however, this approach underestimates costs related to outbreaks overall. Importantly, while bed day costs are estimated in this study for certain members of the CPE family, specifically colistin- and carbapenem-resistant *E.coli* and *K. pneumoniae*, relative to their susceptible counterparts (Table 3.4), these do not reflect the totality of costs, and are likely a significant underestimate of costs for the treatment and management of CPE in 2019. For example, an outbreak of CPE affecting 40 patients in a group of five hospitals in West London over a period of 10 months (between March and December 2015), was estimated to cost €1.1 million from a hospital perspective.[56]

Besides screening, there are also other substantial costs such as capital investment in infrastructure, information technology systems and hospital wastewater treatment, which may be relevant for estimating the total costs associated with AMR for the health services as well as the potential for costs arising from AMR-related litigation.

Given the significant and ongoing disruption of the coronavirus disease 2019 (COVID-19) pandemic, it was agreed that it would not be appropriate to collect data that would require surveying or interviewing public acute hospital staff. Hence, the costs associated with the AMRIC national governance and surveillance programmes, the implementation of IPC measures, and the management of discrete pathogen-specific AMR outbreaks were not estimated. Instead, this study centred on estimating the additional cost associated with treating resistant infections relative to susceptible infections in public acute hospitals, using existing data sources. Therefore, the cost estimates produced in this report are acknowledged to be an underestimate of the total costs of AMR to public acute hospitals in Ireland and this is an important, yet unavoidable, limitation.

3.6 Conclusions

AMR is associated with a significant clinical and economic burden. This study estimated that over 4,700 resistant infections occurred across all 50 public acute hospitals in Ireland in 2019, treatment of which resulted in approximately €12 million in additional costs due to excess LOS, relative to treating susceptible infections. However, there is substantial uncertainty around the cost estimates produced in this study. These resistant infections accounted for an estimated 215 attributable deaths and almost 5,000 DALYs. This is similar to the estimated total number of DALYs attributable to rheumatoid arthritis (5,000 DALYs) in Ireland in 2019. As noted, a DALY equals the sum of the years of life lost due to premature mortality plus the years lost due to disability for people living with a health condition or its consequences. Given the restriction of the analysis to 16 antibiotic resistance-bacterium combinations in this study, the cost estimates produced in this report are acknowledged to be an underestimate of the total costs of AMR to public acute hospitals in Ireland.

4 Discussion

4.1 Overall summary

The purpose of this study was to estimate the current costs associated with select antimicrobial-resistant micro-organisms of public health concern in the public acute hospital setting in Ireland. Informed by a review of methodological approaches, a two-part methodology was used, which involved estimating the burden of disease followed by estimating the additional cost of treating resistant infections relative to susceptible infections. Irish antimicrobial resistance (AMR) surveillance data, as collated by the Health Protection Surveillance Centre (HPSC) and reported to the European Antimicrobial Resistance Surveillance (EARS-Net) system, were used as the primary data source for this study.[23] Parameter inputs for the micro-simulation model were obtained from systematic reviews of attributable mortality and length of stay (LOS),[28] disease outcome trees,[28, 91] and the Healthcare Pricing Office (HPO).[101]

The AMR rate was estimated to be 13.31% based on the eight resistant pathogens included in this study. This study estimated that the total number of the selected resistant infections in all 50 public acute hospitals in Ireland in 2019 was 4,787 (95% CI: 2,432-14,764), the treatment of which resulted in an expected total additional cost, relating to excess LOS, of €12,020,068 (95% CI: €4,879,603 - €23,267,352), relative to the treatment of susceptible infections. These resistant infections accounted for an estimated 215 (95% UI: 208-222) attributable deaths and 4,961 (95% UI: 4,861-5,062) disability-adjusted life years (DALYs). Given the restriction of the analysis to 16 antibiotic resistance-bacterium combinations in this study, and the fact that costs were limited to those associated with excess LOS, the cost estimates produced in this report are acknowledged to be an underestimate of the total cost of AMR to public acute hospitals in Ireland. Consistent with national HTA guidelines, the perspective adopted was that of the public acute healthcare system. Costs from the patient and societal perspectives are therefore not included in this estimate and may be significant.

4.2 Burden of AMR on the healthcare system

This study estimated that it cost the Health Service Executive (HSE) an additional €12 million on bed days alone, for patients with selected resistant compared with susceptible infections, in public acute hospitals in 2019. This figure is a conservative estimate as it only reflects the additional cost due to excess LOS for a select number of resistant pathogens. Though this estimated additional cost of €12 million represents only 0.075% of the HSE's €16 billion health budget for 2019, it is substantially greater than the €5 million that was allocated for AMR and infection prevention and control (IPC), and progress initiatives in the context of the CPE Public

Health Emergency in 2019.[20, 127] Importantly, if the estimated 4,787 patients with these selected resistant infections had susceptible infections instead, it would not necessarily have generated any cost savings for the HSE, rather it would have allowed for greater efficiencies in care by releasing bed capacity, including ICU bed capacity, arising from the reduction in length of stay. In this way, the estimated additional cost of €12 million reflects an opportunity cost of displaced care, which is particularly important given the very high bed occupancy rates (often greater than 90%) in the Irish public acute hospital system, which is among the highest in the Organisation for Economic Co-operation and Development (OECD).[128] Higher occupancy rates lead to bed shortages which may contribute to higher rates of infection. While acknowledging that not all infections are preventable,[10] the rate of AMR could increase if appropriate measures are not put in place, which might result in even greater costs to the healthcare system in the future.[10, 11] While rates of AMR may be stable or even in decline for some pathogens at the moment in Ireland, it is important to acknowledge that at a global level, resistance rates are growing.[10]

The cost estimates included in this study do not include the direct costs associated with the national governance of the Antimicrobial Resistance and Infection Control (AMRIC) team, the surveillance programmes for carbapenemase producing *Enterobacteriaceae* (CPE) and other resistant pathogens, implementing IPC measures and managing outbreaks, and providing resources for antimicrobial stewardship, laboratories, surveillance and other activities critical for dealing with AMR and healthcare associated infections (HCAI). There has been substantial investment in these national structures in recent years.[20] There are also significant costs associated with the removal of antimicrobial resistant micro-organisms from hospital wastewater,[129] as well as litigation costs arising from claims relating to deaths due to resistant infections, that are not included in this study. The indirect costs associated with AMR, such as the loss of hospital revenue due to cancellation of elective procedures or bed closures, and the opportunity costs due to staff being required to deal with the consequences of AMR instead of undertaking their usual work, were also not included in this study. These costs can be quite substantial. For example, in 2017, the HSE estimated that a CPE outbreak in University Hospital Limerick which resulted in 60 cases of CPE since 2015 cost €4 million, while CPE outbreaks in Tallaght Hospital since 2016 were estimated to have cost €2 million, with 700 operations postponed as a direct consequence of the outbreak.[18] As discussed in Chapter 2, the accurate ascertainment of the direct and indirect costs associated with outbreaks is particularly challenging. However, regardless of the actual cost of these outbreaks, international evidence indicates that these outbreaks of resistant pathogens are particularly burdensome on hospitals.[49-58]

The significance of intensive care unit (ICU) capacity has come to the fore during the coronavirus 2019 (COVID-19) pandemic.[130] The surge of patients critically ill with

COVID-19 overwhelmed ICU in certain jurisdictions, including areas of northern Italy, early in the pandemic.[130, 131] The total number of ICU beds in the public health system in Ireland was estimated to be 255 or 5.2 ICU beds per 100,000 people, before the onset of the pandemic in February 2020.[104, 132] This corresponded to less than half the European and OECD average.[104, 133, 134] Though ICU capacity in the public health system has been increasing throughout 2020 to deal with any potential resurgence of COVID-19 cases, progress has been slow, due to significant expansion challenges particularly the availability of specially trained staff.[135, 136] There is a significant opportunity cost associated with avoidable admissions to ICU due to AMR, particularly in a system with a very high ICU bed occupancy rate of 90%.[104] Not only is there a greater cost associated with ICU admissions as illustrated in this study, but there are also considerable constraints on the number of patients that can be admitted to ICU. Once ICU reaches maximum capacity, clinicians have to decide how critical care is allocated.[137] The conduct of major elective procedures, including cardiac, thoracic, maxillofacial and neurosurgical procedures, may also be impacted if there are limited ICU beds available.[138] Therefore, AMR may be associated with delays in provision of elective care for other conditions, potentially contributing to adverse outcomes and and overall reduction in the efficiency of the healthcare system.

There are other important organisational costs that need to be considered to control AMR over time that are not captured in the current report. When certain resistance thresholds are met for specific pathogens, the approach to the management changes and this can have an impact at a population rather than an individual level. With regards to antimicrobial prescribing practice at a local population level, most infections are treated empirically and therefore the known level of resistance of a pathogen to specific antimicrobials dictates the empiric prescribing policy which in turns, drives the majority of prescribing decisions.[139] As an example, *E. coli* is the predominant cause of UTI, and it is commonly accepted that if resistance to *E. coli* exceeds 20% for a particular antimicrobial in a population, this agent can no longer be used empirically.[140] As a consequence of this, nearly all UTIs across a local population will not receive that empiric agent except those with a microbiologically confirmed infection found to be sensitive to that particular agent. Where trimethoprim, which is cheap, may no longer be used empirically to treat UTIs, other more expensive agents may routinely be needed across the board; this can result in a very sudden increase in expenditure. Other potential examples include a need to use parenteral therapy to treat infection in the case of the key pathogen that causes infection no longer being reliably treated with available oral agents (for example *Neisseria gonorrhoeae*).[141] There is also the potential for empiric prescribing using broad spectrum antimicrobials over concerns of AMR in those with no proven resistant isolate, which in itself has the potential to drive further AMR, in addition to

increased requesting or utilisation of diagnostic tests.

Furthermore, in the event that such resistance thresholds are met, the way services are designed may need to change. For example, there may be a requirement for additional isolation facilities or nursing staff to prevent crossover between patients with resistant and non-resistant infections.[56] There may also be a requirement for additional outpatient clinics to deal with a new cohort of patients, for example additional clinics for thse who have multidrug resistant (MDR) *Neisseria gonorrhoea* or MDR tuberculosis (TB), with associated staffing and treatment costs.[142]

4.3 Burden of AMR on patients

This study estimated that approximately 215 deaths were attributable to AMR in Ireland in 2019, resulting in almost 5,000 DALYs or years of full life lost. The OECD has estimated that around 2.4 million people could die in Europe, North America and Australia between 2015-2050, due to AMR.[10] A seminal United Kingdom (UK) government report, chaired by the economist Lord Jim O'Neill, estimated that globally by 2050, 10 million lives a year are at risk due to the rise of AMR.[11] The international evidence all points towards a growing problem of AMR globally and its significant impact on patients, in terms of increasing mortality and morbidity, if actions are not put in place now.[5, 10, 11, 18, 23, 58, 60, 62, 111]

Patients with infections caused by resistant organisms are more likely to have poorer health and to experience worse outcomes including morbidity and mortality, when compared with those whose infections are caused by antimicrobial susceptible organisms.[10, 112] Beyond mortality and morbidity, patients and their carers and family experience other significant health and economic burdens due to AMR such as increased healthcare and non-healthcare costs,[115] loss of earnings and leisure time,[115] increased anxiety and depression,[112, 115] fear of transmitting infections to others,[113] stigmatisation,[113, 114] reduced treatment options[111] and side effects from last-line antimicrobials.[109] It is also important to consider that AMR is likely to exacerbate existing health inequalities, as different groups in society have different risks of poorer health and therefore are differently at risk of, or impacted by AMR.[143, 144] For example, this study found that males had a greater burden of disease due to AMR, particularly those under the age of one, and those over the age of 65, similar to what was found in other studies.[10, 91]. A systematic review by Alividza et al. found that crowding and homelessness were associated with AMR in community and hospital patients, and that low income was associated with *Streptococcus pneumoniae* and *Acinetobacter baumannii* resistant infections and a seven-fold higher infection rate.[145] Thus highlighting the importance of addressing social determinants of poverty and health inequalities when tackling AMR.[145]

Section 3.4.4 highlighted findings from qualitative studies, which can offer rich

insights into the first hand experiences of the negative effects of AMR, including its potential impact on both the quality of life for the individual, its impact on their earnings and on their families.*(112)* Another study described how patients with resistant infections reported feeling stigmatised, and the limited understanding of risk and appropriate risk-reducing behaviour due to lack of knowledge and information about the condition.(113) Such studies highlight the significant burden that AMR has on patients that is not possible to monetise.

4.4 Burden of AMR on healthcare professionals

The growth of AMR places a strain on healthcare professionals in that the choice of effective antimicrobial therapies are continuously being reduced, while the development of newer antimicrobials has stalled.(10) For some multidrug-resistant gram-negative bacterial infections, healthcare professionals are resorting to last line therapies, such as colistin, which are more expensive, have significant toxicity issues and are less effective.(109) Colistin resistant infections have been reported across Europe in recent years, which are very difficult, if not impossible to treat.(110) The emergence of pathogens that are not susceptible to any known antimicrobials is deeply concerning, given what is known about pathogens that have very limited treatment options such as *Neisseria gonorrhoea*. This pathogen is one of four that has been identified in 2019 by the US Centers for Disease Control and Prevention (CDC) as an urgent public health threat. *N. gonorrhoea* has quickly developed resistance to all but one class of antibiotics, and half of all infections with this pathogen are resistant to at least one antibiotic.(117)

The reduction in effective antimicrobial therapy options produces particularly significant challenges for clinicians working with patients who rely on effective antimicrobials to treat infections and complications, such as patients undergoing chemotherapy or transplants. Given that drug development takes upwards of 10 years from discovery to regulatory approval, should effective antimicrobial options run out before newer therapies become available, many patients could die from these once treatable infections.(10)

4.5 Burden of AMR on society

The financial cost of treating resistant infections places a significant burden on society, as patients infected with drug-resistant micro-organisms are more likely to remain in hospital for a longer period of time, to have poorer outcomes and to be unable to work.(7-9) At a macro-economic level, reduced productivity due to illness or death among working populations can result in the loss of gross domestic product (GDP).(115) Though this study found that the burden of disease due to AMR disproportionately affected those aged 65 years and older and those under the age of one, illness in these age groups are likely to impact on the productivity of carers,

family members and parents. There may be other societal consequences to high levels of AMR, which may include a loss of confidence in the healthcare system. Similar to what was observed during the COVID-19 pandemic, hospitals with high levels of AMR may became viewed as unsafe environments where transmission is likely to occur, and so patients may opt not to attend even if urgent care is warranted.[146]

Smith and Coast argued in a publication in 2013, that many of the cost estimates published in the literature at that time underestimated the total economic burden of AMR on society, and produced estimates that were far lower than those from other health problems such as cancer and heart disease, which may have resulted in inadequate investment in tackling AMR.[147] The authors reasoned that the production of 'modest' cost estimates resulted from a focus on incremental costs, which excludes some of the most critical economic impacts of AMR which is when AMR leads to the loss of many of the advantages in medical care that effective antimicrobials have enabled.[147] The authors described the sigmoidal pattern of resistance, whereby the estimated current costs are low when there is scope to prevent resistance emerging, but once the costs are observably high there may be little that can be done to reverse the growth of resistance. Other important societal impacts that are rarely measured are the costs of AMR on patient safety and public confidence in healthcare. The authors argued that in order to calculate the full potential economic burden of AMR there is a need to consider the burden associated with not having antimicrobial therapies at all.[147]

International reports published since the Smith and Coast article have reported exceptionally high societal costs of AMR. The Review on Antimicrobial Resistance, published in 2016, which is more commonly known as the O'Neill report, estimated that globally by 2050, a cumulative US $100 trillion of economic output could be lost due to AMR, if no action on AMR takes place.[11] The O'Neill report, employed two different consultancy teams (Research and Development (RAND) and Klynveld Peat Marwick Goerdeler (KPMG)) to undertake economic analyses, which provided the basis for the conclusions of the report. The RAND report estimated global GDP losses attributable to AMR of up to US $3 trillion per year over a 40-year time horizon from 2010-2050, resulting in cumulative losses that range between US $2.1 trillion and US $124.5 trillion, in the absence of any progress in tackling AMR.[148] The report by KPMG estimated that by 2050, global GDP could decrease by 1.66% if there was an absolute rise in current rates of resistance of 40%, and GDP could decrease by 3.4% if there was a 100% resistance rate.[149] The World Bank released a report in 2017 that estimated in a best case scenario, as a result of AMR, that annual GDP could fall by 1.1% by 2050, with an annual shortfall of US $1 trillion by 2030. In the worst case scenario, the World Bank estimated that as a result of AMR, annual GDP could fall by 3.8% by 2050, with an annual shortfall of US $3.4 trillion by 2030. In short,

the impact of AMR until 2050 is estimated by the World Bank to be within the same order of magnitude as that of the 2008 global financial crisis.[150]

The projection of societal costs into the future using top-down, extrapolation and modelling approaches, as conducted in these studies, is methodologically challenging, and many key parameters are primarily based on expert opinion in the absence of data.[11, 148-150] Hence, a definitive estimate of the cost of AMR from the societal perspective cannot be derived.[29] However, given the current rate of growth of AMR globally, and the significant impact it is currently having on patients, healthcare professionals and healthcare systems, it is likely that the societal costs associated with AMR will continue to be substantial.

4.6 Implications

The findings from this study will be used to directly inform the second iteration of Ireland's National Action Plan on Antimicrobial Resistance (iNAP2).[18] Establishing the current cost of AMR is useful to inform future investment decisions thereby promoting, and providing a metric against which to measure the use of proposed evidence-based, cost-effective solutions to challenges faced as a result of AMR. Additionally, this study presents a preferred standardised methodology for estimating the economic burden of AMR on public acute hospitals in Ireland based on an international review of the economic literature, which may be used in the future by the Department of Health and other agencies. Hence, findings from this current study provide a baseline cost estimate upon which future iterations of this study can be build.

The need to develop and implement policies to combat the spread of AMR is evident from the findings of this study. To protect the health and economic wellbeing of the population from the harmful effects of AMR, policies should focus on promoting the prudent use of antimicrobials in humans, animals and the environment, increasing vaccination uptake and improving IPC measures.[10] International studies have highlighted the need for investment to improve infrastructure and increase capacity, with the aim of reducing the risk of onward transmission of resistant organisms within the congregated environments where health and social care is delivered,[151] and to do so before the level of antimicrobial resistance becomes uncontrollable.[147] To this end, the OECD recommends a multi-pronged approach targeting a variety of stakeholders with different intervention goals (that is, reducing the development of AMR, preventing its spread, and promoting immunisation).[10] A One Health perspective is also critical for policy-making, in that the determinants of AMR across human, animal, and environmental health are carefully considered before implementing policies.[115] With regards to third-line antimicrobials, these are usually less effective, more toxic and more costly than first or second line agents.[152] The

older agents may be unlicensed medicinal products, can be difficult to source and can be very costly. The newly developed agents tend to be very expensive given the impact of drug patents.[10] In the future, consideration may need to be given to alternative funding models (both for the older unlicensed products and the newly developed agents) to safeguard their availability.

There is a need for expanded surveillance of AMR, and investment in public health in Ireland, given the increasing number of antimicrobials for which resistance is developing, and the need to rapidly manage outbreaks of resistant pathogens in the community through an advanced public health response.[153] This should include surveillance of both phenotypic resistance (that is, based on antimicrobial sensitivity tests) and novel resistance genotypes (that is, based on the genetic sequence) with mechanisms of resistance that may have a high public health impact.[154] Ireland participates in the World Health Organization (WHO) Global Antimicrobial Resistance and Use Surveillance System (GLASS) initiative, which was established "to standardise the collection of official data on AMR for common bacterial infections in order to provide a clearer, more comprehensive picture of dynamics and drivers of AMR globally".[155] In 2019, the Irish data submitted to GLASS was limited to the pathogens reported to EARS-Net, with the addition of *N. gonorrhoea* (from genital swabs). For example, no data on *Salmonella spp.* (from blood or stool samples), *Shigella spp*. (from stool samples), *E. coli* (from urine samples) or *K. pneumonaie* (from urine samples) were submitted to WHO-GLASS in 2019. Additionally, Ireland did not provide data to the antimicrobial consumption surveillance arm of GLASS, nor the fungi surveillance arm,[155] despite the growing threat of antifungal-resistant infections.[153] Greater resources are required to enhance surveillance activities in Ireland, in order to effectively identify and manage AMR threats rapidly, as well as allow broader evaluations of the economic cost of AMR in Ireland.

4.7 Strengths and limitations

The main strength of this study was the rigorous methods that were used by the evaluation team who are experienced in the areas of evidence synthesis, health economics and pharmacotherapy. Furthermore, the assistance of the Expert Advisory Group (EAG) with contextual knowledge and strong clinical experience of managing AMR added important insights to this study. Hence the robustness of the study led to findings that were strongly rooted in the evidence, relevant and important for informing national health policy.

The main limitation of this study was that its scope was restricted to the costs of excess length of hospital stay associated with 16 antibiotic resistance-bacterium combinations. It is important to acknowledge that these 16 antibiotic resistance-bacterium combinations do not represent the entire spectrum of AMR in Ireland. For

example, fluoroquinolone-resistant *E. coli* and *K. pneumoniae* are not included in this list, despite 20% and 17% of all tested invasive isolates of *E. coli* and *K. pneumoniae* being resistant to fluoroquinolones in Ireland in 2019.[23] Additionally, though relatively rare in Ireland,[24] the healthcare costs for patients with MDR or extensively drug-resistant (XDR) TB are substantial.[25] Furthermore, drug-resistant viral (for example, human immunodeficiency virus (HIV)) and fungal infections (for example, *Candida auris)* can have substantial clinical and economic impacts on patients, healthcare systems and society.[26, 27] Hence, the estimated figures from this study are indicative of the scale of the cost on the public acute hospital system in Ireland, but are acknowledged to be an underestimate of the total costs.

This study was impacted by the onset of the COVID-19 pandemic in early 2020. Specifically, cost and resource utilisation data for personal protective equipment (PPE) used for the control of AMR-related outbreaks prior to the pandemic, are likely to be of limited applicability in the context of COVID-19 due to the widespread use of, and high demand for PPE in healthcare settings. Given the lack of a centralised cost database in Ireland, there would be a need to contact individual hospitals to obtain their cost and resource utilisation data. In light of the increased demands on acute services as they deal with the ongoing impact of COVID-19, it was agreed that it would not be feasible nor appropriate to ascertain this information from acute hospital staff at this time, and this represents another important limitation of this study.

4.8 Future research

A number of other direct costs (beyond excess length of stay) may also be attributable to AMR, such as the costs associated with governance, surveillance, screening, and prevention and control of AMR (including the management of discrete pathogen-specific AMR outbreaks and the potential disruption to both routine and scheduled care due to requirements for patient cohorting, ward closures etc.).

Future research, aligned with the iNAP2 should endeavour to estimate these broader costs associated with AMR, along with inclusion of a broader range of drug-resistant pathogens, in a broader range of settings (for example, acute hospitals, community and long-term care) and over a longer time period. With regards to the indirect effect of AMR, *Clostridioides difficile* may be a relevant pathogen to include in a future study. While *C. difficile* is not in itself considered an antimicrobial resistant pathogen, healthcare-associated *C. difficile* infection is strongly associated with the use of certain broad spectrum antibiotics, such as carbapenems and third- and fourth-generation cephalosporins, that are required to treat resistant infections.[156] Tackling AMR may in turn reduce the need for broad spectrum empiric agents which in turn may reduce the risk of *C. difficile* infection and costs associated with

managing these infections.

Consideration should be given to surveying acute hospital staff on the management of discrete pathogen-specific AMR outbreaks.[57, 58] The survey might include questions regarding direct (for example, isolation bed usage, ICU admission, additional staffing, additional cleaning, additional screening, Public Health involvement, stewardship activities), and indirect costs (for example, cancelled elective procedures, ward closures and opportunity costs for staff such as time required for controlling the outbreak, education and audit) during the largest and smallest outbreaks experienced on a ward in a calendar year. The ascertainment of accurate outbreak costings is an important research gap that will be critical for informing IPC policy. Given the clinical and cost implications of changes to empiric antimicrobial practices,[152] future research should examine how prescribing practices at a population level change in response to growing AMR concerns. There is also a need for an agreed national cost dataset, to facilitate comparison of different economic evaluations undertaken to inform decision-making across the public healthcare system.

5 Conclusions

AMR has a significant burden on patients, healthcare professionals, the healthcare system, and society. This study estimated that over 4,700 resistant infections occurred across all 50 public acute hospitals in Ireland in 2019, treatment of which resulted in approximately €12 million in additional costs due to excess LOS, relative to treating susceptible infections. However, there are some limitations associated with this study that reduces the certainty of the cost estimates produced.

In order to better estimate the economic burden of AMR in Ireland, there is a need for more high quality data. Firstly, there is a need to standardise data collection for outbreak investigations using a minimum dataset, so that outbreaks involving resistant pathogens can be accurately costed. Secondly, there is a need for expanded surveillance of resistant pathogens in Ireland. As a greater number of pathogens become resistant to a greater number of antimicrobials, it is important that surveillance is enhanced beyond a core number of resistant pathogens. Thirdly, there is a need to make better use of existing surveillance data and epidemiological models. Pooling of databases may allow for a more comprehensive analysis. Finally, there is a need for agreed Irish cost models, so that cost estimates that accurately reflect the economic impact of AMR on the Irish healthcare system can be produced.

References

1. World Health Organization. Antimicrobial Resistance: Key Facts. 2020 [updated 13 Oct 2020; cited 2021 4 Jan]. Available from: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance.
2. Chatterjee A, Modarai M, Naylor NR, Boyd SE, Atun R, Barlow J, et al. Quantifying drivers of antibiotic resistance in humans: a systematic review. The Lancet Infectious Diseases. 2018;18(12):e368-e78.
3. Fletcher S. Understanding the contribution of environmental factors in the spread of antimicrobial resistance. Environmental Health and Preventive Medicine. 2015;20(4):243-52.
4. Katale BZ, Misinzo G, Mshana SE, Chiyangi H, Campino S, Clark TG, et al. Genetic diversity and risk factors for the transmission of antimicrobial resistance across human, animals and environmental compartments in East Africa: a review. Antimicrobial Resistance & Infection Control. 2020;9(1):127.
5. World Health Organization. Global Action Plan on Antimicrobial Resistance. 2015 [updated May 2015; cited 2021 4 Jan]. Available from: http://www.emro.who.int/health-topics/drug-resistance/global-action-plan.html.
6. World Health Organization. Antimicrobial resistance: global report on surveillance: World Health Organization; 2014 [updated April 2014; cited 2021 4 Jan]. Available from: https://www.who.int/drugresistance/documents/surveillancereport/en/.
7. Cosgrove SE. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. Clinical Infectious Diseases. 2006;42(Supplement_2):S82-9.
8. Nathwani D, Raman G, Sulham K, Gavaghan M, Menon V. Clinical and economic consequences of hospital-acquired resistant and multidrug-resistant Pseudomonas aeruginosa infections: a systematic review and meta-analysis. Antimicrobial Resistance and Infection Control. 2014;3(1):32.
9. Naylor NR, Atun R, Zhu N, Kulasabanathan K, Silva S, Chatterjee A, et al. Estimating the burden of antimicrobial resistance: a systematic literature review. Antimicrob Resist Infect Control. 2018;7:58.
10. OECD. Stemming the Superbug Tide: Just A Few Dollars More. Paris: OECD Publishing; 2018 [updated 2018; cited 2020 15 Dec]. Available from: https://read.oecd-ilibrary.org/social-issues-migration-health/stemming-the-superbug-tide_9789264307599-en.
11. O'Neill J. The Review of Antimicrobial Resistance. Tackling drug-resistant infections globally: final report and recommendations London2016 [updated 19 May 2016; cited 2021 4 Jan]. Available from: https://amr-review.org/Publications.html.
12. Livermore DM, Nicolau DP, Hopkins KL, Meunier D. Carbapenem-Resistant Enterobacterales, Carbapenem Resistant Organisms, Carbapenemase-Producing Enterobacterales, and Carbapenemase-Producing Organisms: Terminology Past its "Sell-By Date" in an Era of New Antibiotics and Regional Carbapenemase Epidemiology. Clinical Infectious Diseases. 2020;71(7):1776-82.
13. Health protection surveillance centre. Carbapenemase-producing Enterobacteriaceae* (CPE) infection or colonisation 2019 [updated 5 Feb 2019; cited 2020 8 Dec]. Available from: https://www.hpsc.ie/a-z/microbiologyantimicrobialresistance/strategyforthecontrolofantimicrobialresistanceinirelands ari/carbapenemresistantenterobacteriaceaecre/casedefinition/.
14. Health Protection surveillance centre. Carbapenemase Producing Enterobacteriaceae (CPE) 2018 [updated 3 April 2020; cited 2020 8 Dec]. Available from: https://www.hpsc.ie/a-z/microbiologyantimicrobialresistance/strategyforthecontrolofantimicrobialresistanceinirelands ari/carbapenemresistantenterobacteriaceaecre/.
15. Centers for Disease Prevention and Control. CRE Technical Information 2019 [updated 22 Nov 2019; cited 2021 4 Jan]. Available from: https://www.cdc.gov/hai/organisms/cre/technical-info.html#Difference.
16. Department of Health. Public Health Emergency Plan to tackle CPE Dublin2017 [updated 26 Oct 2020; cited 2021 4 Jan]. Available from: https://health.gov.ie/national-patient-safety-office/patient-safety-surveillance/antimicrobial-resistance-amr-2/public-health-emergency-

plan-to-tackle-cpe/.

17. Logan LK, Weinstein RA. The Epidemiology of Carbapenem-Resistant Enterobacteriaceae: The Impact and Evolution of a Global Menace. The Journal of infectious diseases. 2017;215(suppl_1):S28-s36.
18. Department of Health. Ireland's National Action Plan on Antimicrobial Resistance 2017-2020. (iNAP) Dublin: Department of Health; 2017 [updated 25 Oct 2017; cited 2021 4 Jan]. Available from: https://health.gov.ie/wp-content/uploads/2017/10/iNAP_web-1.pdf.
19. Keane S. Antimicrobial Resistance and Infection Control Team Role and Function [Conference Presentation] University College Cork. 2019 [updated 2 Sep 2019; cited 2021 17 Feb]. Available from: https://www.ucc.ie/en/media/academic/epidemiologyandpublichealth/PresentationFormat-SafePatientCare.BugsandDrugs2019-ShirleyKeane-30-08-2019(1).pdf.
20. Department of Health. Department of Health allocates €7 million for antimicrobial resistance and infection prevention & control 2019 [updated 4 Jun 2019; cited 2021 22 Feb]. Available from: https://www.gov.ie/en/press-release/daa2df-department-of-health-allocates-7-million-for-antimicrobial-resistanc/.
21. Health Service Executive. Costings for Antimicrobial Resistance and Infection Control (AMRIC) implementation plan, 2019 [Personal Communication] 2019 [updated 24 May 2019.
22. European Centre for Disease Prevention and Control. Surveillance of antimicrobial resistance in Europe – Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net) 2017 Stockholm: ECDC; 2018 [updated 15 Nov 2018; cited 2021 4 Jan]. Available from: https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-resistance-europe-2017.
23. European Centre for Disease Prevention and Control. Antimicrobial resistance in the EU/EEA (EARS-Net) - Annual Epidemiological Report for 2019 Stockholm: ECDC; 2020 [updated 18 Nov 2020; cited 2020 23 Nov]. Available from: https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-resistance-europe-2019#no-link.
24. Health Protection Surveillance Centre. National TB surveillance in Ireland, 2018 2019 [updated Feb 2019; cited 2020 23 Nov]. Available from: https://www.hpsc.ie/a-z/vaccinepreventable/tuberculosistb/tbdataandreports/annualreports/AER_TB_2018data_v1.0.pdf.
25. Günther G. Multidrug-resistant and extensively drug-resistant tuberculosis: a review of current concepts and future challenges. Clin Med (Lond). 2014;14(3):279-85.
26. Jeffery-Smith A, Taori SK, Schelenz S, Jeffery K, Johnson EM, Borman A, et al. Candida auris: a Review of the Literature. Clinical Microbiology Reviews. 2018;31(1):e00029-17.
27. Millham LRI, Scott JA, Sax PE, Shebl FM, Reddy KP, Losina E, et al. Clinical and Economic Impact of Ibalizumab for People With Multidrug-Resistant HIV in the United States. Journal of acquired immune deficiency syndromes (1999). 2020;83(2):148-56.
28. Cassini A, Högberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. The Lancet Infectious Diseases. 2019;19(1):56-66.
29. Wozniak TM, Barnsbee L, Lee XJ, Pacella RE. Using the best available data to estimate the cost of antimicrobial resistance: a systematic review. Antimicrobial Resistance & Infection Control. 2019;8(1):26.
30. Dunachie SJ, Day NPJ, Dolecek C. The challenges of estimating the human global burden of disease of antimicrobial resistant bacteria. Current Opinion in Microbiology. 2020;57:95-101.
31. Smith RD, Yago M, Millar M, Coast J. Assessing the macroeconomic impact of a healthcare problem: The application of computable general equilibrium analysis to antimicrobial resistance. Journal of Health Economics. 2005;24(6):1055-75.
32. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated health economic evaluation reporting standards (CHEERS)—explanation and elaboration: a report of the ISPOR health economic evaluation publication guidelines good reporting practices task force. Value in Health. 2013;16(2):231-50.
33. Graves N, Harbarth S, Beyersmann J, Barnett A, Halton K, Cooper B. Estimating the cost of health care-associated infections: mind your p's and q's. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2010;50(7):1017-21.

34. Barnett AG, Beyersmann J, Allignol A, Rosenthal VD, Graves N, Wolkewitz M. The time-dependent bias and its effect on extra length of stay due to nosocomial infection. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2011;14(2):381-6.
35. Birgand G, Moore LSP, Bourigault C, Vella V, Lepelletier D, Holmes AH, et al. Measures to eradicate multidrug-resistant organism outbreaks: how much do they cost? Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2016;22(2):162.e1-.e9.
36. Zhen X, Lundborg CS, Sun X, Hu X, Dong H. Economic burden of antibiotic resistance in ESKAPE organisms: a systematic review. Antimicrob Resist Infect Control. 2019;8:137.
37. Health Protection Surveillance Centre. Definition of outbreak: HPSC; 2019 [cited 2021 4 Jan]. Available from: https://www.hpsc.ie/notifiablediseases/casedefinitions/outbreak/.
38. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.
39. Cheah A, Spelman T, Liew D, Peel T, Howden B, Spelman D, et al. Enterococcal bacteraemia: factors influencing mortality, length of stay and costs of hospitalization. Clinical Microbiology and Infection. 2013;19(4):E181-E9.
40. Healthcare Pricing Office. Hospital In-Patient Enquiry (HIPE) Instruction Manual 2021. 2020 [cited 2021 4 Jan]. Available from: http://www.hpo.ie/hipe/hipe_instruction_manual/HIPE_Instruction_Manual_2021_V1.0.pdf.
41. Healthcare Pricing Office. Activity Based Funding 2019 Admitted Patient Price List 2019 [updated 2019; cited 2020 15 Dec]. Available from: http://www.hpo.ie/abf/ABF2019AdmittedPatientPriceList.pdf.
42. Tripathy JP. Secondary Data Analysis: Ethical Issues and Challenges. Iran J Public Health. 2013;42(12):1478-9.
43. Clarke N, Vale G, Reeves EP, Kirwan M, Smith D, Farrell M, et al. GDPR: an impediment to research? Irish Journal of Medical Science (1971 -). 2019;188(4):1129-35.
44. Itani KM, Merchant S, Lin SJ, Akhras K, Alandete JC, Hatoum HT. Outcomes and management costs in patients hospitalized for skin and skin-structure infections. American journal of infection control. 2011;39(1):42-9.
45. Anderson DJ, Kaye KS, Chen LF, Schmader KE, Choi Y, Sloane R, et al. Clinical and financial outcomes due to methicillin resistant Staphylococcus aureus surgical site infection: a multi-center matched outcomes study. PloS one. 2009;4(12):e8305.
46. Health Service Executive. Hospital charges 2020 [cited 2020 25 Nov]. Available from: https://www.hse.ie/eng/about/who/acute-hospitals-division/patient-care/hospital-charges/.
47. Jo C. Cost-of-illness studies: concepts, scopes, and methods. Clin Mol Hepatol. 2014;20(4):327-37.
48. Larg A, Moss JR. Cost-of-illness studies. Pharmacoeconomics. 2011;29(8):653-71.
49. Ayraud-Thévenot S, Huart C, Mimoz O, Taouqi M, Laland C, Bousseau A, et al. Control of multi-drug-resistant Acinetobacter baumannii outbreaks in an intensive care unit: feasibility and economic impact of rapid unit closure. Journal of Hospital Infection. 2012;82(4):290-2.
50. Daroukh A, Delaunay C, Bigot S, Ceci JM, Siddhoun N, Bukreyeva I, et al. Characteristics and costs of carbapenemase-producing enterobacteria carriers (2012/2013). Médecine et Maladies Infectieuses. 2014;44(7):321-6.
51. Dik J-WH, Dinkelacker AG, Vemer P, Lo-Ten-Foe JR, Lokate M, Sinha B, et al. Cost-analysis of seven nosocomial outbreaks in an academic hospital. PloS one. 2016;11(2):e0149226.
52. Escaut L, Bouam S, Frank-Soltysiak M, Rudant E, Saliba F, Kassis N, et al. Eradication of an outbreak of vancomycin-resistant Enterococcus (VRE): the cost of a failure in the systematic screening. Antimicrobial Resistance and Infection Control. 2013;2(1):18.
53. Gagnaire J, Gagneux-Brunon A, Pouvaret A, Grattard F, Carricajo A, Favier H, et al. Carbapenemase-producing Acinetobacter baumannii: An outbreak report with special highlights on economic burden. Med Mal Infect. 2017;47(4):279-85.
54. Jiang Y, Resch S, Liu X, Rogers SO, Jr., Askari R, Klompas M, et al. The Cost of Responding to an Acinetobacter Outbreak in Critically Ill Surgical Patients. Surg Infect (Larchmt). 2016;17(1):58-64.
55. Mollers M, Lutgens SP, Schoffelen AF, Schneeberger PM, Suijkerbuijk AWM. Cost of

Nosocomial Outbreak Caused by NDM-1-Containing Klebsiella pneumoniae in the Netherlands, October 2015-January 2016. Emerg Infect Dis. 2017;23(9):1574-6.

56. Otter JA, Burgess P, Davies F, Mookerjee S, Singleton J, Gilchrist M, et al. Counting the cost of an outbreak of carbapenemase-producing Enterobacteriaceae: an economic evaluation from a hospital perspective. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2017;23(3):188-96.
57. Morii D, Tomono K, Imanaka Y. Economic impact of antimicrobial-resistant bacteria outbreaks on Japanese hospitals. American journal of infection control. 2020;48(10):1195-9.
58. Public Health Agency of Sweden. Future costs of antibiotic resistance Stockholm2018 [updated 2018; cited 2020 15 Dec]. Available from: https://www.folkhalsomyndigheten.se/contentassets/488c4abcf0ff4f2b9d72a6a17de3cae1/future-costs-antibiotic-resistance-18010.pdf.
59. Bartsch SM, McKinnell JA, Mueller LE, Miller LG, Gohil SK, Huang SS, et al. Potential economic burden of carbapenem-resistant Enterobacteriaceae (CRE) in the United States. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2017;23(1):48.e9-.e16.
60. Council of Canadian Academies. When Antibiotics Fail Ottawa2019 [updated 2019; cited 2020 15 Dec]. Available from: https://cca-reports.ca/wp-content/uploads/2018/10/When-Antibiotics-Fail-1.pdf.
61. de Kraker ME, Davey PG, Grundmann H. Mortality and hospital stay associated with resistant Staphylococcus aureus and Escherichia coli bacteremia: estimating the burden of antibiotic resistance in Europe. PLoS Med. 2011;8(10):e1001104.
62. European Centre for Disease Prevention and Control. The bacterial challenge: time to react Stockholm: ECDC; 2009 [updated 17 Sep 2009; cited 2020 15 Dec]. Available from: https://www.ecdc.europa.eu/en/publications-data/ecdcemea-joint-technical-report-bacterial-challenge-time-react.
63. Johnston KJ, Thorpe KE, Jacob JT, Murphy DJ. The incremental cost of infections associated with multidrug-resistant organisms in the inpatient hospital setting—A national estimate. Health services research. 2019.
64. Klein EY, Jiang W, Mojica N, Tseng KK, McNeill R, Cosgrove SE, et al. National Costs Associated With Methicillin-Susceptible and Methicillin-Resistant Staphylococcus aureus Hospitalizations in the United States, 2010-2014. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2019;68(1):22-8.
65. Lemos EV, de la Hoz FP, Alvis N, Einarson TR, Quevedo E, Castaneda C, et al. Impact of carbapenem resistance on clinical and economic outcomes among patients with Acinetobacter baumannii infection in Colombia. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2014;20(2):174-80.
66. Naylor NR, Pouwels KB, Hope R, Green N, Henderson KL, Knight GM, et al. The health and cost burden of antibiotic resistant and susceptible Escherichia coli bacteraemia in the English hospital setting: A national retrospective cohort study. PloS one. 2019;14(9):e0221944.
67. Nelson RE, Schweizer ML, Perencevich EN, Nelson SD, Khader K, Chiang HY, et al. Costs and Mortality Associated With Multidrug-Resistant Healthcare-Associated Acinetobacter Infections. Infect Control Hosp Epidemiol. 2016;37(10):1212-8.
68. Nguyen HQ, Nguyen NTQ, Hughes CM, O'Neill C. Trends and impact of antimicrobial resistance on older inpatients with urinary tract infections (UTIs): A national retrospective observational study. PloS one. 2019;14(10).
69. Resch A, Wilke M, Fink C. The cost of resistance: incremental cost of methicillin-resistant Staphylococcus aureus (MRSA) in German hospitals. Eur J Health Econ. 2009;10(3):287-97.
70. Stewardson AJ, Allignol A, Beyersmann J, Graves N, Schumacher M, Meyer R, et al. The health and economic burden of bloodstream infections caused by antimicrobial-susceptible and non-susceptible Enterobacteriaceae and Staphylococcus aureus in European hospitals, 2010 and 2011: a multicentre retrospective cohort study. Eurosurveillance. 2016;21(33):30319.
71. Touat M, Opatowski M, Brun-Buisson C, Cosker K, Guillemot D, Salomon J, et al. A Payer Perspective of the Hospital Inpatient Additional Care Costs of Antimicrobial Resistance in France: A Matched Case–Control Study. Applied health economics and health policy. 2019;17(3):381-9.

72. Wozniak TM, Bailey EJ, Graves N. Health and economic burden of antimicrobial-resistant infections in Australian hospitals: a population-based model. Infect Control Hosp Epidemiol. 2019;40(3):320-7.
73. Lee XJ, Stewardson A, Worth L, Graves N, Wozniak T. Attributable Length of Stay, Mortality Risk, and Costs of Bacterial Health Care–Associated Infections in Australia: A Retrospective Case-cohort Study. Clinical Infectious Diseases. 2020.
74. Cantón R, Huarte R, Morata L, Trillo-Mata JL, Muñoz R, González J, et al. Determining the burden of infectious diseases caused by carbapenem-resistant gram-negative bacteria in Spain. Enfermedades Infecciosas y Microbiología Clínica. 2020.
75. Jit M, Ng DHL, Luangasanatip N, Sandmann F, Atkins KE, Robotham JV, et al. Quantifying the economic cost of antibiotic resistance and the impact of related interventions: rapid methodological review, conceptual framework and recommendations for future studies. BMC Medicine. 2020;18(1):38.
76. World Health Organization. Impact of COVID-19 on people's livelihoods, their health and our food systems 2020 [updated 13 Oct 2020; cited 2021 4 Jan]. Available from: https://www.who.int/news/item/13-10-2020-impact-of-covid-19-onpeople's-livelihoods-their-health-and-our-food-systems.
77. John Hopkins University. COVID-19 Dashboard 2021 [updated 4 Jan 2021; cited 2021 4 Jan]. Available from: https://coronavirus.jhu.edu/map.html.
78. Monnet DL, Harbarth S. Will coronavirus disease (COVID-19) have an impact on antimicrobial resistance? Eurosurveillance. 2020;25(45):2001886.
79. Langford BJ, So M, Raybardhan S, Leung V, Westwood D, MacFadden DR, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clinical Microbiology and Infection. 2020.
80. European Centre for Disease Prevention and Control. Health Protection Surveillance Centre - EPIET 2021 [updated 7 Jan 2021. Available from: https://www.ecdc.europa.eu/en/health-protection-surveillance-centre-epiet.
81. Health Protection Surveillance Centre. Notifiable Diseases 2020 [updated 6 Mar 2020; cited 2021 19 Jan]. Available from: https://www.hpsc.ie/notifiablediseases/listofnotifiablediseases/.
82. European Centre for Disease Prevention and Control. Antimicrobial resistance (AMR) reporting protocol 2020: European Antimicrobial Resistance Surveillance Network (EARS-Net) surveillance data for 2019 2020 [updated 31 Mar 2020; cited 2021 9 Feb]. Available from: https://www.ecdc.europa.eu/en/publications-data/ears-net-reporting-protocol-2020.
83. European Committee on Antimicrobail Susceptibility Testing (EUCAST). EUCAST SOPs and Guidance documents 2021 [cited 2021 9 Feb]. Available from: https://www.eucast.org/ast_of_bacteria/guidance_documents/.
84. Stephen Murchan - HPSC [Personal Communication]. EARS-Net 2019 Data. 2021.
85. European Centre for Disease Prevention and Control. External quality assessment (EQA) of performance of laboratories participating in the European Antimicrobial Resistance Surveillance Network (EARS-Net), 2019 2020 [updated 15 Oct 2020; cited 2021 9 Feb]. Available from: https://www.ecdc.europa.eu/en/publications-data/antibiotic-resistance-external-quality-assessment-laboratories-earsnet.
86. Murray CJ, Ezzati M, Flaxman AD, Lim S, Lozano R, Michaud C, et al. GBD 2010: design, definitions, and metrics. The Lancet. 2012;380(9859):2063-6.
87. World Health Organization. Metrics: Disability-Adjusted Life Year (DALY) 2019 [cited 2021 11 Feb]. Available from: https://www.who.int/healthinfo/global_burden_disease/metrics_daly/en/.
88. Kretzschmar M, Mangen M-JJ, Pinheiro P, Jahn B, Fèvre EM, Longhi S, et al. New Methodology for Estimating the Burden of Infectious Diseases in Europe. PLOS Medicine. 2012;9(4):e1001205.
89. European Centre for Disease Prevention and Control. BCoDE toolkit [software application]. Version 2.0 Solna: European Centre for Disease Prevention and Control2020 [updated Jan 2020; cited 2021 11 Feb]. Available from: https://ecdc.europa.eu/en/toolkit-application-calculate-dalys.
90. Eckmanns T, Robert Koch Institute. Burden of Healthcare Associated Infection (BHAI)-evidence-based and comorbidity-adjusted outcome trees for estimation of burden of disease. Robert Koch Institute (RKI), 2016.

91. Cassini A, Plachouras D, Eckmanns T, Abu Sin M, Blank HP, Ducomble T, et al. Burden of Six Healthcare-Associated Infections on European Population Health: Estimating Incidence-Based Disability-Adjusted Life Years through a Population Prevalence-Based Modelling Study. PLoS Med. 2016;13(10):e1002150.
92. Haagsma JA, De Noordhout CM, Polinder S, Vos T, Havelaar AH, Cassini A, et al. Assessing disability weights based on the responses of 30,660 people from four European countries. Population health metrics. 2015;13(1):10.
93. European Centre for Disease Prevention and Control. EARS-Net: Data collection and analysis 2020 [cited 2021 10 Feb]. Available from: https://www.ecdc.europa.eu/en/about-us/networks/disease-networks-and-laboratory-networks/ears-net-data.
94. European Centre for Disease Prevention and Control. Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals - ECDC PPS validation protocol version 3.1.2 2019 [updated 10 Jan 2019; cited 2021 10 Feb]. Available from: https://www.ecdc.europa.eu/en/publications-data/point-prevalence-survey-healthcare-associated-infections-and-antimicrobial-use-4.
95. Health protection surveillance centre. Point Prevalence Survey of Hospital-Acquired Infections & Antimicrobial Use in European Acute Care Hospitals: May 2017. National Report Ireland. Dublin: 2018.
96. European Centre for Disease Prevention and Control. Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals 2011-2012. Stockholm: ECDC, 2013.
97. Colzani E, Cassini A, Lewandowski D, Mangen MJ, Plass D, McDonald SA, et al. A Software Tool for Estimation of Burden of Infectious Diseases in Europe Using Incidence-Based Disability Adjusted Life Years. PloS one. 2017;12(1):e0170662.
98. Central Statistics Office. Annual Population Estimates, 2019 2021 [updated 9 Nov 2020. Available from: https://data.cso.ie/.
99. EUnetHTA. Joint Action 2, Work Package 8. HTA Core Model ® version 3.0 2016 [Available from: www.htacoremodel.info/BrowseModel.aspx. .
100. Krahn MD, Bielecki JM, Bremner KE, de Oliveira C, Almeida N, Clement F, et al. Picturing ELSI+: a visual representation of ethical, legal, and social issues, and patient experiences in Health Technology Assessment in Canada. International journal of technology assessment in health care. 2020;36(1):40-9.
101. Healthcare Pricing Office. ICU cost per bed day [personal communication] 2021 [updated 2 Feb 2021.
102. HIQA. Guidelines for the Economic Evaluation of Health Technologies in Ireland Dublin2020 [updated Sep 2020; cited 2021 13 Feb]. Available from: https://www.hiqa.ie/reports-and-publications/health-technology-assessment/guidelines-economic-evaluation-health.
103. Healthcare Pricing Office. Hospital Inpatient Enquiry (HIPE) Dataset 2020 [
104. National Office of Clinical Audit. Irish National ICU Audit Interim Report 2019 2020 [updated 18 Dec 2020; cited 2021 13 Feb]. Available from: https://www.noca.ie/documents/irish-national-icu-audit-interim-report-2019.
105. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Medical Research Methodology. 2014;14(1):135.
106. Friedman ND, Temkin E, Carmeli Y. The negative impact of antibiotic resistance. Clinical Microbiology and Infection. 2016;22(5):416-22.
107. Eliopoulos GM, Cosgrove SE, Carmeli Y. The Impact of Antimicrobial Resistance on Health and Economic Outcomes. Clinical Infectious Diseases. 2003;36(11):1433-7.
108. World Health Organization. Global health estimates: Leading causes of DALYs, Ireland 2019 2020 [cited 2021 11 Feb]. Available from: https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/global-health-estimates-leading-causes-of-dalys.
109. Falagas ME, Kasiakou SK. Toxicity of polymyxins: a systematic review of the evidence from old and recent studies. Crit Care. 2006;10(1):R27-R.
110. European Centre for Disease Prevention and Control. Outbreak of carbapenemase-producing (NDM-1 and OXA-48) and colistin-resistant Klebsiella pneumoniae ST307, north-east Germany, 2019 2019 [updated 28 Oct 2019; cited 2021 22 Feb]. Available from:

https://www.ecdc.europa.eu/en/publications-data/outbreak-Klebsiella-pneumoniae-Germany.
111. Smith R, Coast J. The true cost of antimicrobial resistance. Bmj. 2013;346.
112. Foster S. Challenges for Health Care: the Impact of AMR on Costs of Care 2011 [Available from: https://www.paho.org/hq/dmdocuments/2011/3_Foster_DMS_2011.pdf.
113. Currie K, Melone L, Stewart S, King C, Holopainen A, Clark AM, et al. Understanding the patient experience of health care–associated infection: A qualitative systematic review. American journal of infection control. 2018;46(8):936-42.
114. King C, Grandison T, Cawthorne J, Currie K. Patient experience of hospital screening for carbapenemase-producing Enterobacteriaceae: A qualitative study. Journal of clinical nursing. 2019;28(21-22):3890-900.
115. Morel CM, Alm RA, Årdal C, Bandera A, Bruno GM, Carrara E, et al. A one health framework to estimate the cost of antimicrobial resistance. Antimicrobial Resistance & Infection Control. 2020;9(1):187.
116. Friedman C, Borg M, Allegranzi B, Brenner P, Bruce M, Callery S. The costs of healthcare associated infections. IFIC basic concepts of infection control. 2011.
117. Centers for Disease Prevention and Control. ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES, 2019 2019 [Available from: https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf.
118. World Health Organization. WHO-CHOICE 2010 [cited 2021 18 Feb]. Available from: https://www.who.int/choice/cost-effectiveness/en/.
119. World Health Organization. Global Health Estimates 2019: Disease burden by Cause, Age, Sex, by Country and by Region, 2000-2019. 2020 [updated Dec 2020; cited 2021 19 Feb]. Available from: https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates
120. Esterly JS, Griffith M, Qi C, Malczynski M, Postelnick MJ, Scheetz MH. Impact of carbapenem resistance and receipt of active antimicrobial therapy on clinical outcomes of Acinetobacter baumannii bloodstream infections. Antimicrobial agents and chemotherapy. 2011;55(10):4844-9.
121. Jamulitrat S, Arunpan P, Phainuphong P. Attributable mortality of imipenem-resistant nosocomial Acinetobacter baumannii bloodstream infection. Medical journal of the Medical Association of Thailand. 2009;92(3):413.
122. Halpern SD. ICU capacity strain and the quality and allocation of critical care. Current Opinion in Critical Care. 2011;17(6):648-57.
123. Kahn JM. The risks and rewards of expanding ICU capacity. Crit Care. 2012;16(5):156-.
124. López-Causapé C, Rojo-Molinero E, Macià MD, Oliver A. The problems of antibiotic resistance in cystic fibrosis and solutions. Expert review of respiratory medicine. 2015;9(1):73-88.
125. Lapointe-Shaw L, Voruganti T, Kohler P, Thein H-H, Sander B, McGeer A. Cost-effectiveness analysis of universal screening for carbapenemase-producing Enterobacteriaceae in hospital inpatients. European Journal of Clinical Microbiology & Infectious Diseases. 2017;36(6):1047-55.
126. Berry C, Davies K, Woodford N, Wilcox M, Chilton C. Survey of screening methods, rates and policies for the detection of carbapenemase-producing Enterobacteriaceae in English hospitals. Journal of Hospital Infection. 2019;101(2):158-62.
127. Health Service Executive. National Service Plan 2019 2018 [updated 20 Dec 2018; cited 2021 21 Feb]. Available from: https://www.hse.ie/eng/services/news/media/pressrel/hse-publishes-national-service-plan-2019.html.
128. OECD. Health at a Glance 2019: Hospital beds and discharge rates 2019 [cited 2021 11 Mar]. Available from: https://www.oecd-ilibrary.org/sites/0d67e02a-en/index.html?itemId=/content/component/0d67e02a-en.
129. Majumder A, Gupta AK, Ghosal PS, Varma M. A review on hospital wastewater treatment: A special emphasis on occurrence and removal of pharmaceutically active compounds, resistant microorganisms, and SARS-CoV-2. J Environ Chem Eng. 2021;9(2):104812-.
130. Grasselli G, Pesenti A, Cecconi M. Critical Care Utilization for the COVID-19 Outbreak in Lombardy, Italy: Early Experience and Forecast During an Emergency Response. JAMA. 2020;323(16):1545-6.
131. Bottiroli M, Calini A, Pinciroli R, Mueller A, Siragusa A, Anelli C, et al. The repurposed use of

anesthesia machines to ventilate critically ill patients with Coronavirus Disease 2019 (COVID-19). Research square. 2021.
132. Kennelly B, O'Callaghan M, Coughlan D, Cullinan J, Doherty E, Glynn L, et al. The COVID-19 pandemic in Ireland: An overview of the health service and economic policy response. Health Policy Technol. 2020;9(4):419-29.
133. Walsh B, Keegan C, Brick A, Lyons S. How is Ireland's healthcare system coping with coronavirus? 2020 [updated 21 Oct 2020; cited 2021 22 Feb]. Available from: https://www.economicsobservatory.com/how-irelands-healthcare-system-coping-coronavirus.
134. OECD. Intensive care beds capacity 2020 [updated 20 Apr 2020; cited 2021 11 Mar]. Available from: https://www.oecd.org/coronavirus/en/data-insights/intensive-care-beds-capacity.
135. Phua J, Weng L, Ling L, Egi M, Lim C-M, Divatia JV, et al. Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations. The Lancet Respiratory Medicine. 2020;8(5):506-17.
136. TheJournal.ie. What's the total ICU bed capacity for the latest Covid-19 surge? 2021 [updated 6 Jan 2021; cited 2021 25 Feb]. Available from: https://www.thejournal.ie/icu-capacity-5316578-Jan2021/.
137. Tyrrell CSB, Mytton OT, Gentry SV, Thomas-Meyer M, Allen JLY, Narula AA, et al. Managing intensive care admissions when there are not enough beds during the COVID-19 pandemic: a systematic review. Thorax. 2021;76(3):302-12.
138. Wong DJN, Harris SK, Moonesinghe SR, Moonesinghe SR, Wong DJN, Harris SK, et al. Cancelled operations: a 7-day cohort study of planned adult inpatient surgery in 245 UK National Health Service hospitals. British Journal of Anaesthesia. 2018;121(4):730-8.
139. Leekha S, Terrell CL, Edson RS. General principles of antimicrobial therapy. Mayo Clin Proc. 2011;86(2):156-67.
140. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clinical Infectious Diseases. 2011;52(5):e103-e20.
141. Yang F, Yan J. Antibiotic Resistance and Treatment Options for Multidrug-Resistant Gonorrhea. Infectious Microbes & Diseases. 2020;2(2):67-76.
142. World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis: World Health Organization; 2014.
143. World Health Organization. Tackling Antimicrobial Resistance (AMR) Together. Working Paper 5.0: Enhancing the focus on gender and equity 2018 [cited 2021 22 Feb]. Available from: https://apps.who.int/iris/bitstream/handle/10665/336977/WHO-WSI-AMR-2018.3-eng.pdf.
144. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet (London, England). 2012;380(9836):37-43.
145. Alividza V, Mariano V, Ahmad R, Charani E, Rawson TM, Holmes AH, et al. Investigating the impact of poverty on colonization and infection with drug-resistant organisms in humans: a systematic review. Infectious Diseases of Poverty. 2018;7(1):76.
146. Nourazari S, Davis SR, Granovsky R, Austin R, Straff DJ, Joseph JW, et al. Decreased hospital admissions through emergency departments during the COVID-19 pandemic. The American Journal of Emergency Medicine. 2021;42:203-10.
147. Smith R, Coast J. The economic burden of antimicrobial resistance: why it is more serious than current studies suggest. 2012.
148. Taylor J, Hafner M, Yerushalmi E, Smith R, Bellasio J, Vardavas R, et al. Estimating the economic costs of antimicrobial resistance. Model and Results (RAND Corporation, Cambridge, UK). 2014.
149. KPMG. The global economic impact of anti-microbial resistance 2014 [updated 11 Dec 2014. Available from: https://home.kpmg/content/dam/kpmg/pdf/2014/12/amr-report-final.pdf.
150. Jonas OB, Irwin A, Berthe FCJ, Le Gall FG, Marquez PV. Drug-resistant infections: A threat to our economic future World Bank Group: Washington DC.2017 [updated Mar 2017; cited 2021 22 Feb].
151. Blanco N, O'Hara LM, Harris AD. Transmission pathways of multidrug-resistant organisms in

the hospital setting: a scoping review. Infection control and hospital epidemiology. 2019;40(4):447-56.

152. Prestinaci F, Pezzotti P, Pantosti A. Antimicrobial resistance: a global multifaceted phenomenon. Pathog Glob Health. 2015;109(7):309-18.
153. Geddes-McAlister J, Shapiro RS. New pathogens, new tricks: emerging, drug-resistant fungal pathogens and future prospects for antifungal therapeutics. Annals of the New York Academy of Sciences. 2019;1435(1):57-78.
154. World Health Organization. Emerging antimicrobial resistance reporting framework 2018 [updated Aug 2018; cited 2021 22 Feb]. Available from: https://apps.who.int/iris/bitstream/handle/10665/274956/9789241514590-eng.pdf.
155. World Health Organization. Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report 2020 [updated 26 May 2020; cited 2021 23 Feb]. Available from: https://www.who.int/glass/resources/publications/early-implementation-report-2020/en/.
156. Slimings C, Riley TV. Antibiotics and healthcare facility-associated Clostridioides difficile infection: systematic review and meta-analysis 2020 update. Journal of Antimicrobial Chemotherapy. 2021.

Appendices

Appendix 1 — Search terms for electronic databases

PubMed search:

(("Health Care Costs"[Mesh]) OR "Cost of Illness"[Mesh] OR "Hospital Costs"[Mesh]) AND "Drug Resistance, Bacterial"[Mesh])) restricted to 2009 onwards.

Appendix 2 — Grey literature sources

The following grey literature sources were searched:

- Centre for Health Economics and Policy Analysis (CHEPA)
- Cost Effectiveness Analysis Registry
- HTAi vortal
- Health Service Executive (HSE)
- Health Information and Quality Authority (HIQA)
- Health Research Board (HRB) Ireland
- Health Protection Surveillance Centre (HPSC) Ireland
- Institute of Health Economics (Alberta Canada)
- Lenus
- National Coordinating Centre for Health Technology Assessment (NCCHTA)
- National Institute for Health and Clinical Excellence (NICE)
- NHS Evidence database (UK)
- OpenGrey
- The World Health Organization (WHO)
- Public Health England
- Review on Antimicrobial Resistance (UK)
- Organisation for Economic Co-operation and Development (OECD)
- European Centre for Disease Prevention and Control (ECDC).
- Google and Google Scholar (first five pages)
- BMC Antimicrobial Resistance & Infection Control Journal.

Only studies published in the last 10 years (2009 onwards), and in the English language were included.

Appendix 3 - Tables of characteristics and outcomes

Table A.1: Table of characteristics of included outbreak costing studies (n=10)

First author (year) Country	Study design (n) Year of data collection	Sub-population	Perspective	Methodology (Top-down vs. Bottom-up)	Antimicrobial resistance (infection)	Comparator	Cost valuation year (currency)	Costs included	Author-reported economic costs
Ayraud-Thevenot (2012) **France**	Retrospective case series (n=27)** 2006	Surgical ICU patients	Healthcare system perspective - hospital	Costing (Top down and bottom-up)	MDRAB (not reported)	None	2009 (€)	Direct costs: Rectal swabs, surface swabs, hygiene measures, bed closures, ICU closures Indirect costs: None	**Total costs** 2006 outbreak: **€539,325**. 2009 outbreak: **€202,214** Direct costs 2006 outbreak: €23,485 2009 outbreak: €6441 Bed Closures: 2006 outbreak: 515,840, 2009 outbreak: 195,773
Daroukh (2014) **France**	Retrospective case series (n=16)** 2012-2013	None reported	Healthcare system perspective –hospital	Costing (bottom-up)	CPE (peritonitis, catheter infection, obstructive pyelonephritis)	Previous year with no outbreak	2012-2013 (€)	Direct costs: Activity of wards during periods, overtime hours of staff and screening tests Indirect costs: None	Loss of activity due to ward closures = €547,303. Costs due to : extra screening = €30,931 overtime paid to staff = €63,870. **Total costs = €642,104**
Dik (2016) **The Netherlands**	Retrospective case series (n=90) 2012-2014	None reported	Healthcare system perspective –hospital	Costing (Top down and bottom-up)	MRSA, ESBL, VRE, Pantoea spp. Norovirus, S. marcescens (not reported)	None	2015 (€)	Direct costs: Microbiological diagnostics/ surveillance costs; additional cleaning costs; additional personnel; costs made for contact or strict isolation of patients and other costs (e.g. purchase	**MRSA outbreak €657.08** (cost per patient per outbreak day **ESBL outbreak** #1 **€1,368.92** (cost per patient per outbreak day; ESBL outbreak #2 €980.51 (per patient per outbreak day, **VRE outbreak €197.26** (per patient per outbreak day) **Pantoea spp.outbreak**

First author (year) Country	Study design (n) Year of data collection	Sub-population	Perspective	Methodology (Top-down vs. Bottom-up)	Antimicrobial resistance (infection)	Comparator	Cost valuation year (currency)	Costs included	Author-reported economic costs
								of extra materials, possible prolonged length of stay, extra medication) Indirect costs: Missed revenue due to closed beds	**€88.1**1 per patient per outbreak day, **Norovirus outbreak €10.40** per patient per outbreak day, **S. marcescens outbreak €518.54** per patient per outbreak day.
Escaut (2013) **France**	Retrospective case series (n=13)** 2008	Hepato-biliary patients	Healthcare system perspective -hospital	Costing (Top down and bottom-up)	VRE (not reported)	None	2008 (€)	Direct costs: Cost of staffing, disposable materials, hygiene procedures, and surveillance cultures Indirect costs: Loss of income due to reduced availability of isolation rooms	**Total cost €171,439**. The direct cost of the outbreak (2008 Euros) due to infection control measures was €60,524 and the loss of income from reduced activity of isolation beds was €110,915
Gagnaire (2017) **France**	Retrospective case series (n=5)** 2012-2013	Neuro-surgery patients	Healthcare system perspective -hospital	Costing (Top down and bottom-up)	CP-AB (not reported)	i) None ii) Hypothetical dedicated unit	2012 (USD)	Direct costs: Staff costs, environmental sampling costs, screening costs, carbapenemase identification and routine examination costs, drug costs, environmental disinfection Indirect costs: Loss of ward activity, DRG-related loss of income	**Observed outbreak cost: $474,474**. Simulated dedicated unit estimate: $190,265

First author (year) Country	Study design (n) Year of data collection	Sub-population	Perspective	Methodology (Top-down vs. Bottom-up)	Antimicrobial resistance (infection)	Comparator	Cost valuation year (currency)	Costs included	Author-reported economic costs
Jiang (2015) **US**	Retrospective case series (n=9) 2011	General surgery ICU and trauma ICU patients	Healthcare system perspective -hospital	Costing (bottom-up)	MDRAB (not reported)	Pre-outbreak period	2011 (USD)	Direct costs: Nursing costs, respiratory therapy, deep cleaning labour and supply, transport, supplies, administration time, environmental testing Indirect costs: None	**Overall excess cost $371,079**
Mollers (2017) **The Netherlands**	Retrospective case series (n=29) 2015-2016	None reported	Healthcare system perspective -hospital	Costing (Top down and bottom-up)	CPE - (NDM)-producing Klebsiella pneumoniae (not reported)	None	2015 (USD and €)	Direct costs: Diagnostics, ward-related costs, and other outbreak control costs (infection prevention experts, patients in isolation, staff meetings, communication, costs for mailings) Indirect costs: None	**Total outbreak costs $804,263 or €653,801**, corresponding to a cost of $27,700 per patient.
Morii (2020) **Japan**	Cross-sectional survey (n=104 outbreaks, 23 provided cost data. Unclear how many patients involved in the	None reported	Healthcare system perspective –hospital	Costing (Top down and bottom-up)	VRE; CRE; MRSA multidrug-resistant Pseudomonas aeruginosa; ESBL-producing Enterobacteriaceae, multidrug	None	2015 (USD)	Direct costs: Costs for containment (including surveillance, screening, cleaning and decontamination, disposal and repurchase)	The maximum observed productivity loss was 4.62 million USD. The minimum observed productivity loss resulted in an increase of 587,000 USD. Across 23 included studies, the **median estimated productivity loss was 674,000 USD per hospital**.

First author (year) Country	Study design (n) Year of data collection	Sub-population	Perspective	Methodology (Top-down vs. Bottom-up)	Antimicrobial resistance (infection)	Comparator	Cost valuation year (currency)	Costs included	Author-reported economic costs
	outbreaks) 2006-2016				resistant Acinetobacter; Clostridioides difficile and multidrug-resistant Corynebacterium striatum (unclear)			Indirect costs: productivity loss	The maximum and minimum observed total cost for containment was 678,000 USD and 1,110 USD respectively. Across 23 included studies the median **estimated containment cost was 43,900 USD per hospital**.
Otter (2017) **UK**	Retrospective case series (n=40) 2014-2015	None reported	Healthcare system perspective –hospital	Costing (Top down and bottom-up)	CPE - (NDM)-producing Klebsiella pneumoniae (not reported)	None	2016 (€)	Direct costs: Additional bed-days for infected patients, anti-infective costs, lab/screening costs, IPC team time, staff time outside of IPC, isolation, ward based monitors, environment/ equipment Indirect costs: Elective surgical missed revenue, closed beds	The **outbreak cost a total of €1,133,000** (range €943,000 - €1,424,000) over 10 months, comprising €312,000 of actual expenditure and €822,000 (range €631,000 - €1,112,000) in opportunity cost. An additional €153,000 was spent on Estates renovations prompted by the outbreak.
Public Health Sweden (2018)* **Sweden**	Cross-sectional survey	None reported	healthcare system	Costing (Top down and bottom-up)	MRSA, VRE (not reported)	None	2016 (SEK)	Direct costs: 1) Cleaning, laundry, 2) Screening, sampling (patients, staff, environment), 3)staff costs, 4) longer care period, 5) reduction of care	An **average cost of approximately SEK 73,000** (SEK 14,000-137,000) per case in an outbreak was estimated. According to estimates, approximately 30–40 outbreaks per year occurred between 2013–2015, with 8–

First author (year) Country	Study design (n) Year of data collection	Sub-population	Perspective	Methodology (Top-down vs. Bottom-up)	Antimicrobial resistance (infection)	Comparator	Cost valuation year (currency)	Costs included	Author-reported economic costs
	(n=106 cases, 21 infection control/care hygiene units surveyed) 2013-2015							places, 6)administration education, information <u>Indirect costs:</u> Lost production	14 cases per outbreak on average. **Outbreaks in Sweden are estimated to cost SEK 29 million per year**, based on average cost per case.

Key: AMR – antimicrobial resistance; BGI - bacterial gastro-intestinal infection; BSI – bloodstream infection; CDI – *Clostridioides/Clostridium difficile* infection; CP-AB - Carbapenemase-producing *Acinetobacter baumannii*; CPE - carbapenemase-producing Enterobacteriales (Enterobacteriaceae); CRE - carbapenem-resistant *Enterobacteriaceae;* CRAB - carbapenem-resistant *Acinetobacter baumannii*; DRG - Diagnosis-related Group; ESBL - extended-spectrum beta-lactamases; GNB – gram negative bacilli; IAI - intra-abdominal infection; ICU – intensive care unit; IPC – infection prevention and control; MDRAB – multidrug resistant Acinetobacter Baumannii; MRSA – meticillin-resistant Staphylococcus aureus; MSI - musculoskeletal infection; NDM - New Delhi metallo-beta-lactamase 1; PNSP - penicillin-non-susceptible pneumococci; (U)/(L)/RTI – (upper)/(lower) respiratory tract infection; SEK - Swedish Krona; STI – sexually transmitted infection; SSI – surgical site infection; SSTI – skin and soft tissue infection; TB – tuberculosis; UK – United Kingdom; US – United States; USD – United States Dollars; UTI – urinary tract infection; VRE - vancomycin-resistant enterococci; 3GC - third-generation cephalosporin; 3GCRE - third-generation cephalosporin-resistant Enterobacteriaceae.

*Public Health Sweden 2018 presented both population & modelling and outbreak data separately, this report has therefore been included in both sets of tables.

Table A.2: Table of characteristics of included population & modelling costing studies (n=18)

First author (year) Country Sub population	Study design (n) Year of data collection	Perspective	Methodology (Top-down vs. Bottom-up) Epidemiological approach	Antimicrobial resistance (infection)	Comparator	Cost valuation year (currency)	Reported costs	Author reported economic costs
Bartsch (2017) **US** None	Economic model (N/A) 2012-2013	Hospital, third-party payer, and societal perspectives	Decision-tree analysis (Top-down and bottom-up) Incidence-based	CRE (Bacteraemia, pneumonia, complicated intra-abdominal infection, complicated UTI)	None	2016 (USD)	Direct Costs: ICU bed days, General ward bed days, Hospitalisation costs (for bacteraemia/ intra-abdominal infection/pneumonia/VAP/UTI), Drug treatments per day, PICC line insertion, urine analysis, urine culture, abdom CT, Bronchoscopy, wound culture, CXR, sputum culture, blood culture, nurse hourly wage Indirect costs: Productivity losses	Depending on the infection type, the **median cost of a single CRE infection can range from $22,484 to $66,031 for hospitals.** An infection incidence of 2.93 per 100,000 population in the USA (9418 infections) would cost hospitals $275 million (95% CR $217-334 million), with a 25% attributable mortality. An incidence of 15 per 100,000 (48,213 infections) would cost hospitals $1.4 billion (95% CR $1.1-1.7 billion).
Canton (2020) **Spain** Nosocomial, excluding community-acquired infections	Cross-sectional study (n=12,090) 2017	Societal perspective, but direct costs also reported	Burden of disease (Top down) Prevalence-based	Carbapenem resistant Klebsiella pneumoniae, Pseudomonas aeruginosa and Acinetobacter baumannii (Not specified)	None	2017 (€)	Direct costs: Hospitalisation costs Indirect costs: Productivity losses	Direct costs total €389,843,161. (breakdown A. baumannii €71,330,596 (18% of total); K. pneumoniae €15,007,790 (4% of total); P. aeruginosa €303,504,775 (78% of total)). **Total cost overall €471,591,266** - consisting of €81,748104 in indirect costs and €389,843,161 in direct costs.

First author (year) Country Sub population	Study design (n) Year of data collection	Perspective	Methodology (Top-down vs. Bottom-up) Epidemiological approach	Antimicrobial resistance (infection)	Comparator	Cost valuation year (currency)	Reported costs	Author reported economic costs
CCA (2019) **Canada** None	Evidence synthesis (N/A) 2018	Healthcare system and societal perspectives	Evidence synthesis and expert opinion (Top down) Prevalence-based	MRSA, ESBL bacteria, VRE, C. dif (BGI, BSI, CDI, IAI, MSI, pneumonia, STI, SSTI, TB, UTI)	No infection	2018 (CAD)	Direct Costs: Hospital costs (no details on what these comprised) Indirect costs: Gross Domestic Product Loss	**$18000 CAD per patient** = average cost of a resistant bacterial infection in the hospital in 2018. **$1.4 Billion CAD** = **cost to the Canadian healthcare system in 2018**
de Kraker (2011) 31 European countries None	Cross-sectional study (n=42,894) 2007	Healthcare system perspective	Burden of disease (Top down) Prevalence-based	MRSA and G3CREC (BSI)	Susceptible pathogen	2007 (€ and international dollars)	Direct Costs: Bed days Indirect costs: None	Total costs: **MRSA: €44.0 million** (95% CI €23.8 million-67.8 million) (63.1 million international dollars), **G3REC: €18.1 million** (95% CI €7.5 million-32.2 million) (29.7 million international dollars)
ECDC (2009) **30 EU/EEA countries** None	Cross-sectional study (NR) 2007	Healthcare system and societal perspectives	Cost-of-illness (Top-down and bottom-up) Prevalence-based	MRSA, vancomycin-resistant Enterococcus faecium, Penicillin-resistant Streptococcus pneumoniae, third-generation cephalosporin-resistant Escherichia coli and Klebsiella pneumoniae and carbapenem-resistant Pseudomonas aeruginosa (BSI, LRTI, SSTI and UTI)	Susceptible pathogens	2007 (€)	Direct Costs: Bed days, outpatient (GP) consultations Indirect costs: Productivity losses	**Total overall costs €1.534 billion** (including €927.8 million for in-hospital bed days, €10 million for extra out-patient visits and €150.4 million for productivity losses due to absence from work and €445.9 million for productivity losses due to mortality)

First author (year) Country Sub population	Study design (n) Year of data collection	Perspective	Methodology (Top-down vs. Bottom-up) Epidemiological approach	Antimicrobial resistance (infection)	Comparator	Cost valuation year (currency)	Reported costs	Author reported economic costs
Johnston (2019) **US** None	Cross-sectional study (n= 6,385,258) 2014	Healthcare system perspective - hospital	Regression analysis (Econometric) Prevalence-based	MRSA, C. diff, other non-specified MDROs (Meningitis, Encephalitis, Cellulitis, Endocarditis, Pneumonia, Pyelonephritis, Septic arthritis, Osteomyelitis, Bacteraemia, Sepsis/severe sepsis, SSI, UTI, Complicated IAI, Intestinal infections due to other organisms/enteritis, Bacterial infection in conditions classified elsewhere and of unspecified site)	Patients with infection without any MDRO	2017 (USD)	Direct Costs: Cost-to-charge estimates per hospital stay Indirect costs: None	The **national cost of infections associated with MDROs is at least $2.39 billion** (95% CI: $2.25-$2.52 billion) and as high as $3.38 billion (95% CI: $3.13-$3.62 billion) if undercoded infections are accounted for. MRSA, C. difficile, another MDRO, and the presence of more than one MDRO are associated with $1718 (95% CI: $1609-$1826), $4617 (95% CI: $4407-$4827), $2302 (95% CI: $2044-$2560), and $3570 (95% CI: $3019-$4122) in additional costs per hospital stay, respectively The mean cost per hospital stay for stays with any diagnosis of bacterial infection is $19 037.
Klein (2019) **US** None	Cross-sectional study (n=616,070) 2010-2014	Healthcare system perspective - hospital	Matching (Econometric) Prevalence-based	MRSA (Septicaemia, Pneumonia and unspecified infection)	MSSA	2014 (USD)	Direct Costs: Cost-to-charge estimates per hospital stay Indirect costs: None	Propensity score–adjusted costs for MSSA pneumonia- and other S.aureus–related hospitalisations were 5.5% ($40,725 vs $38,561; P = .045) and 5.2% ($15,578 vs $14,792; P < .001) higher than for MRSA related hospitalisations, respectively. **MRSA–related septicaemia hospitalisation costs were not significantly different from MRSA-related hospitalisation costs** ($34 526 vs $34 175; P = .69). However,

First author (year) Country Sub population	Study design (n) Year of data collection	Perspective	Methodology (Top-down vs. Bottom-up) Epidemiological approach	Antimicrobial resistance (infection)	Comparator	Cost valuation year (currency)	Reported costs	Author reported economic costs
								among pneumonia-related hospitalisations, patients with MRSA infections had a higher rate of mortality than patients with MSSA infections (P < .001)
Lee (2020) **Australia** None	Retrospective case-cohort study (n=96,025) 2012-2016	Healthcare system	Matching, multistate survival model (Econometric) Prevalence-based	1. 3GC-resistant K. pneumoniae; 2. 3GC-sensitive K. pneumoniae; 3. 3GC-resistant E. coli; 4. 3GC-sensitive E. coli; 5. Ceftazidime-resistant P. aeruginosa; 6. Ceftazidime-sensitive P. aeruginosa; 7. Meticillin-resistant S. aureus (MRSA); 8. Meticillin-sensitive S. aureus (MSSA); 9. Vancomycin-resistant E. faecium (VRE); 10. Vancomycin-sensitive E. faecium (VSE) (BSI, UTI and RTI)	i) Matched no infection group. ii) Susceptible infection group.	2020 (AUD)	Direct costs: Length of stay and value of a bed day. Calculated as an opportunity cost (defined as "willingness to pay" to release a bed day from some infection-reducing intervention, 250.40 AUD) and a accounting cost (obtained by dividing the total annual hospital budget by the number of bed days supplied during the same period, 2721.8 AUS $ in 2020 prices) Indirect costs: None	Data are the cost of resistance calculated as the difference in cost between resistant and sensitive infection, represented as opportunity (*OC*) and accounting costs (*AC*) associated with healthcare-associated infections in Queensland in AUD (SD) (2012-2016). BSI: S. aureus *OC*: 503.2 (172.9); *AC*: 5422.9 (1744.2) E. faecium *OC:* −442.3 (90.8); *AC*: −4805.0 (916.7) E. coli *OC*: 2.7 (62.7); *AC*: 51.8 (634.2) K. pneumoniae *OC* 753.5 (147.9). *AC*: 8206.1 (1516.8) P. aeruginosa *OC*: 342.6 (123.1). *AC*: 3718.9 (1262.2) UTI: S. aureus *OC*: 180.5 (59.6). *AC:* 1953.1 (608.5) E. faecium *OC*: 92.6 (36). *AC*: 1010.0 (370.6) E. coli *OC*: 83.2 (27.3). *AC:* 905.5 (283.5) K. pneumoniae *OC*: 381.8 (55.7). *AC*: 4160.3 (588.9) P. aeruginosa *OC:* 209.5 (44). *AC*: 2273.3 (457.8) RTI: P. aeruginosa *OC:* −86.4 (71.6).

First author (year) Country Sub population	Study design (n) Year of data collection	Perspective	Methodology (Top-down vs. Bottom-up) Epidemiological approach	Antimicrobial resistance (infection)	Comparator	Cost valuation year (currency)	Reported costs	Author reported economic costs
								AC: −946 (734.2)
Lemos (2013) **Colombia** ICU patients	Prospective cohort study (n=165) 2006-2010	Third party payer perspective - hospital	Regression analysis (Econometric) Prevalence-based	CRAB (Pneumonia, bacteraemia, central venous catheter-associated infection, surgical infection, UTI, soft tissue, intra-abdominal infections)	Susceptible pathogen	2011 (USD)	Direct Costs: Hospital costs (days of stay in the ICU, fees for health professionals, surgical procedures, laboratory tests, microbiological cultures and radiological examinations) and antimicrobial therapy and other drugs Indirect costs: None	**The average total cost of hospitalisation among patients with CRAB was significantly higher than that among patients with CSAB** in both the univariate and multivariate analyses (adjusted US$ **11,359 versus US$ 7049**; p <0.01; Table 4). Carbapenem resistance was associated with an additional treatment cost of US$ 4309 (95% CI US$ 2819–5645; p <0.01) after adjusting for age, gender, APACHE II score and site of infection. Patients with CRAB had significantly higher costs for hospital-related cost and for cost of antimicrobial drugs than patients with CSAB (both p <0.01 and p <0.01).
Naylor (2019) **UK** None	Retrospective cohort study (n=8,933,326) 2011-2012	Healthcare system perspective – hospital	Multistate modelling (Top down) Prevalence-based	Resistant E. Coli (BSI)	i) Not infected with E. Coli ii) susceptible pathogen	2012 (£)	Direct Costs: Bed days Indirect costs: None	Cost per spell (per in-patient) with E. coli bacteraemia = £1,020 (95% CI; £970 –£1,070). Utilising this cost per spell and number of spells, **the estimated annual cost burden to hospitals due to E. coli bacteraemia in 2011/12 was £14,346,400.** Adjusting only for time dependency bias, excess annual costs associated with third generation cephalosporin resistance and piperacillin/ tazobactam (comparative to if these had been susceptible infections) were £366,600

First author (year) Country Sub population	Study design (n) Year of data collection	Perspective	Methodology (Top-down vs. Bottom-up) Epidemiological approach	Antimicrobial resistance (infection)	Comparator	Cost valuation year (currency)	Reported costs	Author reported economic costs
								(95% CI; £194,927 –£550,000) and £275,400 (95% CI; £105,200 - £436,600) respectively. That is to say, **if all third generation cephalosporin resistant infections had been susceptible it was estimated that £366,600 would not have been spent on those infections** (based on reduced LoS). Third-generation cephalosporin resistance associated with excess costs per infection of £420 (95% CI: 220–630)
Nelson (2016) **US** None	Economic modelling study (N/A) 2005-2009	Hospital and third-party payer perspectives	Multistate modelling and matching (Top down) Incidence-based	MDRAB (not reported)	No infection	2014 (USD)	Direct Costs: Bed day Indirect costs: None	This study generated costs per HAI using 3 methods: (1) overall cost estimates, (2) multiplying LOS estimates by a cost per inpatient-day ($4,350) from the payer perspective, and (3) multiplying LOS estimates by a cost per inpatient-day from the hospital ($2,030) perspective. **The cost per infection were $129,917 (method 1), $72,025 (method 2), and $33,510 (method 3).** Adjusting for the timing of infection, the cost per infection were $68,359 (method 1), $37,916 (method 2), and $17,646 (method 3). Using a multistate mode, the cost per infection were $38,423 (method 1), $21,294 (method 2), and $9,906 (method 3)

First author (year) Country Sub population	Study design (n) Year of data collection	Perspective	Methodology (Top-down vs. Bottom-up) Epidemiological approach	Antimicrobial resistance (infection)	Comparator	Cost valuation year (currency)	Reported costs	Author reported economic costs
Nguyen (2019) **US** Older patients (≥65 years)	Cross-sectional study (n=546,305) 2009-2016	Healthcare system perspective – hospital	Regression analysis (Econometric) Prevalence-based	MRSA, beta-lactam resistance, multidrug-resistance, quinolone resistance and other unspecified AMR (UTI)	UTI patients without AMR	2016 (USD)	Direct Costs: Cost-to-charge estimates per hospital stay Indirect costs: None	Unadjusted costs associated with hospitalisation with AMR were 2730 USD (95%CI, 2596–2864) higher than non-AMR group (p<0.001). **In the multivariable regression, admissions with AMR, on average, consumed 1259 USD (95%:1178–1340) more than those without AMR**, though distinct patterns were observed in different types of AMR.
OECD (2018) **33 OECD and EU/EEA countries** None	Economic modelling study (N/A) 2015	Healthcare system perspective – hospital	Micro-simulation modelling study (Top-down) Incidence-based	Resistance to†: Acinetobacter spp., S. pneumoniae, S. aureus, E. coli, K. pneumoniae, P. aeruginosa, E faecalis and E faecium (BSI, RTI, UTI, surgical site and other infections)	Susceptible pathogens	2017 (USD PPP)	Direct Costs: Length of stay Indirect costs: None	**AMR cost the health systems of the countries included in the analysis around USD purchasing parity (PPP) 3.5 billion per year**. For EU/EEA countries this amounts to USD PPP 1.5 billion per year which means that in less than 10 years, the impact of AMR on healthcare expenditure has increased by 60%. 2015-2050 - AMR will have cost the health systems of EU/EEA countries a total of USD PPP 60 billion, while USA, Canada and Australia, this amount will reach a combined total of approx USD PPP 74 billion. In absence of antimicrobial treatments, cost to different health systems a total of USD PPP 16.3 billion annually.

First author (year) Country Sub population	Study design (n) Year of data collection	Perspective	Methodology (Top-down vs. Bottom-up) Epidemiological approach	Antimicrobial resistance (infection)	Comparator	Cost valuation year (currency)	Reported costs	Author reported economic costs
Public Health Sweden (2018)* **Sweden** None	Economic model (N/A) 2012-2016	Societal and healthcare system	Micro-simulation modelling study (Top down) Incidence - based	ESBL, MRSA, PNSP, VRE (not reported)	Susceptible pathogen	2016 (SEK)	Direct Costs: Inpatient care days, outpatient care visits, primary care visits, contact tracing Indirect costs: Productivity losses	**Overall cost for Swedish society of at approximately SEK 4.3 billion** up to 2030 (which includes 4 billion of healthcare costs) and SEK 15.8 billion by 2050 (which includes 14.9 billion of healthcare costs). The cost of the final year 2030 was roughly SEK 400 million and for 2050 SEK 600 million.
Resch (2009) **Germany** None	Retrospective case-control study (n=313,943) 2004	Healthcare system perspective – hospital	Matching (Econometric) Prevalence-based	MRSA (not reported)	Non-MRSA (with or without infection)	2004 (€)	Direct Costs: Length of stay, mechanical ventilation Indirect costs: None	The **total burden for German hospitals can be estimated at around € 761.5 million annually**. Incremental cost per MRSA case € 8,198
Stewardson (2016) **6 European countries** None	Retrospective cohort study (n=606,649) 2010-2011	Healthcare system perspective – hospital	Multistate modelling (Top down) Prevalence-based	MRSA, 3GCRE (BSI)	Susceptible pathogens	2011-2012 (€)	Direct Costs: Length of stay Indirect costs: None	Estimated cost per infection EUR (95% CrI): MSSA BSI: economic cost 760 (190–3,000), Accounting cost 9,500 (5,800-16,000). MRSA BSI: economic cost 890 (220-3,600), accounting cost (11,000 (6,600-19,000). Meticillin resistance: economic costing 120 (-60-740), accounting cost 1,600 (-700 to 5000). 3GCSE BSI: economic cost: 320 (80-1,300), accounting cost 4,000 (2,400-6,700). 3GCRE BSI: economic cost 560 (140-2,300), accounting cost 7,300 (4,300-12,000). 3GC resistance: economic cost 250 (60-1,100),

First author (year) Country Sub population	Study design (n) Year of data collection	Perspective	Methodology (Top-down vs. Bottom-up) Epidemiological approach	Antimicrobial resistance (infection)	Comparator	Cost valuation year (currency)	Reported costs	Author reported economic costs
								accounting cost 3,200 (1,600-6,000). Estimated cost per hospital year EUR 1,000 (95% CrI): MSSA BSI: economic cost 77 (19-300), accounting cost 970 (590-1,600). MRSA BSI: economic cost 17(4.1-67), accounting cost 210 (130-360). 3GCSE BSI: economic cost 77 (19-300), accounting cost 970 (590-1,600). 3GCRE BSI: economic cost 24 (5-94), accounting cost 300 (180-510).
Touat (2019) **France** None	Retrospective case-control study (n=318,234) 2015	Public health insurance perspective	Matching (Econometric) Prevalence-based	Resistance to: E. coli, Klebsiella, other Enter-obacteriaceae, S. aureus, other Staphylococcus, Pneumococcus, Enterococcus, other Streptococcus, GNB (urinary and genital tract, devices and prosthesis-related infection, SSTI, LRTI, bacteraemia and sepsis (alone), gastrointestinal and abdominal, bone and joint, during pregnancy, heart and mediastinum, infection in	Susceptible pathogens	2015 (€)	Direct Costs: Medical procedures, nursing care, administration, routine drug consumption, and room service. Cost from expenses of innovative drugs for the National Health Insurance Funds and expenditure from transfer in ICU were added to DRG Indirect costs: None	**For 2015 AMR overall cost reached EUR 109.3 million in France with a mean of EUR 1103 per stay**; extrapolation to the entire database shows that the overall cost could potentially reach EUR 287.1 million if all cases would be identified. The mean excess length of hospital stay attributable to AMR was estimated at 1.6 days

First author (year) Country Sub population	Study design (n) Year of data collection	Perspective	Methodology (Top-down vs. Bottom-up) Epidemiological approach	Antimicrobial resistance (infection)	Comparator	Cost valuation year (currency)	Reported costs	Author reported economic costs
				newborn, ear, nose and throat, eye, and nervous system)				
Wozniak (2019) Australia None	Economic model (N/A) 2014	Healthcare system perspective – hospital	Simulation model (Top-down and bottom-up) Prevalence-based	Ceftriaxone resistant E. coli; ceftriaxone-resistant K. pneumonia (KP); ceftazidime-resistant P. aeruginosa (PA); vancomycin-resistant E. faecium (VRE); and MRSA (BSI, UTI and RTI)	Susceptible pathogens	2014 (AUD)	Direct Costs: Length of stay, treatment costs Indirect costs: None	For the five AMR pathogens included in the analysis, Australian hospitals spent an estimated additional AUD $16.8 million per year. Ceftriaxone-resistant E.coli BSI total cost $5.8 million (95% uncertainty interval, $2.2–$11.2 million) per year. Ceftriaxone-resistant KP BSI $1,351,360 (358,717–3,158,370) per year. Ceftazidime-resistant PA BSI $108,581 (48,551–202,756) per year. Ceftazidime-resistant PA RTI $1,296,324 (456,198–2,577,397) per year. VRE BSI $1,404,064 (415,766–3,287,542) per year. MRSA BSI $5.5 million per year (339,633–22.7 million) MRSA RTI $1,525,552 (726,903–2,791,453)

AC – accounting costs; AMR – antimicrobial resistance; AUD – Australian Dollars, BGI - bacterial gastro-intestinal infection; BSI – bloodstream infection; CDI – *Clostridioides/Clostridium difficile* infection; CP-AB - Carbapenemase-producing *Acinetobacter baumannii*; CPE - carbapenemase-producing Enterobacteriales (Enterobacteriaceae); CRE - carbapenem-resistant *Enterobacteriaceae;* CRAB - carbapenem-resistant *Acinetobacter baumannii*; CSAB - carbapenem-sensitive *Acinetobacter baumannii* ; CT – computerised tomography; CXR – chest x-ray, DRG - Diagnosis-related Group; ESBL - extended-spectrum beta-lactamases; GNB – gram negative bacilli; IAI - intra-abdominal infection; ICU – intensive care unit; IPC – infection prevention and control; LOS, length of stay; MDRAB – multidrug resistant Acinetobacter Baumannii; MDRO – multi-drug resistant organism; MSSA – meticillin-sensitive *Staphylococcus aureus*; MRSA – meticillin-resistant Staphylococcus aureus; MSI - musculoskeletal infection; N/A – not applicable; NR – not reported; NDM - New Delhi metallo-beta-lactamase 1; OC – opportunity costs; PNSP - penicillin-non-susceptible pneumococci; (U)/(L)/RTI – (upper)/(lower) respiratory tract infection; SEK - Swedish Krona; STI – sexually transmitted infection; SSI – surgical site infection; SSTI – skin and soft tissue infection; TB – tuberculosis; UK – United Kingdom; US – United States; USD – United States Dollars; UTI – urinary tract infection; VAP – ventilator associated pneumonia, VRE - vancomycin-resistant enterococci; VSE - . Vancomycin-sensitive E. faecium; 3GC - third-generation cephalosporin; 3GCRE - third-generation cephalosporin-resistant Enterobacteriaceae.

*Public Health Sweden 2018 presented both population & modelling and outbreak data separately, this report has therefore been included in both sets of tables

Appendix 4 — Quality appraisal tool

This tool was developed by the Welsh Public Health Observatory, but based on Larg et al. 2011 (Cost of illness studies: a guide to critical evaluation).[48] http://www2.nphs.wales.nhs.uk:8080/PubHObservatoryProjDocs.nsf/($All)/3F7F34D64C70747180257DBD00411C39/$File/Cost%20of%20illness%20studies%20critical%20appraisal%20checklist.docx?OpenElement

The tool was modified slightly to better meet the aims of the current project.

Questions to assist with the critical appraisal of a Cost of Illness/ Risk factor Analysis (Type ** evidence)[a]

A. Is the cost-of-illness study likely to be relevant and usable (what costs should have been measured)?

	Yes	Can't tell	No
1. Is the costing methodology described in enough detail to replicate?			
2. Are some or all of the cost inputs relevant to an Irish setting?			
3. Is the necessary data likely to be available in Ireland?			

Is it worth continuing? (delete as appropriate) YES/NO/Discuss

Only complete the next section if the answer to the question above was 'Yes'

B. Methodology and data: how well were resource use measured?

	Yes	Can't tell	No
4. Was an appropriate method(s) of quantification used, such that: (i) additional, or excess, costs were measured? (ii) only costs specific to (caused by) the health problem were included (confounders controlled)? (iii) all important effects were captured? (iv) important differences across subpopulations were accounted for? (v) the required level of detail could be provided?			
5. Was the resource quantification method(s) well executed?			

(i) For population-based studies, were cost allocation methods, data and assumptions valid? (ii) For person-based studies, were appropriate statistical tests performed and reported? (iii) Were data representative of the study population? (iv) Were there any other relevant resource quantification issues?			
6. Were healthcare resources valued appropriately?			

Is it worth continuing? (delete as appropriate) YES/NO/Discuss

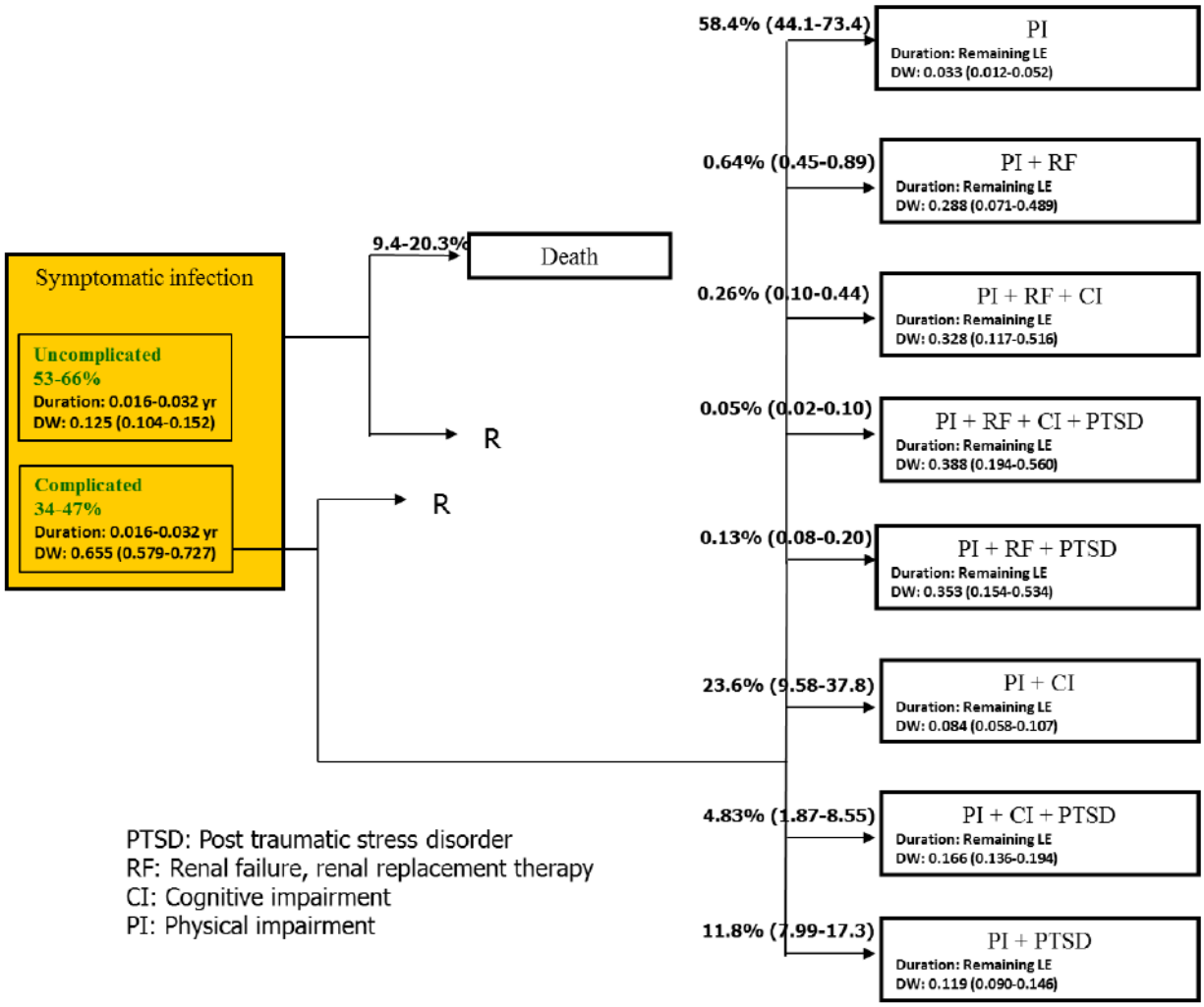
Only complete the next two sections if the answer to the question above was 'Yes'

C. What did they find (analysis and reporting)?

	Yes	Can't tell	No
7. Did the analysis address the study question?			
8. Was a range of estimates presented?			
9. Were the main uncertainties identified?			
10. Was a sensitivity analysis performed on: (i) important (uncertain) parameter estimates? (ii) key assumptions? (including the counterfactual) (iii) point estimates? (based on confidence or credible intervals)			
11. Was adequate documentation and justification given for cost components, data and sources, assumptions and methods?			
12. Was uncertainty around the estimates and its implications adequately discussed?			
13. Were important limitations discussed regarding the cost components, data, assumptions and methods?			
14. Were the results presented at the appropriate level of detail to answer the study question (cost components; disease subtypes, severity, stage; subpopulation groups, cost bearers)?			

Appendix 5 — Disease outcome trees

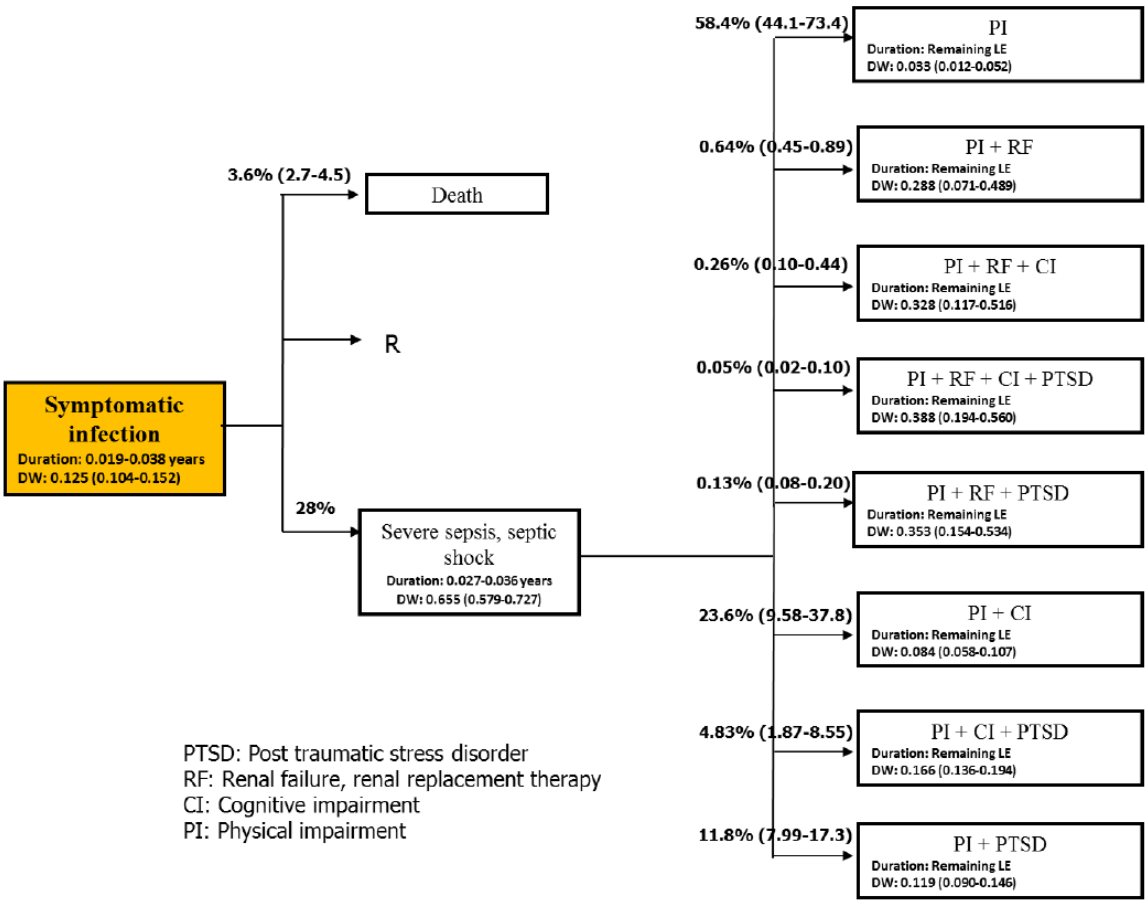
Figure A.1: Baseline disease outcome tree for blood stream infections (BSIs)



Key: DW – disability weight; R - recovery.

DOI:https://doi.org/10.1016/S1473-3099(18)30605-4 (CC BY 4.0)

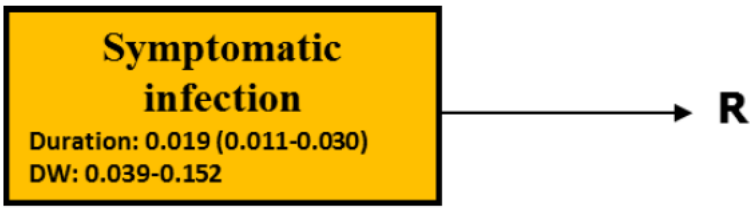
Figure A.2: Baseline disease outcome tree for respiratory tract infections (RTIs)



Key: DW – disability weight; R - recovery.

DOI:https://doi.org/10.1016/S1473-3099(18)30605-4 (CC BY 4.0)

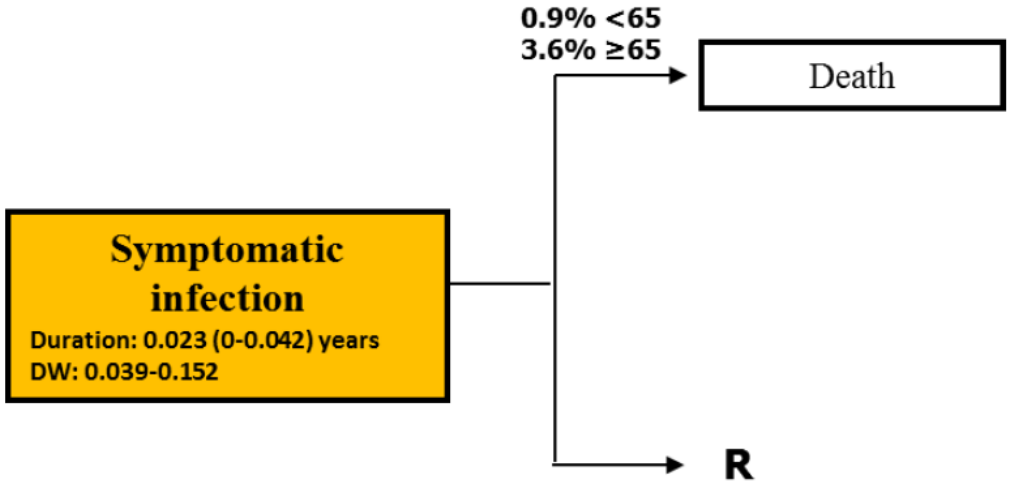
Figure A.3: Baseline disease outcome trees for urinary tract infections (UTIs)



Key: DW – disability weight; R - recovery.

DOI:https://doi.org/10.1016/S1473-3099(18)30605-4 (CC BY 4.0)

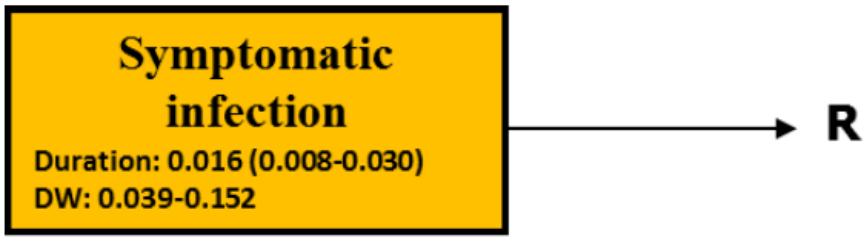
Figure A.4: Baseline disease outcome tree for surgical site infections (SSIs)



Key: DW – disability weight; R – recovery.

DOI:https://doi.org/10.1016/S1473-3099(18)30605-4 (CC BY 4.0)

Figure A.5: Baseline disease outcome tree for other site infections



Key: DW – disability weight; R – recovery.

DOI:https://doi.org/10.1016/S1473-3099(18)30605-4 (CC BY 4.0)

Appendix 6 — Health outcome parameters

Table A.3: Summary of disease health outcome parameters: case fatality proportion (CFP) and length of stay (LOS).

	Baseline model	*Klebsiella pneumoniae*			*Escherichia coli*			*Acinetobacter* spp.			*Pseudomonas aeruginosa*			*Staphylococcus aureus*	*Enterococcus faecalis* and *E. faecium*	*Streptococcus pneumoniae*	
		3GCRKP	CRKP	ColRKP	3GCREC	CREC	ColREC	MDRACI	CRACI	ColRACI	MDRPA	CRPA	ColRPA	MRSA	VRE	PRSP	PMRSP
BSI																	
Case fatality proportion (%)	7.1-20.3	14.4-19	20-51.3	32-88.8	17.1 (9.5-26)	20-51.3	32-88.8	7.1-32.9	7.1-34	7.1-34	7.1-35.2	7.1-38.7	7.1-38.7	17.9 (14.4-21.8)	22.9 (21.8-23.8)	15.7-20.3	15.7-20.3
Duration (days)	5.87-11.5	9.28 (9.20–9.35)	15-35	15-39.1	6-18.5	15-35	15-39.1	5.87-20.1	5.87-20.1	5.87-20.1	14.87-21.5	14.87-21.5	14.87-21.5	8.99-14.62	6.97-18.3	Baseline	Baseline
RESP																	
Case fatality proportion (%)	3.6 (2.7-4.5)	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	2.7-9.8	2.7-10.5	2.7-10.5	Baseline	Baseline	Baseline	Baseline
Duration (days)	7-14	13.6-18.1	13.6-18.1	13.6-18.1	Baseline	13.6-18.1	13.6-18.1	Baseline	Baseline	Baseline	10-17	15-22	15-22	Baseline	Baseline	Baseline	Baseline
UTI																	
Case fatality proportion (%)	0	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	N/A	N/A
Duration (days)	7 (4-11)	7 (5-12)	7.5 (4-14)	7.5 (4-14)	7 (5-12)	7.5 (4-14)	7.5 (4-14)	8 (4-11)	8 (4-11)	8 (4-11)	8 (4-11)	8 (4-11)	8 (4-11)	Baseline	Baseline	N/A	N/A
SSI																	
Case fatality proportion (%)	0.9<65; 3.6>64	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	N/A	N/A
Duration (days)	8.5 (0-15.2)	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	N/A	N/A
OTHER																	
Case fatality proportion (%)	0	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	0	0
Duration (days)	6 (3-11)	12 (8-21)	12 (6-27)	12 (6-27)	12 (8-21)	12 (6-27)	12 (6-27)	14.5 (9-19)	14.5 (9-19)	14.5 (9-19)	14.5 (9-19)	14 (9-19)	14.5 (9-19)	12 (8-19)	Baseline	5-10	5-10

Key: CFP – case fatality proportion; LOS – length of stay; BSI – blood stream infection; RESP – respiratory tract infection; UTI – urinary tract infection; SSI – surgical site infection.

Appendix 7 — ECDC Conversion and reducing factors 2016/2017

Table A.4: ECDC conversion and reducing factors 2016/2017

Pathogen Antibiotic	Infection site	Conversion factor lower 95% CI	Median conversion factor	Conversion factor upper 95% CI	Reducing factor
ec 3GCR	RESP	0.24691358	0.619469027	1.425219941	0.025
ec 3GCR	UTI	1.155555556	1.819690265	3.66359447	0.376
ec 3GCR	SSI	0.492929293	1.138274336	2.741935484	0.057
ec 3GCR	OTH	0.327272727	0.72878709	1.935887097	0.156
kp 3GCR	RESP	0.641935484	1.164001084	2.128495843	0.085
kp 3GCR	UTI	0.860125448	1.499423963	2.577475435	0.146
kp 3GCR	SSI	0.403225806	0.803937997	2.240983245	0.038
kp 3GCR	OTH	0.634408602	1.275839368	2.665608466	0.146
ab CAR	RESP	0.84241259	1.855670103	4.151141827	0.162
ab CAR	UTI	0.227871537	0.695876289	1.569808804	0.027
ab CAR	SSI	0.448622089	1.07674685	2.403708791	0.014
ab CAR	OTH	0.508438368	1.408934708	3.099519231	0.0946
kp 3GCRCAR	RESP	0.282335907	0.650793651	2.0625	0.085
kp 3GCRCAR	UTI	0.391891892	0.807539683	1.643303571	0.146
kp 3GCRCAR	SSI	0.273648649	0.611111111	1.359375	0.038
kp 3GCRCAR	OTH	0.287331081	0.731150794	1.729166667	0.146
pa CAR	RESP	0.964469697	2.125	7.622222222	0.094
pa CAR	UTI	0.438825794	1.083333333	4.977777778	0.118

pa CAR	SSI	0.410718269	1.1375	4.888888889	0.071
pa CAR	OTH	0.764924242	2.029411765	7.2	0.079
sa OXAR	RESP	0.54529767	1.212871287	3.237804878	0.061
sa OXAR	UTI	0.174863388	0.524170064	1.364111498	0.017
sa OXAR	SSI	1.108196721	2.413366337	6.201219512	0.119
sa OXAR	OTH	0.870342772	1.712871287	4.075209604	0.122
ef VAN	RESP	0.140039063	0.490909091	3.398926655	0.02
ef VAN	UTI	0.344711538	1.136363636	5.520061334	0.08
ef VAN	SSI	1.353710938	3.513368984	13.65065167	0.075
ef VAN	OTH	1.050292969	2.681818182	20.13193202	0.206
ec 3GCRCAR	RESP	0.24691358	0.619469027	1.425219941	0.025
ec 3GCRCAR	UTI	1.155555556	1.819690265	3.66359447	0.376
ec 3GCRCAR	SSI	0.492929293	1.138274336	2.741935484	0.057
ec 3GCRCAR	OTH	0.327272727	0.72878709	1.935887097	0.156
ec 3GCRCARCOLR	RESP	0.24691358	0.619469027	1.425219941	0.025
ec 3GCRCARCOLR	UTI	1.155555556	1.819690265	3.66359447	0.376
ec 3GCRCARCOLR	SSI	0.492929293	1.138274336	2.741935484	0.057
ec 3GCRCARCOLR	OTH	0.327272727	0.72878709	1.935887097	0.156
kp 3GCRCARCOLR	RESP	0.282335907	0.650793651	2.0625	0.085
kp 3GCRCARCOLR	UTI	0.391891892	0.807539683	1.643303571	0.146
kp 3GCRCARCOLR	SSI	0.273648649	0.611111111	1.359375	0.038
kp 3GCRCARCOLR	OTH	0.287331081	0.731150794	1.729166667	0.146
pa CARCOLR	RESP	0.964469697	2.125	7.622222222	0.094

pa CARCOLR	UTI	0.438825794	1.083333333	4.977777778	0.118
pa CARCOLR	SSI	0.410718269	1.1375	4.888888889	0.071
pa CARCOLR	OTH	0.764924242	2.029411765	7.2	0.079
pa multi	RESP	0.964469697	2.125	7.622222222	0.094
pa multi	UTI	0.438825794	1.083333333	4.977777778	0.118
pa multi	SSI	0.410718269	1.1375	4.888888889	0.071
pa multi	OTH	0.764924242	2.029411765	7.2	0.079
ab CARCOLR	RESP	0.84241259	1.855670103	4.151141827	0.162
ab CARCOLR	UTI	0.227871537	0.695876289	1.569808804	0.027
ab CARCOLR	SSI	0.448622089	1.07674685	2.403708791	0.014
ab CARCOLR	OTH	0.508438368	1.408934708	3.099519231	0.0946
ab multi	RESP	0.84241259	1.855670103	4.151141827	0.162
ab multi	UTI	0.227871537	0.695876289	1.569808804	0.027
ab multi	SSI	0.448622089	1.07674685	2.403708791	0.014
ab multi	OTH	0.508438368	1.408934708	3.099519231	0.0946
ec 3GCR	BSI	1	1	1	0
kp 3GCR	BSI	1	1	1	0
ab CAR	BSI	1	1	1	0
kp 3GCRCAR	BSI	1	1	1	0
pa CAR	BSI	1	1	1	0
sa OXAR	BSI	1	1	1	0
ef VAN	BSI	1	1	1	0
ec 3GCRCAR	BSI	1	1	1	0

ec 3GCRCARCOLR	BSI	1	1	1	0
kp 3GCRCARCOLR	BSI	1	1	1	0
pa CARCOLR	BSI	1	1	1	0
pa multi	BSI	1	1	1	0
ab CARCOLR	BSI	1	1	1	0
ab multi	BSI	1	1	1	0
sp PEN	BSI	1	1	1	0
sp PEN	RESP	2.7	2.97	8.33	0
sp PEN	UTI	0	0	0	0
sp PEN	SSI	0	0	0	0
sp PEN	OTH	0.28	0.33	0.54	0
sp PENMAC	BSI	1	1	1	0
sp PENMAC	RESP	2.7	2.97	8.33	0
sp PENMAC	UTI	0	0	0	0
sp PENMAC	SSI	0	0	0	0
sp PENMAC	OTH	0.28	0.33	0.54	0

Pathogen Key - ab - *Acinetobacter* spp; ec - *Escherichia coli;* ef - *Enterococcus faecalis and Enterococcus faecium;* kp - *Klebsiella pneumoniae;* pa - *Pseudomonas aeruginosa*; *sa - Staphylococcus aureus;* sp - *Streptococcus pneumoniae*.

Antibiotic key - 3GCR - Third-generation cephalosporin-resistant; 3GCRCAR - Third-generation cephalosporin- and carbapenem-resistant; 3GCRCARCOLR - Third-generation cephalosporin-, carbapenem- and colistin resistant; CAR - Carbapenem-resistant; CARCOLR - Carbapenem- and colistin resistant; multi - multidrug-resistant; OXAR – Oxacillin- (meticillin-) resistant; PEN - Penicillin-resistant; PENMAC - Penicillin- and macrolide-resistant; VAN –vancomycin-resistant.

Key – CI – confidence interval.

Appendix 8 — Length of stay parameter inputs

Table A.5: Length of stay parameter inputs for the simulation model

Description	Deterministic	Lower 95% CI*	Upper 95% CI*	Source
BLOODSTREAM RESISTANT INFECTIONS				
Third-generation cephalosporin-resistant Escherichia coli	12.25	6.00	18.50	(Cassini et al, 2019)
Carbapenem-resistant Escherichia coli	25.00	15.00	35.00	(Cassini et al, 2019)
Colistin-resistant Escherichia coli	27.05	15.00	39.10	(Cassini et al, 2019)
Third-generation cephalosporin-resistant Klebsiella pneumoniae * (excluding isolates also resistant to colistin and/or carbapenem)	9.28	9.20	9.35	(Cassini et al, 2019)
Carbapenem-resistant Klebsiella pneumoniae (excluding isolates also resistant to colistin)	25.00	15.00	35.00	(Cassini et al, 2019)
Colistin-resistant Klebsiella pneumoniae	27.05	15.00	39.10	(Cassini et al, 2019)
Multidrug-resistant Pseudomonas aeruginosa	18.19	14.87	21.50	(Cassini et al, 2019)
Carbapenem-resistant Pseudomonas aeruginosa	18.19	14.87	21.50	(Cassini et al, 2019)
Colistin-resistant Pseudomonas aeruginosa	18.19	14.87	21.50	(Cassini et al, 2019)
Multidrug-resistant Acinetobacter species	12.99	5.87	20.10	(Cassini et al, 2019)
Carbapenem-resistant Acinetobacter species	12.99	5.87	20.10	(Cassini et al, 2019)
Colistin-resistant Acinetobacter species	12.99	5.87	20.10	(Cassini et al, 2019)
Penicillin-resistant Streptococcus pneumoniae	8.69	5.87	11.50	(Cassini et al, 2019)
Penicillin- and macrolide-resistant Streptococcus. pneumoniae	8.69	5.87	11.50	(Cassini et al, 2019)
Meticillin-resistant Staphylococcus aureus	11.81	8.99	14.62	(Cassini et al, 2019)
Vancomycin-resistant enterococci (Enterococcus faecalis / Enterococcus faecium)	12.64	6.97	18.30	(Cassini et al, 2019)
RESPIRATORY RESISTANT INFECTIONS				
Third-generation cephalosporin-resistant Escherichia coli	10.50	7.00	14.00	(Cassini et al, 2019)

Carbapenem-resistant Escherichia coli	15.85	13.60	18.10	(Cassini et al, 2019)
Colistin-resistant Escherichia coli	15.85	13.60	18.10	(Cassini et al, 2019)
Third-generation cephalosporin-resistant Klebsiella pneumoniae * (excluding isolates also resistant to colistin and/or carbapenem)	15.85	13.60	18.10	(Cassini et al, 2019)
Carbapenem-resistant Klebsiella pneumoniae (excluding isolates also resistant to colistin)	15.85	13.60	18.10	(Cassini et al, 2019)
Colistin-resistant Klebsiella pneumoniae	15.85	13.60	18.10	(Cassini et al, 2019)
Multidrug-resistant Pseudomonas aeruginosa	13.50	10.00	17.00	(Cassini et al, 2019)
Carbapenem-resistant Pseudomonas aeruginosa	18.50	15.00	22.00	(Cassini et al, 2019)
Colistin-resistant Pseudomonas aeruginosa	18.50	15.00	22.00	(Cassini et al, 2019)
Multidrug-resistant Acinetobacter species	10.50	7.00	14.00	(Cassini et al, 2019)
Carbapenem-resistant Acinetobacter species	10.50	7.00	14.00	(Cassini et al, 2019)
Colistin-resistant Acinetobacter species	10.50	7.00	14.00	(Cassini et al, 2019)
Penicillin-resistant Streptococcus pneumoniae	10.50	7.00	14.00	(Cassini et al, 2019)
Penicillin- and macrolide-resistant Streptococcus. pneumoniae	10.50	7.00	14.00	(Cassini et al, 2019)
Meticillin-resistant Staphylococcus aureus	10.50	7.00	14.00	(Cassini et al, 2019)
Vancomycin-resistant enterococci (Enterococcus faecalis / Enterococcus faecium)	10.50	7.00	14.00	(Cassini et al, 2019)
URINARY TRACT RESISTANT INFECTIONS				
Third-generation cephalosporin-resistant Escherichia coli	7	5.00	12.00	(Cassini et al, 2019)
Carbapenem-resistant Escherichia coli	7.5	4.00	14.00	(Cassini et al, 2019)
Colistin-resistant Escherichia coli	7.5	4.00	14.00	(Cassini et al, 2019)
Third-generation cephalosporin-resistant Klebsiella pneumoniae * (excluding isolates also resistant to colistin and/or carbapenem)	7	5.00	12.00	(Cassini et al, 2019)
Carbapenem-resistant Klebsiella pneumoniae (excluding isolates also resistant to colistin)	7.5	4.00	14.00	(Cassini et al, 2019)
Colistin-resistant Klebsiella pneumoniae	7.5	4.00	14.00	(Cassini et al, 2019)

Multidrug-resistant Pseudomonas aeruginosa	8	4.00	11.00	(Cassini et al, 2019)
Carbapenem-resistant Pseudomonas aeruginosa	8	4.00	11.00	(Cassini et al, 2019)
Colistin-resistant Pseudomonas aeruginosa	8	4.00	11.00	(Cassini et al, 2019)
Multidrug-resistant Acinetobacter species	8	4.00	11.00	(Cassini et al, 2019)
Carbapenem-resistant Acinetobacter species	8	4.00	11.00	(Cassini et al, 2019)
Colistin-resistant Acinetobacter species	8	4.00	11.00	(Cassini et al, 2019)
Penicillin-resistant Streptococcus pneumoniae	-	-	-	(Cassini et al, 2019)
Penicillin- and macrolide-resistant Streptococcus. pneumoniae	-	-	-	(Cassini et al, 2019)
Meticillin-resistant Staphylococcus aureus	7	4.00	11.00	(Cassini et al, 2019)
Vancomycin-resistant enterococci (Enterococcus faecalis / Enterococcus faecium)	7	4.00	11.00	(Cassini et al, 2019)
SURGICAL SITE RESISTANT INFECTIONS				
Third-generation cephalosporin-resistant Escherichia coli	8.5	0.00	15.20	(Cassini et al, 2019)
Carbapenem-resistant Escherichia coli	8.5	0.00	15.20	(Cassini et al, 2019)
Colistin-resistant Escherichia coli	8.5	0.00	15.20	(Cassini et al, 2019)
Third-generation cephalosporin-resistant Klebsiella pneumoniae * (excluding isolates also resistant to colistin and/or carbapenem)	8.5	0.00	15.20	(Cassini et al, 2019)
Carbapenem-resistant Klebsiella pneumoniae (excluding isolates also resistant to colistin)	8.5	0.00	15.20	(Cassini et al, 2019)
Colistin-resistant Klebsiella pneumoniae	8.5	0.00	15.20	(Cassini et al, 2019)
Multidrug-resistant Pseudomonas aeruginosa	8.5	0.00	15.20	(Cassini et al, 2019)
Carbapenem-resistant Pseudomonas aeruginosa	8.5	0.00	15.20	(Cassini et al, 2019)
Colistin-resistant Pseudomonas aeruginosa	8.5	0.00	15.20	(Cassini et al, 2019)
Multidrug-resistant Acinetobacter species	8.5	0.00	15.20	(Cassini et al, 2019)
Carbapenem-resistant Acinetobacter species	8.5	0.00	15.20	(Cassini et al, 2019)
Colistin-resistant Acinetobacter species	8.5	0.00	15.20	(Cassini et al, 2019)

Penicillin-resistant Streptococcus pneumoniae	-	-	-	(Cassini et al, 2019)
Penicillin- and macrolide-resistant Streptococcus. pneumoniae	-	-	-	(Cassini et al, 2019)
Meticillin-resistant Staphylococcus aureus	8.5	0.00	15.20	(Cassini et al, 2019)
Vancomycin-resistant enterococci (Enterococcus faecalis / Enterococcus faecium)	8.5	0.00	15.20	(Cassini et al, 2019)
OTHER RESISTANT INFECTION SITES				
Third-generation cephalosporin-resistant Escherichia coli	12	8.00	21.00	(Cassini et al, 2019)
Carbapenem-resistant Escherichia coli	12	6.00	27.00	(Cassini et al, 2019)
Colistin-resistant Escherichia coli	12	6.00	27.00	(Cassini et al, 2019)
Third-generation cephalosporin-resistant Klebsiella pneumoniae * (excluding isolates also resistant to colistin and/or carbapenem)	12	8.00	21.00	(Cassini et al, 2019)
Carbapenem-resistant Klebsiella pneumoniae (excluding isolates also resistant to colistin)	12	6.00	27.00	(Cassini et al, 2019)
Colistin-resistant Klebsiella pneumoniae	12	6.00	27.00	(Cassini et al, 2019)
Multidrug-resistant Pseudomonas aeruginosa	14.5	9.00	19.00	(Cassini et al, 2019)
Carbapenem-resistant Pseudomonas aeruginosa	14.5	9.00	19.00	(Cassini et al, 2019)
Colistin-resistant Pseudomonas aeruginosa	14.5	9.00	19.00	(Cassini et al, 2019)
Multidrug-resistant Acinetobacter species	14.5	9.00	19.00	(Cassini et al, 2019)
Carbapenem-resistant Acinetobacter species	14.5	9.00	19.00	(Cassini et al, 2019)
Colistin-resistant Acinetobacter species	14.5	9.00	19.00	(Cassini et al, 2019)
Penicillin-resistant Streptococcus pneumoniae	7.5	5.00	10.00	(Cassini et al, 2019)
Penicillin- and macrolide-resistant Streptococcus. pneumoniae	7.5	5.00	10.00	(Cassini et al, 2019)
Meticillin-resistant Staphylococcus aureus	12	8.00	19.00	(Cassini et al, 2019)
Vancomycin-resistant enterococci (Enterococcus faecalis / Enterococcus faecium)	6	3.00	11.00	(Cassini et al, 2019)

SUSCEPTIBLE INFECTIONS				
Bloodstream infection	8.69	5.87	11.50	(Cassini et al, 2019)
Respiratory infection	10.50	7.00	14.00	(Cassini et al, 2019)
Urinary tract infection	7.00	4.00	11.00	(Cassini et al, 2019)
Surgical site infection	8.50	0.00	15.20	(Cassini et al, 2019)
Other infection sites (excluding BSI, UTI, RESP and SSI)	6.00	3.00	11.00	(Cassini et al, 2019)

** Average of 95% CIs. All parameters assumed a gamma distribution.

Appendix 9 — Supplementary results

Figure A.6: Resistant *E. coli* infections by age group and sex

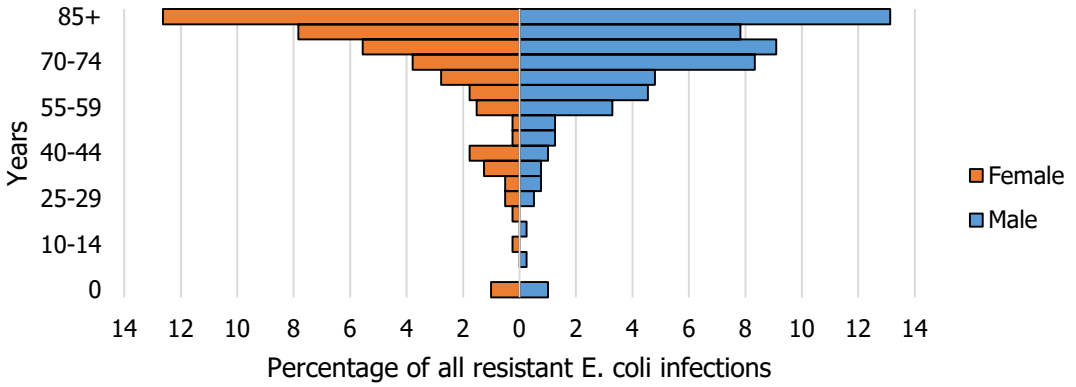


Figure A.7: Resistant *S. aureus* infections by age group and sex

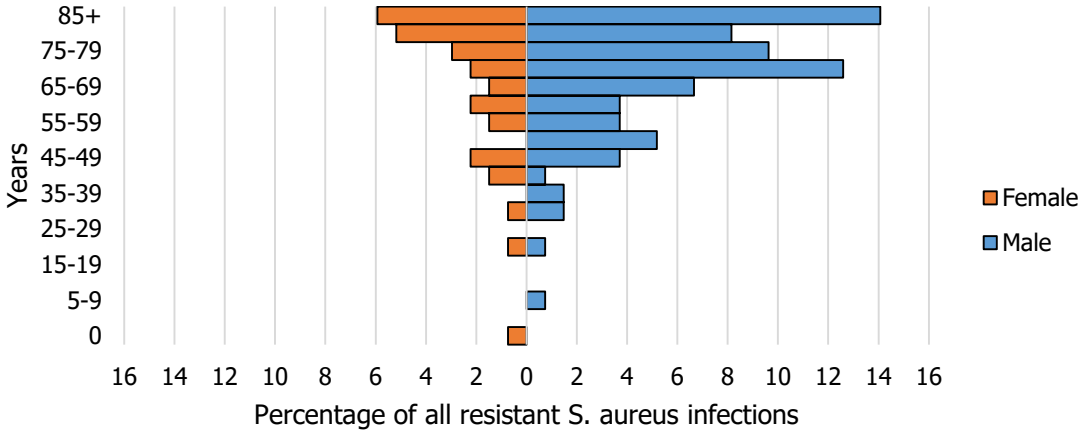


Figure A.8: Resistant *E. faecalis/faecium* infections by age group and sex

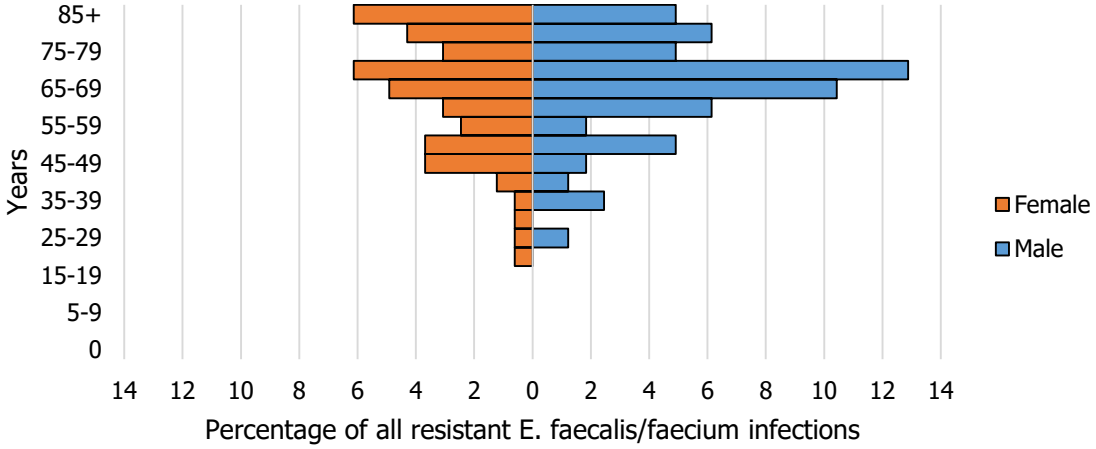


Figure A.9: Resistant *K. pneumoniae* infections by age group and sex

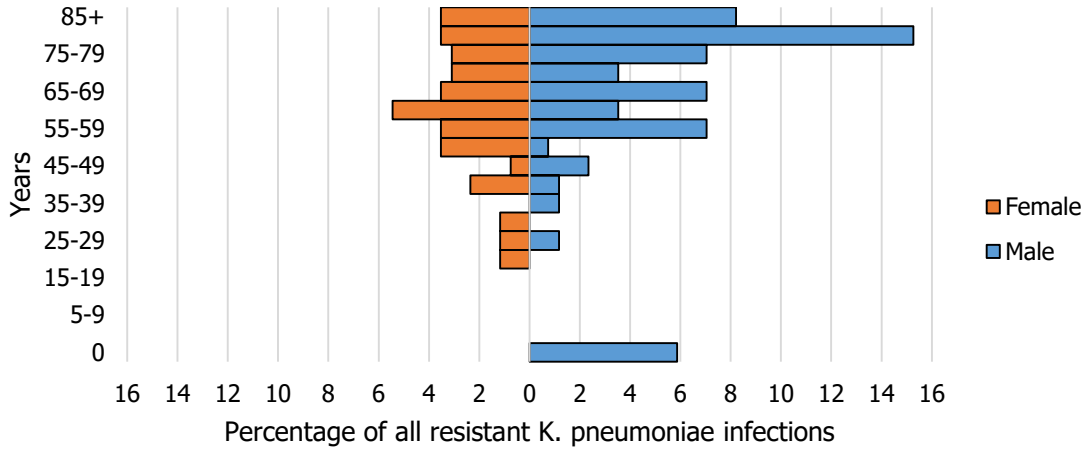


Figure A.10: Resistant *P. aeruginosa* infections by age group and sex

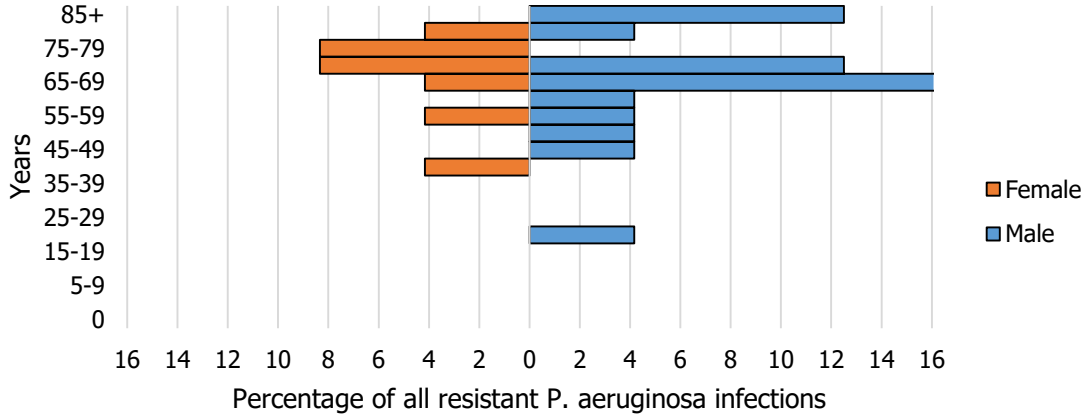


Figure A.11: Resistant *Acinetobacter spp.* infections by age group and sex

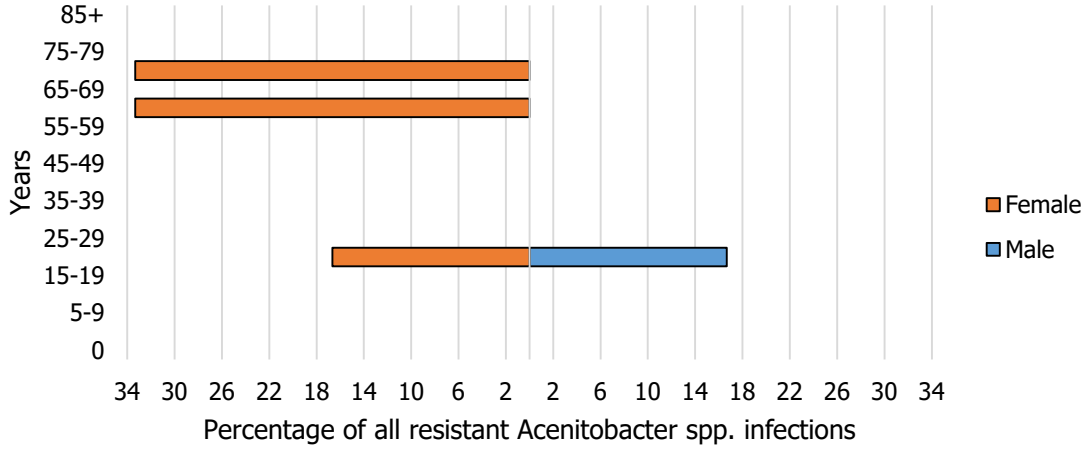


Figure A.12: Resistant *S. pneumoniae* infections by age group and sex

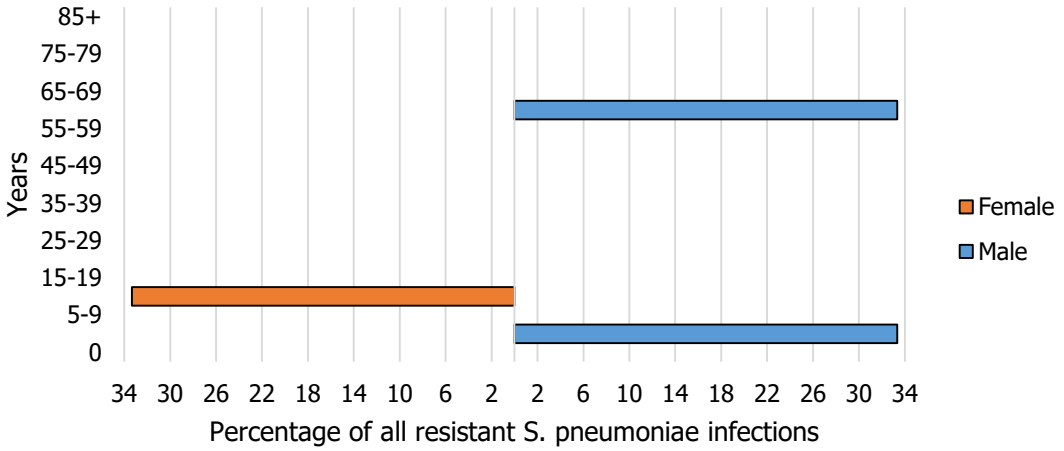
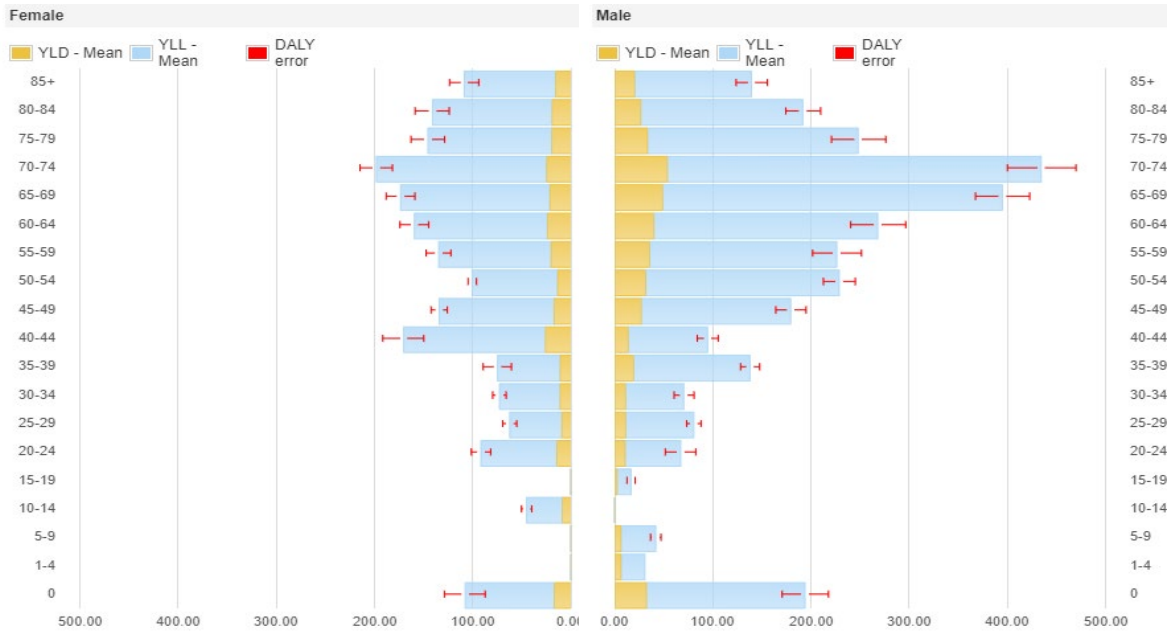
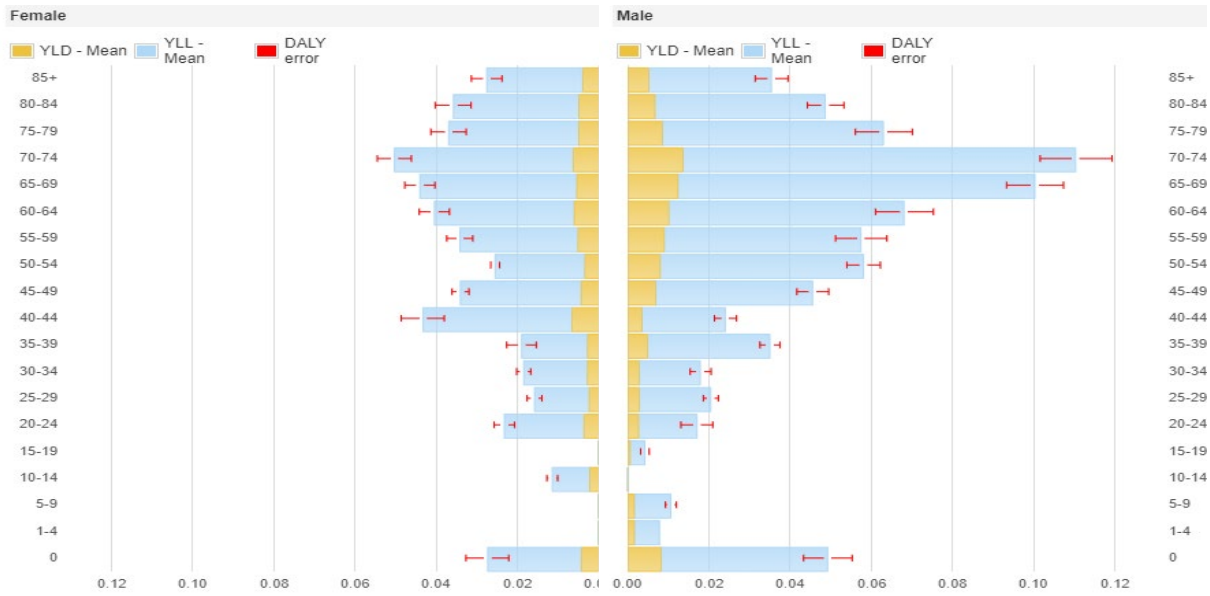


Figure A.13: Total DALYs, according to age group and sex



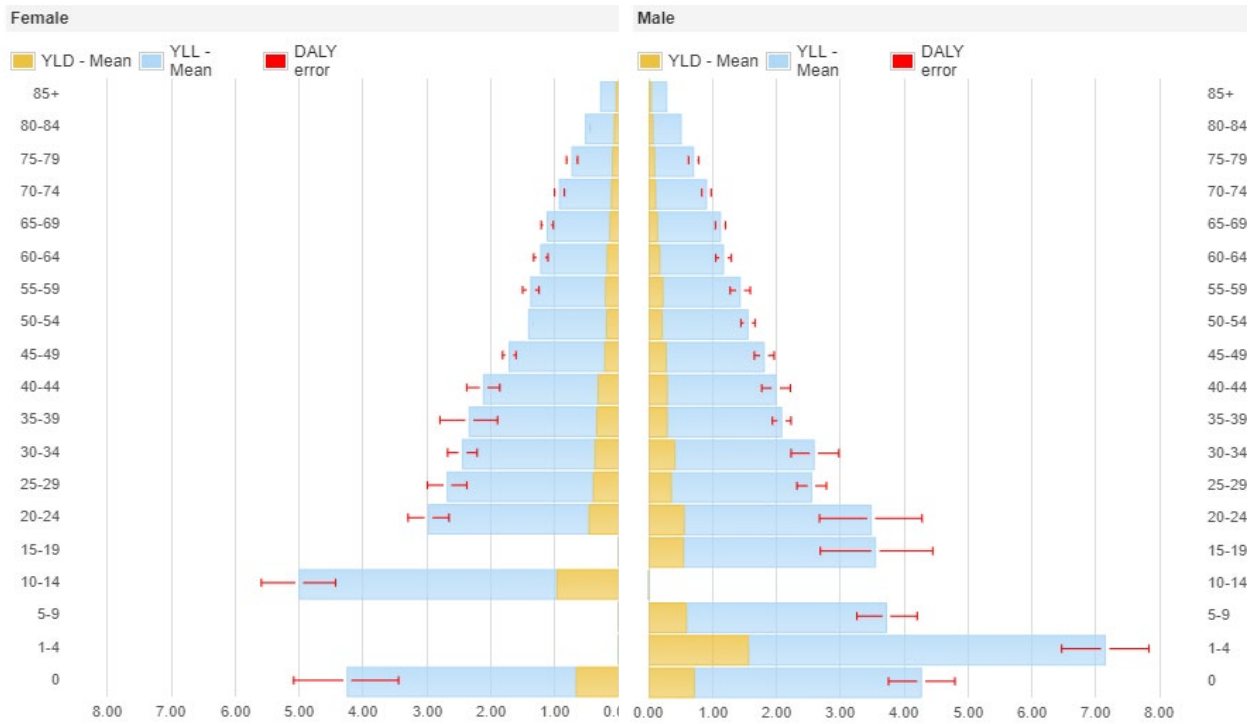
Key - DALY – disability-adjusted life year; YLD – years lost due to disability; YLL – years of life lost.

Figure A.14: Total DALYs per 100,000 population, according to age group and sex



Key - DALY – disability-adjusted life year; YLD – years lost due to disability; YLL – years of life lost.

Figure A.15: Total DALYs per case, according to age group and sex



Key - DALY – disability-adjusted life year; YLD – years lost due to disability; YLL – years of life lost.

Table A.6: Results of first scenario analysis (assumption A)

Assumption A; the proportion of patients with resistant infections that experienced complications was used as a proxy for the duration of stay in ICU.

Pathogen	BSI	RESP	UTI	SSI	OTHER	Total cost (pathogen)
Escherichia coli						
Third-generation cephalosporin- resistant	€1069380 (€0 to €3094238)	€196519 (€0 to €1056744)	€491117 (€0 to €2572300)	€777774 (€0 to €4341315)	€1315864 (€0 to €3607358)	€3850653 (€792263 to €8623746)
Carbapenem-resistant	€11374 (€4519 to €20133)	€2642 (€432 to €5671)	€1821 (€0 to €9056)	€1981 (€0 to €10819)	€3372 (€0 to €11751)	€21190 (€10032 to €36856)
Colistin-resistant						**No data**
Total cost	*€1080754 (€7097 to €3108328)*	*€199161 (€442 to €1060578)*	*€492938 (€0 to €2572300)*	*€779755 (€0 to €4343751)*	*€1319236 (€795 to €3615876)*	*€3871844 (€813943 to €8647001)*
Klebsiella pneumoniae						
Third-generation cephalosporin-resistant	€54150 (€0 to €188476)	€367156 (€53280 to €739421)	€85218 (€0 to €441895)	€123870 (€0 to €698982)	€463916 (€0 to €1205985)	€1094310 (€363838 to €2115585)
Carbapenem-resistant	€57129 (€23335 to €98898)	€15454 (€2234 to €36055)	€4017 (€0 to €20337)	€5033 (€0 to €26646)	€15700 (€0 to €53678)	€97334 (€48191 to €160425)
Colistin-resistant						**No data**
Total cost	*€111280 (€26003 to €261462)*	*€382610 (€58070 to €762563)*	*€89235 (€0 to €448927)*	*€128903 (€0 to €709013)*	*€479616 (€4206 to €1225330)*	*€1191644 (€443171 to €2229265)*
Pseudomonas aeruginosa						
Multidrug-resistant	€53493 (€27763 to €81606)	€55109 (€0 to €166668)	€15934 (€0 to €70697)	€21549 (€0 to €124213)	€140232 (€27126 to €317927)	€286316 (€124430 to €517189)
Carbapenem-resistant	€107006 (€56002 to €162725)	€280283 (€78157 to €609599)	€160856 (€53318 to €343828)	€43201 (€0 to €247760)	€280153 (€53906 to €634622)	€871499 (€476657 to €1424131)
Colistin-resistant						**No data**
Total cost	*€160498 (€92276 to €234576)*	*€335392 (€91833 to €705820)*	*€176790 (€61808 to €364960)*	*€64750 (€0 to €301837)*	*€420385 (€116283 to €826657)*	*€1157815 (€671304 to €1800723)*
Acinetobacter species						
Multidrug-resistant	€15807 (€0 to €45564)	€7301 (€0 to €38756)	€4285 (€0 to €17839)	€9160 (€0 to €50356)	€44976 (€9139 to €95556)	€81529 (€28240 to €156370)
Carbapenem-resistant	€3210 (€0 to €9277)	€1433 (€0 to €7575)	€852 (€0 to €3550)	€1783 (€0 to €9883)	€9021 (€1851 to €19317)	€16299 (€5484 to €30856)
Colistin-resistant						**No data**
Total cost	*€19018 (€0 to €50158)*	*€8734 (€0 to €41942)*	*€5138 (€0 to €19536)*	*€10942 (€0 to €54777)*	*€53996 (€13816 to €107488)*	*€97828 (€40264 to €177068)*

Pathogen	BSI	RESP	UTI	SSI	OTHER	Total cost (pathogen)
Penicillin-resistant	€18259 (€12004 to €26058)	€9008 (€0 to €46513)	-	-	€1496 (€0 to €4795)	€28763 (€13854 to €67555)
Penicillin- and macrolide-resistant						**No data**
Total cost	*€18259 (€12004 to €26058)*	*€9008 (€0 to €46513)*	-	-	*€1496 (€0 to €4795)*	*€28763 (€13854 to €67555)*
Staphylococcus aureus						
Meticillin-resistant	€299792 (€0 to €683565)	€143149 (€0 to €773690)	€57733 (€0 to €317366)	€595927 (€0 to €3279148)	€1123398 (€0 to €2817076)	€2220000 (€470823 to €5314966)
Enterococcus faecalis / faecium						
Vancomycin-resistant	€471839 (€0 to €1261176)	€127459 (€0 to €754045)	€217208 (€0 to €1266002)	€1338476 (€0 to €7600331)	€838968 (€0 to €4842287)	€2993950 (€161074 to €10130608)
Total cost (infection)	€2161440 (€347198 to €4650105)	€1205513 (€214923 to €3061779)	€1039041 (€89256 to €3818031)	€2918753 (€0 to €11608840)	€4237095 (€657162 to €9964163)	€11561842 (€4574594 to €22528949)

Table A.7: Results of the first scenario analysis (assumption B)

Assumption B; the proportion of patients with resistant infections that experienced complications, or who died, was used as a proxy for the duration of stay in ICU.

Pathogen	BSI	RESP	UTI	SSI	OTHER	Total cost (pathogen)
Escherichia coli						
Third-generation cephalosporin-resistant	€1105416 (€0 to €3285499)	€198984 (€0 to €1061032)	€477150 (€0 to €2544471)	€814868 (€0 to €4381535)	€1325643 (€0 to €3715053)	€3922062 (€772134 to €8766939)
Carbapenem-resistant	€16267 (€6704 to €27832)	€2666 (€459 to €5664)	€1772 (€0 to €9060)	€2086 (€0 to €11543)	€3381 (€0 to €11823)	€26172 (€12836 to €43652)
Colistin-resistant						**No data**
Total cost	*€1121683 (€9719 to €3305266)*	*€201650 (€480 to €1063506)*	*€478921 (€0 to €2545592)*	*€816954 (€0 to €4384204)*	*€1329025 (€1007 to €3718354)*	*€3948234 (€790553 to €8785316)*
Klebsiella pneumoniae						
Third-generation cephalosporin-resistant	€57000 (€0 to €199159)	€365059 (€62957 to €732803)	€84895 (€0 to €441630)	€129589 (€0 to €715199)	€465155 (€0 to €1201142)	€1101699 (€380088 to €2141522)
Carbapenem-resistant	€81574 (€33219 to €141098)	€15587 (€2264 to €36383)	€3961 (€0 to €20307)	€5151 (€0 to €27615)	€16017 (€0 to €54362)	€122290 (€61452 to €197942)
Colistin-resistant						**No data**
Total cost	*€138574 (€36801 to €305125)*	*€380647 (€68132 to €761705)*	*€88856 (€0 to €449165)*	*€134740 (€0 to €723723)*	*€481172 (€3351 to €1219551)*	*€1223989 (€489435 to €2273237)*
Pseudomonas aeruginosa						
Multidrug-resistant	€61001 (€31370 to €92163)	€58123 (€0 to €176076)	€15882 (€0 to €72475)	€22399 (€0 to €128500)	€140731 (€27080 to €325849)	€298136 (€133257 to €537506)
Carbapenem-resistant	€126077 (€67676 to €190146)	€295919 (€83179 to €649161)	€159120 (€52009 to €347714)	€45071 (€0 to €251392)	€283536 (€51820 to €657368)	€909723 (€496186 to €1476086)
Colistin-resistant						**No data**
Total cost	*€187078 (€107258 to €270198)*	*€354042 (€99728 to €747019)*	*€175001 (€59991 to €368143)*	*€67470 (€0 to €310417)*	*€424267 (€116578 to €862322)*	*€1207859 (€701402 to €1863227)*
Acinetobacter species						
Multidrug-resistant	€17788 (€0 to €51731)	€7231 (€0 to €37902)	€4177 (€0 to €17701)	€9332 (€0 to €51195)	€45613 (€8567 to €96322)	€84141 (€28815 to €158674)
Carbapenem-resistant	€3589 (€0 to €10308)	€1398 (€0 to €7537)	€837 (€0 to €3500)	€1955 (€0 to €10615)	€9045 (€1933 to €19302)	€16822 (€5889 to €32158)
Colistin-resistant						**No data**
Total cost	*€21377 (€0 to €56027)*	*€8629 (€0 to €41855)*	*€5014 (€0 to €19371)*	*€11287 (€0 to €55417)*	*€54658 (€13722 to €108366)*	*€100964 (€40718 to €179297)*

Streptococcus pneumoniae						
Penicillin-resistant	€19768 (€13256 to €27880)	€8801 (€0 to €46571)	-	-	€1527 (€0 to €4810)	€30095 (€14947 to €68657)
Penicillin- and macrolide- resistant						**No data**
Total cost	*€19768 (€13256 to €27880)*	*€8801 (€0 to €46571)*	-	-	*€1527 (€0 to €4810)*	*€30095 (€14947 to €68657)*
Staphylococcus aureus						
Meticillin-resistant	€324728 (€0 to €746261)	€143825 (€0 to €768545)	€58710 (€0 to €323965)	€597695 (€0 to €3300229)	€1139806 (€0 to €2795336)	€2264764 (€515701 to €5423913)
Enterococcus faecalis / faecium						
Vancomycin-resistant	€547605 (€0 to €1450442)	€131505 (€0 to €768958)	€221263 (€0 to €1267889)	€1336082 (€0 to €7515230)	€836478 (€0 to €4881183)	€3072933 (€194134 to €10114450)
Total cost (infection)	€2360813 (€404848 to €5081228)	€1229099 (€224738 to €3133784)	€1027766 (€84459 to €3731599)	€2964228 (€0 to €11640429)	€4266931 (€677863 to €9973062)	€11848838 (€4810681 to €22302611)

Table A.8: Results of the second scenario analysis

Assumption; the total cost at different durations of stay in ICU (as a proportion of excess length of stay).

Threshold	Mean	Lower	Upper
0%	€11,637,513	€4,621,228	€22,957,975
5%	€12,653,590	€5,175,524	€24,235,820
10%	€13,682,894	€5,523,494	€26,216,548
15%	€14,850,237	€6,087,359	€28,173,650
20%	€16,049,755	€6,596,753	€30,165,781
25%	€17,067,642	€7,085,546	€32,605,473
30%	€18,212,236	€7,547,624	€34,498,290
35%	€19,264,181	€7,969,223	€36,604,375
40%	€20,438,286	€8,483,792	€38,940,307
45%	€21,445,906	€8,701,702	€41,154,909
50%	€22,757,940	€9,237,732	€43,822,291
55%	€23,754,733	€9,706,765	€45,666,504
60%	€24,926,834	€10,131,978	€48,016,084
65%	€26,088,656	€10,842,184	€49,424,492
70%	€27,033,583	€10,940,896	€52,056,314
75%	€28,336,748	€11,319,424	€54,041,798
80%	€29,322,716	€12,103,069	€56,569,599
85%	€30,461,702	€12,539,250	€58,968,957
90%	€31,645,216	€12,769,093	€60,500,489
95%	€32,842,765	€12,963,841	€63,411,888
100%	€33,949,931	€14,060,290	€64,224,879

Table A.9: Results of the third scenario analysis

Assumption; the total cost at different durations of stay in ICU (as a proportion of excess length of stay), assuming a ratio of 65% (BSI): 17% (RESP): 2% (UTI): 14% (SSI): 2% (OTH) admission to ICU at each threshold.

Threshold	Mean	Lower	Upper
0%	€11,440,096	€4,560,465	€22,188,549
5%	€11,766,794	€4,696,564	€22,650,755
10%	€11,972,759	€4,876,694	€22,613,395
15%	€12,155,050	€5,038,329	€22,767,375
20%	€12,386,220	€5,035,870	€23,525,152
25%	€12,508,428	€5,224,849	€23,818,335
30%	€12,811,302	€5,275,249	€24,153,148
35%	€12,939,156	€5,476,377	€24,401,740
40%	€13,165,858	€5,469,883	€24,632,132
45%	€13,332,976	€5,642,456	€25,052,125
50%	€13,542,385	€5,720,697	€25,411,593
55%	€13,735,960	€5,844,071	€25,509,983
60%	€13,950,937	€5,824,884	€25,915,283
65%	€14,171,874	€5,844,803	€26,583,154
70%	€14,451,164	€6,175,300	€26,821,340
75%	€14,616,496	€6,234,845	€27,194,803
80%	€14,729,534	€6,270,587	€27,639,465
85%	€14,966,018	€6,286,895	€27,661,620
90%	€15,201,415	€6,338,865	€28,118,663
95%	€15,324,798	€6,606,071	€28,012,461
100%	€15,515,044	€6,594,222	€28,723,702

Appendix 10 —BCoDE disease model outputs

Model	YLD			YLL			DALY			Cases per year			Deaths per year		
Ireland - Acinetobacter spp. CRACI BSI - model 45	0.33	0.45	0.59	1.30	3.42	5.57	1.75	3.88	6.03	1.00	1.00	1.00	0.08	0.20	0.33
Ireland - Acinetobacter spp. CRACI OTH - model 41	2.03E-03	4.87E-03	8.47E-03	0.00	0.00	0.00	2.03E-03	4.87E-03	8.47E-03	1.31	1.31	1.31	0.00	0.00	0.00
Ireland - Acinetobacter spp. CRACI RESP - model 44	0.41	0.53	0.65	0.84	1.02	1.20	1.33	1.55	1.77	1.69	1.69	1.69	0.05	0.06	0.07
Ireland - Acinetobacter spp. CRACI SSI - model 42	5.63E-04	2.06E-03	4.90E-03	0.64	0.64	0.64	0.64	0.64	0.64	1.06	1.06	1.06	0.04	0.04	0.04
Ireland - Acinetobacter spp. CRACI UTI - model 43	5.40E-04	1.33E-03	2.43E-03	0.00	0.00	0.00	5.40E-04	1.33E-03	2.43E-03	0.67	0.67	0.67	0.00	0.00	0.00
Ireland - Acinetobacter spp. ColRACI BSI - model 40	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Ireland - Acinetobacter spp. ColRACI OTH - model 36	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Ireland - Acinetobacter spp. ColRACI RESP - model 39	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Ireland - Acinetobacter spp. ColRACI SSI - model 37	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Ireland - Acinetobacter spp. ColRACI UTI - model 38	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Ireland - Acinetobacter spp. MDRACI BSI - model 50	4.42	5.18	6.03	23.85	39.15	54.19	29.04	44.34	59.41	5.00	5.00	5.00	0.62	1.00	1.37
Ireland - Acinetobacter spp. MDRACI OTH - model 46	0.02	0.02	0.03	0.00	0.00	0.00	0.02	0.02	0.03	6.56	6.56	6.56	0.00	0.00	0.00
Ireland - Acinetobacter spp. MDRACI RESP - model 49	5.33	6.07	6.84	10.70	11.90	13.09	16.53	17.96	19.37	8.46	8.46	8.46	0.28	0.30	0.33
Ireland - Acinetobacter spp. MDRACI SSI - model 47	6.08E-03	0.01	0.02	2.35	2.35	2.35	2.35	2.36	2.36	5.31	5.31	5.31	0.08	0.08	0.08
Ireland - Acinetobacter spp. MDRACI UTI - model 48	4.32E-03	6.79E-03	9.78E-03	0.00	0.00	0.00	4.32E-03	6.79E-03	9.78E-03	3.35	3.35	3.35	0.00	0.00	0.00
Ireland - Enterococcus faecalis and E. faecium VRE BSI - model 15	90.20	96.60	103.24	819.55	825.88	831.97	913.54	922.40	931.36	163.00	163.00	163.00	36.98	37.28	37.57
Ireland - Enterococcus faecalis and E. faecium VRE OTH - model 11	0.54	0.66	0.81	0.00	0.00	0.00	0.54	0.66	0.81	403.58	403.58	403.58	0.00	0.00	0.00

Model	YLD			YLL			DALY			Cases per year			Deaths per year		
Ireland - Enterococcus faecalis and E. faecium VRE RESP - model 14	29.86	31.52	33.22	58.61	61.22	63.84	89.69	92.73	95.96	76.76	76.76	76.76	2.64	2.76	2.89
Ireland - Enterococcus faecalis and E. faecium VRE SSI - model 12	0.92	1.20	1.51	247.53	247.60	247.67	248.56	248.80	249.07	560.47	560.47	560.47	14.70	14.70	14.70
Ireland - Enterococcus faecalis and E. faecium VRE UTI - model 13	0.26	0.32	0.39	0.00	0.00	0.00	0.26	0.32	0.39	172.18	172.18	172.18	0.00	0.00	0.00
Ireland - Escherichia coli 3GCREC BSI - model 65	183.67	194.89	206.54	1,167.53	1,257.28	1,347.06	1,361.42	1,451.84	1,543.22	395.00	395.00	395.00	61.88	68.39	74.96
Ireland - Escherichia coli 3GCREC OTH - model 61	0.60	0.76	0.92	0.00	0.00	0.00	0.60	0.76	0.92	226.24	226.24	226.24	0.00	0.00	0.00
Ireland - Escherichia coli 3GCREC RESP - model 64	76.63	80.29	84.01	149.41	155.38	161.26	228.68	235.71	242.57	234.78	234.78	234.78	8.02	8.45	8.88
Ireland - Escherichia coli 3GCREC SSI - model 62	0.69	0.91	1.18	165.66	165.72	165.78	166.45	166.63	166.86	427.11	427.11	427.11	12.57	12.57	12.57
Ireland - Escherichia coli 3GCREC UTI - model 63	0.90	1.12	1.36	0.00	0.00	0.00	0.90	1.12	1.36	570.23	570.23	570.23	0.00	0.00	0.00
Ireland - Escherichia coli CREC BSI - model 60	0.34	0.46	0.60	3.48	5.98	8.45	3.94	6.44	8.91	1.00	1.00	1.00	0.21	0.36	0.51
Ireland - Escherichia coli CREC OTH - model 56	6.75E-04	1.87E-03	4.10E-03	0.00	0.00	0.00	6.75E-04	1.87E-03	4.10E-03	0.57	0.57	0.57	0.00	0.00	0.00
Ireland - Escherichia coli CREC RESP - model 59	0.14	0.18	0.23	0.29	0.36	0.42	0.46	0.54	0.62	0.59	0.59	0.59	0.02	0.02	0.02
Ireland - Escherichia coli CREC SSI - model 57	5.61E-04	2.14E-03	4.91E-03	0.65	0.65	0.65	0.65	0.65	0.66	1.08	1.08	1.08	0.04	0.04	0.04
Ireland - Escherichia coli CREC UTI - model 58	1.11E-03	2.83E-03	5.77E-03	0.00	0.00	0.00	1.11E-03	2.83E-03	5.77E-03	1.44	1.44	1.44	0.00	0.00	0.00
Ireland - Escherichia coli ColREC BSI - model 55	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Ireland - Escherichia coli ColREC OTH - model 51	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Ireland - Escherichia coli ColREC RESP - model 54	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Ireland - Escherichia coli ColREC SSI - model 52	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Ireland - Escherichia coli ColREC UTI - model 53	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Model	YLD			YLL			DALY			Cases per year			Deaths per year		
Ireland - Klebsiella pneumoniae 3GCRKP BSI - model 80	50.25	54.53	59.17	328.30	342.99	357.30	382.11	397.58	412.66	82.00	82.00	82.00	13.08	13.69	14.24
Ireland - Klebsiella pneumoniae 3GCRKP OTH - model 76	0.25	0.31	0.37	0.00	0.00	0.00	0.25	0.31	0.37	92.66	92.66	92.66	0.00	0.00	0.00
Ireland - Klebsiella pneumoniae 3GCRKP RESP - model 79	38.51	41.12	43.70	75.70	79.78	83.85	116.11	120.87	125.78	88.51	88.51	88.51	3.03	3.19	3.34
Ireland - Klebsiella pneumoniae 3GCRKP SSI - model 77	0.10	0.13	0.17	26.07	26.08	26.09	26.19	26.22	26.25	62.85	62.85	62.85	1.56	1.56	1.56
Ireland - Klebsiella pneumoniae 3GCRKP UTI - model 78	0.18	0.22	0.26	0.00	0.00	0.00	0.18	0.22	0.26	110.96	110.96	110.96	0.00	0.00	0.00
Ireland - Klebsiella pneumoniae CRKP BSI - model 75	3.03	3.49	3.99	34.99	45.93	56.72	38.43	49.45	60.23	5.00	5.00	5.00	1.38	1.78	2.17
Ireland - Klebsiella pneumoniae CRKP OTH - model 71	6.66E-03	0.01	0.01	0.00	0.00	0.00	6.66E-03	0.01	0.01	2.95	2.95	2.95	0.00	0.00	0.00
Ireland - Klebsiella pneumoniae CRKP RESP - model 74	1.22	1.37	1.52	2.42	2.65	2.88	3.75	4.01	4.29	2.85	2.85	2.85	0.09	0.10	0.11
Ireland - Klebsiella pneumoniae CRKP SSI - model 72	3.61E-03	6.06E-03	8.97E-03	1.12	1.12	1.12	1.12	1.12	1.13	2.85	2.85	2.85	0.06	0.06	0.06
Ireland - Klebsiella pneumoniae CRKP UTI - model 73	4.55E-03	6.85E-03	9.59E-03	0.00	0.00	0.00	4.55E-03	6.85E-03	9.59E-03	3.30	3.30	3.30	0.00	0.00	0.00
Ireland - Klebsiella pneumoniae ColRKP BSI - model 70	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Ireland - Klebsiella pneumoniae ColRKP OTH - model 66	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Ireland - Klebsiella pneumoniae ColRKP RESP - model 69	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Ireland - Klebsiella pneumoniae ColRKP SSI - model 67	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Ireland - Klebsiella pneumoniae ColRKP UTI - model 68	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Ireland - Pseudomonas aeruginosa CRPA BSI - model 30	8.85	9.77	10.75	61.34	83.02	103.85	71.00	92.78	113.81	16.00	16.00	16.00	2.75	3.66	4.57

Model	YLD			YLL			DALY			Cases per year			Deaths per year		
Ireland - Pseudomonas aeruginosa CRPA OTH - model 26	0.09	0.11	0.14	0.00	0.00	0.00	0.09	0.11	0.14	31.20	31.20	31.20	0.00	0.00	0.00
Ireland - Pseudomonas aeruginosa CRPA RESP - model 29	12.69	13.73	14.79	37.86	48.57	59.36	51.60	62.33	73.17	32.48	32.48	32.48	1.69	2.14	2.60
Ireland - Pseudomonas aeruginosa CRPA SSI - model 27	0.03	0.04	0.05	7.83	7.84	7.84	7.86	7.87	7.88	17.09	17.09	17.09	0.47	0.47	0.47
Ireland - Pseudomonas aeruginosa CRPA UTI - model 28	0.02	0.03	0.04	0.00	0.00	0.00	0.02	0.03	0.04	15.49	15.49	15.49	0.00	0.00	0.00
Ireland - Pseudomonas aeruginosa ColRPA BSI - model 25	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Ireland - Pseudomonas aeruginosa ColRPA OTH - model 21	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Ireland - Pseudomonas aeruginosa ColRPA RESP - model 24	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Ireland - Pseudomonas aeruginosa ColRPA SSI - model 22	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Ireland - Pseudomonas aeruginosa ColRPA UTI - model 23	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Ireland - Pseudomonas aeruginosa MDRPA BSI - model 35	3.68	4.15	4.67	22.24	32.37	42.74	26.39	36.53	46.91	8.00	8.00	8.00	1.19	1.69	2.20
Ireland - Pseudomonas aeruginosa MDRPA OTH - model 31	0.04	0.06	0.08	0.00	0.00	0.00	0.04	0.06	0.08	15.60	15.60	15.60	0.00	0.00	0.00
Ireland - Pseudomonas aeruginosa MDRPA RESP - model 34	5.27	5.80	6.37	14.20	19.44	24.73	20.00	25.24	30.56	16.24	16.24	16.24	0.76	1.01	1.27
Ireland - Pseudomonas aeruginosa MDRPA SSI - model 32	0.01	0.02	0.03	4.30	4.30	4.30	4.31	4.32	4.32	8.55	8.55	8.55	0.25	0.25	0.25

Model	YLD			YLL			DALY			Cases per year			Deaths per year		
Ireland - Pseudomonas aeruginosa MDRPA UTI - model 33	0.01	0.02	0.02	0.00	0.00	0.00	0.01	0.02	0.02	7.75	7.75	7.75	0.00	0.00	0.00
Ireland - Staphylococcus aureus MRSA BSI - model 20	68.66	73.50	78.62	476.20	493.17	510.71	548.92	566.75	584.70	135.00	135.00	135.00	23.26	24.26	25.27
Ireland - Staphylococcus aureus MRSA OTH - model 16	0.56	0.70	0.85	0.00	0.00	0.00	0.56	0.70	0.85	214.74	214.74	214.74	0.00	0.00	0.00
Ireland - Staphylococcus aureus MRSA RESP - model 19	55.72	58.69	61.76	109.03	113.84	118.57	166.85	172.54	178.20	155.48	155.48	155.48	5.32	5.59	5.88
Ireland - Staphylococcus aureus MRSA SSI - model 17	0.50	0.66	0.85	124.10	124.14	124.18	124.66	124.80	124.96	309.70	309.70	309.70	8.55	8.55	8.55
Ireland - Staphylococcus aureus MRSA UTI - model 18	0.10	0.13	0.16	0.00	0.00	0.00	0.10	0.13	0.16	68.47	68.47	68.47	0.00	0.00	0.00
Ireland - Streptococcus pneumoniae PMRSP BSI - model 6	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Ireland - Streptococcus pneumoniae PMRSP OTH - model 2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Ireland - Streptococcus pneumoniae PMRSP RESP - model 5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Ireland - Streptococcus pneumoniae PMRSP SSI - model 3	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Ireland - Streptococcus pneumoniae PMRSP UTI - model 4	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Ireland - Streptococcus pneumoniae PRSP BSI - model 10	3.97	4.81	5.76	30.06	32.94	35.80	34.71	37.76	40.81	3.00	3.00	3.00	0.50	0.54	0.58
Ireland - Streptococcus pneumoniae PRSP OTH - model 7	1.15E-03	1.92E-03	2.84E-03	0.00	0.00	0.00	1.15E-03	1.92E-03	2.84E-03	0.99	0.99	0.99	0.00	0.00	0.00
Ireland - Streptococcus pneumoniae PRSP RESP - model 1	8.53	9.92	11.40	17.32	19.57	21.80	26.88	29.49	32.17	8.91	8.91	8.91	0.29	0.32	0.36

Model	YLD			YLL			DALY			Cases per year			Deaths per year		
Ireland - Streptococcus pneumoniae PRSP SSI - model 8	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Ireland - Streptococcus pneumoniae PRSP UTI - model 9	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Aggregate	**688.55**	**704.75**	**720.80**	**4,157.21**	**4,255.59**	**4,356.23**	**4,860.70**	**4,960.60**	**5,061.70**	**2431.91**	**4787.05**	**14764.32**	**208.38**	**215.11**	**221.90**

Published by the Health Information and Quality Authority (HIQA).
For further information please contact:
Health Information and Quality Authority
George's Court
George's Lane
Smithfield
Dublin 7
D07 E98Y

+353 (0)1 8147400
info@hiqa.ie
www.hiqa.ie