The economics of a silent pandemic

A health economic analysis of antibiotic resistance in Sweden

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Gothenburg 2022

Inside cover illustration: microscopic image of methicillin-resistant *Staphylococcus aureus* (MRSA). Photo credit to Janice Haney Car. Photo publicly available at https://phil.cdc.gov/Details.aspx?pid=10046.

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ISBN 978-91-8009-885-4 (PRINT)
ISBN 978-91-8009-886-1 (PDF)

Printed in Borås, Sweden 2022
Printed by Stema Specialtryck AB

If everything was perfect,
you would never learn and you would never grow.

Beyoncé Knowles

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ABSTRACT

The overall aim of this thesis was to analyze the health economic consequences of antibiotic resistance in Sweden, and to assess the implications of methodological assumptions related to measuring health in health economic analysis.

The thesis consists of four papers. Paper I analyze the development of antibiotic resistance in Sweden and estimates the associated costs of healthcare. In total, healthcare costs were estimated to more than EUR 23 million in 2018 and were expected to more than triple by 2050. The analysis is based on the additional costs of resistance compared to susceptible bacteria. Paper II estimates the cost of production loss for hospitalized patients absent from work due to a resistant infection. Results shows that sick leave days were, on average, eight days more than for infections caused by susceptible bacteria. Paper III analyzes how QALY estimates from different instruments and value sets relates to each other. Results show that the EQ-5D Burström and the SF-6D Brazier value sets rendered most comparable estimates, independent of health state severity. Finally, paper IV examines whether it is cost-effective to treat patients with severe urinary tract infection with temocillin instead of cefotaxime. The results show that it is cost-effective given a certain price level.

The results from this thesis, and the studies included, suggest a significant health economic impact of antibiotic resistance in Sweden. Even with its limitations, health economic analysis is an essential tool in understanding serious health problems in the light of limited resources. Such analyses enable allocation of resources towards interventions with the most value for money.

Keywords: health economics, cost-effectiveness analysis, antibiotic resistance, cost-of-illness, production loss, QALY instruments, QALY value set.

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SAMMANFATTNING PÅ SVENSKA

Antibiotikaresistens är ett stort och växande problem över hela världen. Ända sedan det första antibiotikumet introducerades som behandling på 1940-talet har forskare varnat för utvecklingen av resistens. De huvudsakliga effekterna av resistens ses inom sjukvården där vissa infektioner som vi länge tagit för givet är behandlingsbara nu är svåra att bota. Men effekterna av resistens sträcker sig längre än så, bland annat leder det till ökade kostnader för vården då patienter blir inneliggande på sjukhuset längre och kostnader för samhället i form av minskad produktion när anställda är frånvarande från arbetet.

I denna avhandling utreder jag de hälsoekonomiska konsekvenserna av antibiotikaresistens i Sverige. Hälsoekonomisk analys, som är en disciplin inom nationalekonomin, syftar till att utreda kostnader i relation till hälsoeffekter för sjukdomar, andra tillstånd eller åtgärder inom sjukvården. Denna typ av utredningar syftar till att stödja beslutsfattare vid prioritering av olika insatser inom hälso- och sjukvården. Prioriteringar är nödvändiga eftersom efterfrågan på hälsa är oändlig, medan budgeten är begränsad.

Hälsoekonomiska analyser kan göras utifrån ett hälso- och sjukvårdsperspektiv, vilket innebär att hänsyn tas till de kostnader och effekter som uppkommer inom sjukvårdssystemet, eller ur ett samhällsperspektiv, vilket syftar till att ta hänsyn till alla relevanta kostnader och effekter oavsett vem de faller på. Denna avhandling syftar till att utreda kostnader relaterade till antibiotikaresistens för hälso- och sjukvården och produktionsbortfall till följd av frånvaro från arbete. Vidare inkluderas en kostnadseffektivitetsanalys av en alternativ behandlingsmetod som kan minska utvecklingen av resistens efter genomgången behandling med antibiotika, samt en analys av hur hälsoekonomiska metodval kan påverka utfallet.

Delstudie I är en analys av hur antibiotikaresistens förväntas utvecklas över tid i Sverige och vilka kostnader det innebär för sjukvården. Totalt beräknades kostnaderna uppgå till över 230 miljoner kronor för vården 2018 och väntas öka med mer än tre gånger till 2050. Studien tittar på den ökade kostnaden för resistens jämfört med om infektionen var orsakad av en bakterie som var behandlingsbar med antibiotika. Delstudie II undersöker hur stor kostnaden för förlorad produktion är för de personer som vårdas på sjukhus för en infektion orsakad av resistent bakterie. Studien visar att en person med antibiotikaresistent bakterie i genomsnitt är frånvarande åtta dagar mer än de utan resistens. Delstudie III analyserar hur tre olika metoder skattar livskvalitet (QALY), hur dessa skattningar förhåller sig till varandra, samt vilken påverkan eventuella skillnader kan få på resultatet av den hälsoekonomiska analysen. Resultatet visar att två av metoderna resulterar i jämförbara skattningar, och att skillnaden mot den tredje metoden är störst vid hälsotillstånd med sämre hälsa. Slutligen, delstudie IV

undersöker om det är kostnadseffektivt att behandla patienter med allvarlig urinvägsinfektion med temocillin istället för cefotaxim (som är det som används idag). Denna studie tar hänsyn till kostnader för sjukvården, produktionsförluster, påverkan på livskvalitet för patienten och risken för utveckling av antibiotikaresistens. Resultaten visar att det är kostnadseffektivt givet att priset för temocillin är i nivå med det genomsnittliga priset i Europa.

Resultaten från denna avhandling, och de studier som ingår, visar på en betydande hälsoekonomisk effekt av antibiotikaresistens i Sverige. Hälsoekonomisk analys är ett viktigt verktyg för att förstå effekten av allvarliga hälsoproblem för samhället. Det möjliggör även prioritering av de insatser inom hälso- och sjukvården som ger mest hälsa för pengarna.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. **Larsson, S.**, Prioux, M., Fasth, T., Ternhag, A., Struwe, J., Dohnhammar, U., Brouwers, L. A microsimulation model projecting the healthcare costs for resistance to antibacterial drugs in Sweden.

European Journal of Public Health, 2019; 29:3: 392–396.

II. **Larsson, S.**, Svensson, M., Ternhag, A. Production loss and sick leave caused by antibiotic resistance: a register-based cohort study.

BMC Public Health, 2022; 22, 527.

III. **Larsson, S.**, Persson, J. Measuring quality of life using different value sets for EQ-5D or SF-6D: Are the results comparable?

Submitted manuscript.

IV. **Larsson, S.**, Edlund, C., Nauclér, P., Svensson M., Ternhag, A. Cost-effectiveness analysis of temocillin treatment in febrile UTI patients accounting for the emergence of antibiotic resistance.

Submitted manuscript.

CONTENT

ABBREVIATIONS

ABR	Antibiotic resistance
AMR	Antimicrobial resistance
ARI	Antimicrobial resistant infections
ASP	Antimicrobial stewardship program
CBA	Cost-benefit analysis
CDC	The Centre for Disease Prevention and Control
CEA	Cost-effectiveness analysis
COI	Cost of illness
CPE	Carbapenemase-producing Enterobacteriaceae
CUA	Cost-utility analysis
DALY	Disability-adjusted life years
DCE	Discrete choice experiment
DSA	Deterministic sensitivity analysis
ECDC	The European Centre for Disease Prevention and Control
EEA	European Economic Area
ESBL	Extended-spectrum beta-lactamase (ESBL) in Enterobacteriaceae
EUR	Euro
GBD	Global burden of disease
GDP	Gross domestic product
HDI	Human Development Index
HRQoL	Health related quality of life
ICD	International Classification of Diseases
ICER	Incremental cost-effectiveness ratio
LTSL	Long-term sick leave
MRSA	Methicillin resistant Staphylococcus aureus
NBHW	The Swedish National Board of Health and Welfare
NICE	The National Institute for Health and Care Excellence
OECD	Organisation for Economic Co-operation and Development
PHAS	The Public Health Agency of Sweden
PNSP	Penicillin non-susceptible Pneumococci
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life years
SEK	Swedish krona (currency)
SSIA	The Swedish Social Insurance Agency
TLV	The Dental and Pharmaceutical Benefit Agency of Sweden
TTO	Time-trade-off
UTI	Urinary tract infection
VRE	Vancomycin-resistant Enterococci
WHO	World Health Organization
WTP	Willingness to pay

DEFINITIONS IN SHORT

Broad-spectrum antibiotics	Active against many different types of bacteria
Incidence	The number of individuals who develop a specific disease or experience a specific health-related event during a defined time period
Morbidity	Refers to having a disease or a symptom of disease, or to the amount of disease within a population
Mortality	Refers to the number of deaths that have occurred due to a specific illness or condition
Narrow-spectrum antibiotics	Active against one or a few types of bacteria
Pathogenic bacteria	Bacteria that can cause infection (compared to *apathogenic bacteria* that do not cause infection)
Prevalence	The total number of individuals in a population who have a disease or health condition at a specific time period
Prophylaxis	Treatment given to prevent infection
Second- or third-line antibiotics	Antibiotics that are given when initial treatment (first- or second-line antibiotics) are not effective to treat the infection
SmiNet	The Swedish communicable disease database

1 INTRODUCTION

The ability of antibiotics to treat bacterial infections was first discovered in 1928 when Alexander Fleming discovered the effect of the penicillin [1, 2]. However, it took over a decade before penicillin was available to treat bacterial infections [3]. Before the discovery of antibiotics, infections were treated with, for example, heavy metals such as mercury or arsenic, which often had side effects worse than the disease [4].

When penicillin was launched as a treatment in the early 1940s, scientists already knew about the possibilities of bacteria developing resistance to antibiotics. In his Nobel lecture in 1945, Fleming warned about the consequences of misusing penicillin and the possible adverse effects of the development of resistance [5].

Antibiotic resistance (ABR) is the ability of bacteria to protect themselves against the effects of certain antibiotics. Meaning, antibiotics could lose their effectiveness in treating infections if the bacteria causing it is resistant to the specific treatment. ABR is part of the broader concept of antimicrobial resistance (AMR), which refers to all kinds of microorganisms' ability to develop resistance to treatment. This thesis will focus on the effects of ABR.

Antibiotics are widely used in healthcare. Besides being the primary treatment option in bacteria-caused infectious diseases, many innovative treatments, for example, cancer care or transplantations, depend on effective antibiotics to avoid infections that could jeopardize the outcome of the treated patient. Without effective antibiotics, many patients beside those with an infectious disease will be exposed to an increased risk of complications. Particularly immunosuppressed patients. Furthermore, infections caused by resistant bacteria are associated with higher mortality, extended hospital stay, and poorer clinical outcome than infections caused by susceptible bacteria [6].

Antibiotic resistance (ABR) has been pointed out as one of the biggest threats to global health today [6, 7]. In the EU and the European Economic Area (EEA) alone, ABR was calculated to cause more than 33,000 deaths in 2015 [8]. With a growing number of cases globally and a small amount of new effective antibiotics

developed, the spread of antibiotic resistant bacteria could undermine health systems worldwide. ABR has therefore been referred to as a *silent pandemic* [9].

Overall, ABR negatively impacts human health. The effects of ABR are greater than the lacking medical effect for patients. The need for the healthcare personnel to search for effective alternative treatments, the resource use of isolating patients to avoid spreading infections, or even death, induce economic consequences on the healthcare system and, by extension, society. However, the total effects of resistance are still debated. Over the last decade, the interest in the economic consequences of ABR has increased significantly. Several studies [10-15] have attempted to calculate the global costs of resistance using hypothetical scenarios of the development of resistance. Most of these calculations are based on average global development and the average effects of resistance, not considering country-specific values.

Health economic analyses are a tool to help decision-makers understand the consequences of healthcare interventions and make an informed decision about which treatments should be funded. Since resources are scarce, while the needs are seemingly endless, prioritizing within healthcare is necessary, and optimal resource allocation is essential. In health economic analyses, the costs and health effects of different interventions are weighed against each other, making it possible to compare both costs and health outcomes of relevant interventions. Furthermore, applying economic evaluation methods to healthcare interventions makes it possible to examine the long-term effects of interventions through economic decision-analytic modeling.

ABR has increased globally over several decades, resulting in a need for new antibiotic drugs that are effective against resistant bacteria [16]. Nevertheless, the pharmaceutical companies developing new antibiotics face significant challenges of both scientific difficulties and high development costs. Making interventions to curb resistance and save effective antibiotics for future use even more critical. Resources are already invested in various antibiotic stewardship programs to enhance the use of antibiotics in, for example, diagnostics, drug choices, and duration of treatment to reduce or slow down the development of resistance [17]. However, to guide the allocation of resources to combat ABR, there is also a need for accurate estimates of the total burden of resistance, including estimates of the economic impact on the healthcare sector and society.

2 HEALTH ECONOMIC PERSPECTIVES

The cost of healthcare is increasing rapidly around the world. According to the Organisation for Economic Co-operation and Development (OECD), the average growth of healthcare spending per capita was significantly higher than the gross domestic product (GDP) per capita growth between 1990 and 2019 in most OECD countries, as seen in Figure 1 [18, 19]. Because of changes in allocations of healthcare resource use during the Covid pandemic, data from 2020 and 2021 has been excluded from this analysis.

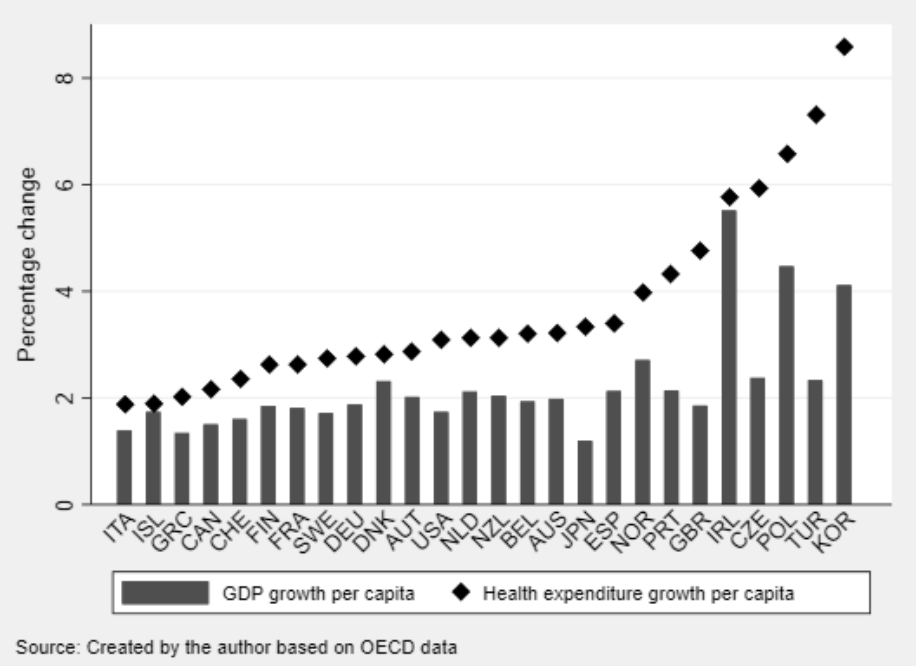

Figure 1. Average growth of healthcare spending and GDP per capita in 1990-2019

In order to use the economic resources as effectively as possible, it is essential to study the allocation of resource use in the healthcare sector. Economic analysis is an essential tool in decision making to prioritize between different interventions

and medical treatments to make sure that the healthcare spending is used to produce as much health as possible.

The choice of most appropriate economic analysis depends on the topic or the question of interest. For example, the analysis can focus on the overall costs of a disease or condition, often referred to as cost-of-illness studies, or it can compare different interventions or treatments, taking the differences in costs and effects into account, often referred to as cost analysis or cost-effectiveness analysis. Table 1 presents different methods of health economic analysis.

Table 1. Methods for health economic analysis

Method	**Costs**	**Health effects**	**Results**
Cost-of-illness analysis	All identifiable	Depends on the area of interest. Ex. life-years, avoided cases, effects on risk factors, DALY	Cost and health effects separately
Cost analysis	All identifiable	No health effects	Net costs
Cost-effectiveness analysis (or cost-utility analysis)	All identifiable	Often Quality of Life measures, such as QALY. Could also be disease-specific measures	Cost per health effect (ICER)
Cost-benefit analysis	All identifiable	Health effects measured in monetary terms	Net present value

A cost-of-illness (COI) study aims to describe the economic and health related burden of an illness or medical condition on society. This means that all relevant costs of the condition, including possible external effects, need to be identified and valued. In addition, health effects are measured and presented separately, as, for example, avoided cases or life-years lost [20]. COIs could, hence, be used to estimate the total burden of antibiotic resistance. Furthermore, since COI studies measure the total economic burden, the results could also be seen as the potential benefits of a healthcare intervention that eradicates the illness [21].

In contrast to COI, cost-effectiveness analysis (CEA) or cost-utility analysis (CUA) are used to compare different interventions to each other, rather than estimating the total burden. CEA is the most commonly used, and considers both the costs and the health benefits of an intervention or a treatment compared to an alternative treatment strategy [22]. The costs and benefits of the alternative treatment are usually measured as opportunity costs, i.e., the potential benefits lost when choosing one option over the other. A CEA is suitable when decision-makers have a limited budget and need to prioritize between two alternatives as it estimates the additional costs and benefits of treatment in relation to the alternative treatment [23].

The result from a CEA is often presented as an incremental cost-effectiveness ratio (ICER). The ICER presents the ratio between the new treatment's cost, treatment A, relative to the cost of the old treatment, treatment B, and the health effects from treatment A relative to that of treatment B. The ICER is calculated through the following formula:

$$ICER = \frac{Cost\ A - Cost\ B}{Effect\ A - Effect\ B} = \frac{\Delta C}{\Delta E}$$

There are four potential outcomes of an ICER demonstrated in the cost-effectiveness plane in Figure 2;

1. new treatment is more costly, but less effective than the alternative treatment and is, hence, dominated by the alternative treatment,
2. new treatment is more costly and more effective than the alternative treatment,
3. new treatment is less costly and less effective than treatment B, and
4. new treatment is less costly but more effective than the alternative treatment, and hence, dominates the alternative treatment.

In outcome 1 and 4, one treatment dominates the other, and the relative cost-effectiveness is given. The implication of outcome 2 and 3, however, is ambiguous, and the cost-effectiveness depends on what given monetary threshold

is considered cost-effective [23]. If an estimated ICER falls within the green shadowed area, the intervention would be considered cost-effective. However, the size of the area depends on the given threshold for cost-effectiveness.

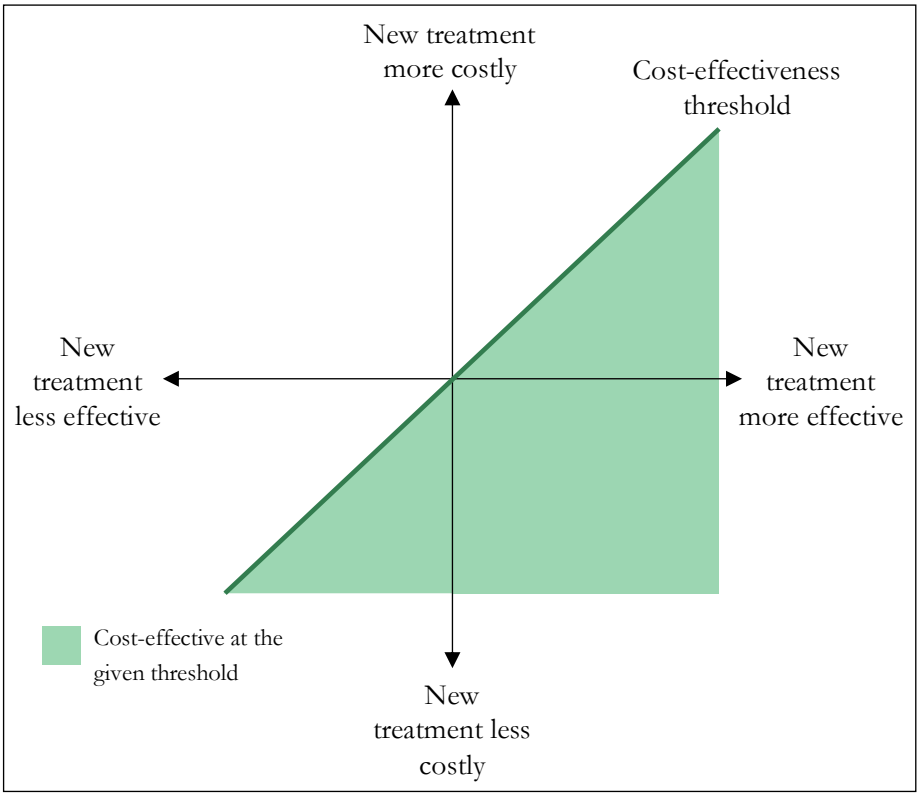

Figure 2. The cost-effectiveness plane

Whether a treatment is considered cost-effective or not depends on the level of the cost-effectiveness threshold. The threshold slope represents the highest acceptable ICER for a specific treatment. Figure 2 shows that larger health effects allow for higher costs [23]. More information on thresholds in section *2.3 Cost-effectiveness threshold.*

Cost analysis or cost-benefit analysis (CBA), are, like CEA and CUA, methods to compare different interventions. However, cost analysis and CBA uses only monetary terms [23]. In the simplest case, only costs are considered, i.e., a cost analysis. However, it is also possible to transform health effects into monetary terms using a willingness to pay to estimate one unit of the health effect. Cost analysis could also be applied if effects are equal or non-inferior between

interventions. Then, the results are presented as a net cost, which is the difference in the sum of costs and monetary health benefits between interventions. In case there is no incremental health effects from the new treatment, results from a CEA will be comparable to the results from a cost analysis.

In paper I, we conducted a COI study to estimate the total economic impact of ABR in Sweden, while we used a CEA to study the incremental effects of using temocillin treatment in febrile UTI patients instead of cefotaxime in paper IV. In both studies, costs were divided into healthcare costs and production loss costs. Analyses that include both healthcare costs and production loss are often referred to as having a societal perspective compared to a healthcare perspective that does not include production loss costs or other costs outside of the healthcare sector.

2.1 COSTS

2.1.1 Healthcare costs

Healthcare costs refer to resource use attributed to a specific disease or treatment within the healthcare sector. Examples of healthcare costs are costs for drugs, personnel, and aids. Healthcare costs could also arise in other sectors than the healthcare sector, for example, in elderly care in the municipality sector [20, 23].

Healthcare costs could be directly and indirectly related to the disease or treatment of interest. Direct healthcare costs are those arising directly from the disease. In contrast, indirect costs could refer to costs related to, for example, secondary infections due to inappropriate antibiotic use in the primary infection or the added treatment costs of contracting a hospital-acquired bacterial infection while treated for something unrelated to the infectious disease. When modeling healthcare consumption, it is essential to identify all relevant aspects that significantly impact the disease to make accurate estimates. It is, however, not always as straightforward as one could wish to estimate the impact of all possible aspects. It is essential to understand its implications if some aspects are left out and how that will impact the cost estimates. For example, if it is not possible to quantify the number of patients with an infectious disease in need of intensive care, only for those in the general infection ward, then the total healthcare costs will probably be underestimated since treatment in the intensive care unit (ICU) usually is more expensive than treatment in a general ward [24]. Under- or overestimations could be considered a conservative assumption if the assumption is not more beneficial to the treatment evaluated than to the alternative treatment. However, as in this example, if costs are assumed to be lower than what is reasonable to believe it is possible that the underestimation could lead to

misinterpretations of the results. It is therefore essential to be aware of how assumptions or choice of different references for cost estimates could impact the result.

In paper I, we used data from national registers and information on resource use for patient care and contact tracing to quantify the additional consumption of healthcare due to infections caused by antibiotic resistance, compared to infections caused by susceptible bacteria. Healthcare costs were defined as the cost of days in hospital care, outpatient visits, primary care visits and the consumption of prescribed antibiotics. Estimates of healthcare costs from paper I were used in paper IV.

More information on the data management for all studies is presented in section *6 Data*.

2.1.2 Non-healthcare costs

Non-healthcare costs, such as production loss cost or cost of increased consumption, are costs outside of the healthcare sector that affect society and are directly or indirectly related to the disease or treatment analyzed.

Production loss cost is often described as the resources lost indirectly due to illness or treatment, such as absence from work or reduced leisure time. The most common way to measure production loss is time away from work (i.e., absenteeism) [23], but it could also be measured as reduced work productivity when working (i.e., presentism) [25]. However, even though presentism is a known phenomenon [25], it is hard to estimate the reduced work capacity to a particular health state or disease that does not occur due to normal fluctuations in work capacity overall. Furthermore, work capacity differs between employees, and a base line capacity is hard to estimate. Because of this, I have chosen to only focus on absenteeism in this thesis.

There are two different methods for estimating the value of production loss: the human capital method and the friction cost method [23]. The human capital method is based on the number of hours lost in work and values the production loss from wage (incl. social fees) [23]. Earlier research has argued that the human capital approach's drawbacks are that an individual absent from work for a more extended period will be (temporarily or permanently) replaced by other work capacities [26], which is not considered in this method.

Because of the potential for overestimating the production loss using the human capital method, several researchers argue that the friction cost method should be used [27, 28]. The friction cost method only considers the time before a former unemployed individual can fully replace the one that is sick.

Production loss is usually not included in health economic analysis if individuals are not of working age. However, this approach has been criticized since retirement pensioners could contribute with informal production that could be included in the analysis [23, 29]. In contrast, when the analysis includes children, it is common to include production loss for parents when absent from work to care of their sick child. Including production loss for individuals under 65 only could mean that interventions aimed at those above 65 could be less cost-effective and hence be given lower priority. In order to overcome these issues, the cost of lost production for people above 65 years of age can instead be based on loss of leisure time, where one hour is valued as 35 percent of the average gross wage [30].

The use of production loss in health economic analyses is well debated since it could imply that human life is more worth saving if people are still of the working-age or for young people with long life expectancy. However, according to Swedish healthcare laws, all humans have the same value (the *human-dignity principle*), and resources should be allocated to those in greatest need (the *need- and solidarity principle*) [31]. Hence, according to these principles, healthcare priorities should not discriminate based on, for example, age or capacity to work.

Overall, the inclusion of production loss costs could impact the comparability between different health economic analyses since different age groups could be treated differently. It is often argued that the inclusion of production loss costs is negative for elderly persons who are not in the workforce and have higher healthcare consumption. Health economic guidelines differ regarding the choice of perspective in different countries. For example, in the UK [32] and France [33] governmental bodies recommend using a healthcare perspective as a base-case analysis, while in Sweden [34, 35] and the Netherlands [36] it is recommend to use a societal perspective, including both effects on the healthcare sector and on productivity. Generally, most countries welcome an analysis of production loss presented in the supplementary material [37]. The European Network for Health Technology Assessments (EUnetHTA) recommends that production loss costs be included in the main analysis [37].

Paper II used registered data to estimate the production loss from sick leave due to ABR in Sweden. In addition, paper II results were used to estimate the production loss costs in paper IV. More information on data management and results from paper II is presented in sections *6 Data* and *7 Results*, respectively.

2.2 HEALTH EFFECTS

Health economic evaluations aim to increase the knowledge about the impact of different health states or interventions on both costs and health in the affected population or society. Depending on the type of analysis, information on the population's health status, often measured as the "burden of disease", or the specific effects of changes in health from an intervention, often measured as "quality of life" are required.

Health effects could be measured in different ways. Population health indicators are, for example, numbers of new and existing cases of a specific disease (i.e., incidence and prevalence), life expectancy, and disease-specific mortality rates [38]. Common for all these measures is that they only measure mortality or morbidity. However, since the quality of life can be just as important as extended life expectancy, measures that combine these aspects are essential in health economic evaluations [39]. These combined measures are often referred to as health-related quality of life (HRQoL). Health effects measured as HRQoL allow for comparison and prioritization between interventions within different therapeutical areas, which is an advantage when resources should be allocated between different therapeutic areas in healthcare. If health effects are measured on a common scale, it is possible to compare the health outcome of an infectious disease to, for example, an episode of multiple sclerosis (MS).

HRQoL can be measured in different ways, which mainly depends on the study's objective. For example, if the objective is the total burden of disease in a population, then disability-adjusted life years (DALY) is the most common used, while if the objective is the improvements of treatment, then quality-adjusted life years (QALY) is the most common used [23].

2.2.1 Disability-adjusted life years (DALY)

Disability-Adjusted Life Year (DALY) measures the number of life-years lost due to bad health and mortality. It stems from the Global Burden of Disease (GBD) projects initiated in the early 1990s [40] and has become a common measure of population health.

Estimating DALY assumes that every person has an initial number of life years potentially lived in optimal health within a lifetime. Healthy life years could be lost by living with illness and/or dying before the assumed life expectancy [40, 41]. The DALY is calculated by summing these losses in healthy life years. For instance, five DALYs correspond to five lost years of a healthy life attributable to morbidity, mortality, or both.

On a population level, diseases that sum to a high amount of DALYs will have a more significant impact on public health than those with a smaller amount of DALYs. DALY is the sum of two parts; Years of Life Lost due to premature mortality (YLL) and Years Lived with Disability (YLD).

The mortality component, YLL, is calculated based on the average remaining life expectancy at the time of death and the number of deaths from that particular health state or disease.

$$\text{YLL} = \text{Number of deaths} \times \text{Remaining life expectancy at the age of death}$$

The first GBD studies used the life at birth of 80 for males and 82.5 for females [40]. Different life expectancies for men and women have been common. However, recent projections have shown that the discrepancy between sexes is likely to shrink by 2030 in most countries [42]. Therefore, the World Health Organization (WHO) Global Health Estimates are based on the projected frontier life expectancy for 2050, with the highest life expectancy at birth being 90 for both males and females [41]. Statistics Sweden has estimated the life expectancy in Sweden to be 82.6 for males and 86.5 for females in 2050 [43]. Using the WHO's estimation to calculate YLL would result in the following example: a person dying at the age of 80 would lose 10 years of life in potentially optimal health, accounting for 10 YLL ($\text{YLL} = 1 \times 10 = 10$).

The morbidity component, YLD, is calculated based on the duration of the disability or disease of interest, a disease-specific disability weight, and the number of cases from that particular health state or disease.

$$\text{YLD} = \text{Number of cases} \times \text{Duration of disability} \times \text{Disability weight}$$

The disability weight ranges from zero (perfect health) to one (worst possible health state) and is supposed to translate morbidity into healthy life years lost to enable comparison of morbidity and mortality. The disability weight can, hence, be interpreted as the proportional reduction in good health due to a poor health state. Thus, living five years with a disability weight of 0.20 or two years with a disability weight of 0.5 both correspond to losing one life year in full health ($\text{YLD} = 1 \times 5 \times 0.2 = 1$, and $\text{YLD} = 1 \times 2 \times 0.5 = 1$, respectively).

In the earliest versions of the GBD study, disability weights reflected societal judgments of the value of averting different diseases rather than individuals' judgment of the disutility of their diseases [40]. Furthermore, weights were

estimated using judgments from health professionals. This method was, however, criticized by several researchers, and in 2012 Salomon et al. suggested a new standardized method where weights were elicited from the general public only [44]. In 2015 Salomon et al. published an updated version, in which they used paired comparison questions for which respondents considered two hypothetical individuals with different health states and specified which person they deemed healthier than the other [45, 46]. Respondents represented four European countries; Hungary, Italy, the Netherlands, and Sweden. To date, these are the weights used in DALY estimations. Disability weights of an acute episode of infectious diseases range from 0.006 to 0.133, depending on the severity of the disease [45].

The total DALY is simply the sum of the YLL and YLD:

$$DALY = YLL + YLD$$

In population-based burden studies, average DALY is calculated separately for sex and age groups. Population totals are then obtained by summing these group-specific DALY. According to the Global Health Estimates 2019, Sweden had a total of 2.6 million DALY [47]. Of which, 42.9 percent was due to YLL, which is less than the estimates for high-income countries in total (44.4 percent) and the total global estimate (60.4 percent) [48]. Furthermore, 1.6 percent of the total DALY in Sweden was attributable to infectious diseases [47].

Section *3.3 Economic analyses of antibiotic resistance* will evolve on studies estimating the burden of antibiotic resistance measured in DALYs.

2.2.2 Quality-adjusted life years (QALY)

Quality-adjusted life years (QALY) is a measure of perceived health, which were first introduced in 1968 [49]. It combines the gains in health with the gains in length of life into one measure and, in theory, ranges between 0 (dead) and 1 (full health) in one year. A QALY is constructed by multiplying one life year lived with the QALY weight during that year, and a QALY of 1 could, thus, be denoted as "one year in full health." Total QALY estimated over several years is the product of years and quality of life during those years. For example, suppose an individual has a quality of life weight of 0.7 in three years, that is equivalent to 2.1 years (QALY = $0.7 \times 3 = 2.1$) of full health [23].

QALY weights can be measured using direct or indirect methods. Direct methods are seldomly used since they are timely to use and evaluate, and often subject to

measurement bias [23]. Instead, indirect methods, with pre-scored systems, are used. Most indirect methods are constructed to evaluate different dimensions of health. The most commonly used instruments are the EQ-5D [50] and the SF-6D [51]. Both are general, and questions are the same no matter the condition of interest. They capture health levels in five (EQ-5D) or six (SF-6D) dimensions, for example, in daily activities, pain/discomfort, or anxiety/depression [23].

Each health state from the EQ-5D or SF-6D questionnaires must be valued to obtain the QALY weights. Valuations could be made each time the questionnaires are used. However, because that is time-consuming and increases the risk of one health state being valued differently in different settings general value sets have been constructed. Furthermore, general value sets ensure the possibility of comparisons between different health conditions since all are measured on the same scale.

2.2.2.1 EQ-5D

The EQ-5D contains five questions on aspects related to the quality of life, based on five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [52]. Each dimension can be answered on a three- or five-level scale (EQ-5D-3L or EQ-5D-5L). Given five health dimensions and three or five levels of each dimension, there are $5^3 = 243$ possible health states in EQ-5D-3L [50, 53] and $5^5 = 3{,}125$ possible health states in EQ-5D-5L [54]. The EQ-5D surveys render a series that can look like this: 11112, which means that the individual has *moderate* or *slight* (depending on if it is 3 or 5 levels) problems with anxiety/depression but no problems in other dimensions (illustrated in Table 2).

Table 2. Illustrating the EQ-5D structure

Mobility	**Self-care**	**Usual activity**	**Pain/ discomfort**	**Anxiety/ depression**	**EQ-5D health state**
1 (*no problem*)	1 (*no problem*)	1 (*no problem*)	1 (*no problem*)	2 (*moderate* or *slight problems*)	11112

The five-level version is an evolvement of the original three-level version. This evolvement was made to improve the instrument's sensitivity and reduce ceiling effects, which could occur due to the highest severity level being too extreme [54]. Levels have changed from 1) no, 2) some, and 3) extreme problems to 1) no, 2) slight, 3) moderate, 4) severe, and 5) extreme problems. A study from 2018

showed that EQ-5D-5L led to an increase in sensitivity and precision in health status measurement compared to EQ-5D-3L. Furthermore, results showed that EQ-5D-3L systematically overestimated health problems and consequently underestimated utilities compared to the five-level version [55].

In order to obtain the QALY weight from the answers given in the EQ-5D questionnaire, answers are transformed using a value set where each possible health state has been given a value. There are currently several value sets for this. Dolan developed the most commonly used value set for EQ-5D-3L in the UK in 1997 [56], which has also been used in many other countries, for example, Sweden. In 2014 Burström et al. presented a Swedish version [57]. There are two ways to transform the EQ-5D-5L to QALY weight; 1) by mapping the results from the EQ-5D-5L to the EQ-5D-3L form [58], and then using the preferred value set as usual, or 2) by using a dedicated value set för EQ-5D-5L.

In the Dolan EQ-5D-3L value set [56], each respondent has been described a number of hypothetical health states separately. Then, using the time-trade-off (TTO) method, the respondents valued each health state. The TTO method presents the individual with two options: Either living for ten years in the current health state, or a shorter period in perfect health. The time of perfect health is varied until the individual is indifferent between the two options. For example, if the individual is indifferent at eight years, the health state has been valued at 0.8 (8/10 years), which equals the QALY weight of that health state [23]. In the Dolan value sets, the estimated QALY weight ranges from -0.543 to 1 [56], meaning some health states have been valued to be worse than death.

The value set by Burström et al. [57] is experience-based, meaning the respondents valued their current health state instead of a health state described to them. Like the Dolan value set, Burström et al. used TTO to estimate each value. The estimated QALY weights range from 0.340 to 0.97.

Since the QALY weights given by the two EQ-5D-3L value sets differ significantly for the same health state, the results of a CEA could be highly dependent on which value set is used. For example, previous research has shown that using the hypothetical value set by Dolan [56] is likely to give higher QALY estimates when comparing life-enhancing interventions, while the value set by Burström et al. [57] is likely to give higher QALY estimates when comparing life-prolonging interventions [59].

QALY weights from EQ-5D-5L could be estimated through mapping to EQ-5D-3L or using a dedicated EQ-5D-5L value set. The mapping algorithm was developed before a specific value set for the 5L version was available. It used the answers from the 5L version and transformed them into corresponding 3L values [58]. Given 3L index values, any of the values sets mentioned above (or any other

value set for EQ-5D-3L) could be applied to estimate the QALY weights. In 2017, a value set for EQ-5D-5L was presented [60]. The study was conducted in the English general public, using TTO and discrete choice experiments (DCE). The TTO part followed the same structure as in previous studies, while the DCE part added a question asking the respondent to choose which of the evaluated health state are the better. The estimated QALY weights range from −0.285 to 0.950.

The advantage of using mapping is that results would be compatible with results from the three-level value sets. However, this compatibility would be on the expenses of lost information from restrictions in the range of index levels from five to three. For example, in the 5L value set, there are fewer "worse than dead" states, 5.1 percent, compared with over 30 percent in the Dolan value set for EQ-5D-3L. Resulting in a higher minimum value than in the Dolan value set [60]. Furthermore, when comparing the outcomes of EQ-5D-3L to 5L, studies have shown that 5L was superior to 3L since it led to an increase in sensitivity and precision in health measurement.

2.2.2.2 SF-6D

In the early 1990s, the Short Form 36-items (SF-36) survey was developed to measure health outcomes in the Medical Outcomes Study (MOS), consisting of 36 questions [61]. Since then versions of the SF-36, for example, one limited to 12 questions (referred to as the SF-12 [62]), has been developed. The SF-12 is shorter and, therefore, more likely to be answered fully without losing too much information [63]. The SF-36 (and SF-12) assesses health in eight dimensions and generates two summary scores for physical and mental health [61]. However, these dimensions and summary scores are not preference-based and, hence, not possible to use directly to derive a QALY weight. The SF-36 (or SF-12) is thus translated into the SF-6D, consisting of six multi-level dimensions: physical functioning, role limitation, social functioning, pain, mental health, and vitality [63]. Dimensions in SF-6D have different number of severity levels, varying from three to five levels.

The SF-6D gives a total of 18,000 health states. The most commonly used value set to transform these health states into QALY weights was developed by Brazier et al. [63, 64]. Health states are valued using the standard gamble method, which is a method that measures the preferences of different health states by introducing risks. The respondent is presented with two options; 1) remaining in the health state that is being valued, or 2) taking a gamble of either experiencing full health or risking death with a given probability. The probability of death is varied until the individual is indifferent between the certainty of remaining in the current health state and the gamble [23]. The probability where the individual is

indifferent equals the value of the health state [23]. The estimated QALY weight ranges from 0.291 to 1 [64].

The advantages of using a questionnaire with more diverse questions and levels of severity, such as EQ-5D and SF-6D, increases the possibility of capturing small health changes. At the same time, more elaborated questionnaires are often time-consuming, which could affect the completion of the survey.

Paper III used data from a simultaneous collection of EQ-5D-3L and SF-6D (SF-12) to analyze differences in estimated QALY weights depending on the value sets used and their implications on cost-effectiveness estimates. Paper IV uses published estimates of QALY to estimate the health effects of different treatment options in febrile UTI patients. Table 3 sum the characteristics of DALY and QALY for comparability.

Table 3. Characteristics of DALY and QALY

Characteristics	**DALY**	**QALY**
Measures	Estimating the disease burden from different health conditions. Also used to track changes in population health by measuring the disease burden over time.	Estimating the quality of life gains of an intervention in comparison to other potential interventions. Often used in economic evaluation and resource allocation.
Perspective	Health loss from life expectancy: based on disabilities.	Health gains: based on quality of life.
Weights	Disability weights: 0 (perfect health) to 1 (death). Weights are estimated for a number of predefined conditions, for example mild or moderate infectious disease.	Utility scores: 1 (full health) to 0 (death). Estimated based on a number of different health states. Different instruments could be used to estimate weights, for example, EQ-5D and SF-6D.

2.3 COST-EFFECTIVENESS THRESHOLD

According to the Swedish healthcare legislation and the communicable disease act [31, 65], priorities within the healthcare sector should be made with respect to all

human's equal value, the need for interventions, ethical implications, and the cost-effectiveness of the evaluated intervention. The cost-effectiveness principle implies that the additional costs of an intervention should be reasonable given the additional health effects it causes, compared to an existing intervention.

The result from a CEA is often presented as an ICER (see section *2*). To decide if the ICER is reasonable, i.e., if the intervention is cost-effective, there needs to be a threshold for what is considered cost-effective. In Sweden, there is no set threshold for the WTP. Two different perspectives has been suggested to estimate a threshold; *demand-side* (representing the societal WTP) and *supply-side* (representing the opportunity cost per QALY gained of the replaced intervention) [66].

The threshold using a demand-side approach is often referred to as the societal WTP. From previous studies, we know that WTP often differs depending on, for example, severity [67-70]. The studies suggest that WTP increases with severity and that a higher ICER more often is considered cost-effective if the patient group lacks other treatment options. Time preferences, time horizons for improvements in health, and whether the intervention is an end-of-life treatment are also likely to influence the WTP for interventions [32, 71]. However, the magnitude WTP is affected by these aspects is less clear.

In contrast, a threshold using a supply-side approach, intend to represent the opportunity cost of implementing cost-increasing interventions when constrained by a fixed budget [72]. Because the healthcare budget is fixed, implementing a new intervention at higher cost would lead to a displacement of existing treatments, and, hence, affect health in other parts of the healthcare system. The supply-side approach, thus, imply that the cost-effectiveness threshold should equals the cost per QALY gained of the displaced intervention [66, 72]. A study from 2019 estimated the marginal cost of a QALY gained to be about SEK 370,000 using Swedish healthcare expenditure [73].

A study based on reimbursement decisions from 2005 to 2011 by the Dental and Pharmaceutical Benefits Agency (TLV) found that the probability of approval was 50/50 at a cost per QALY gained of SEK 700,000 for a non-severe health state and SEK 1 million for a severe health state. The probability of a positive reimbursement approval was 3-4 percent for the non-severe states at an ICER of SEK 1 million and at SEK 1.25 million for the severe states [69].

The Swedish National Board of Health and Welfare presents cut-offs for costs to be considered low, moderate, high, or very high [74]. The threshold for when an intervention is considered cost-effective could vary between therapeutic and geographical areas [75]. However, it also depends on the type of intervention, for example, preventive measures or medical treatment. A recent paper showed that

the average WTP for prevention was higher than for medical treatment using a stated preference methodology [76]. However, these results were measured in a group where the interest in health interventions probably was higher than in the general population, which means that these results need to be validated with further studies in other populations as well.

The value of a DALY averted is usually measured in relation to the GDP per capita. Previously the common threshold was set at three times the GDP per capita [77]. However, this approach has been criticised as not taking country-specific considerations into account [78]. In a recent study the DALY threshold was estimated based on human development index (HDI) classification [79]. According to these estimations the value of a DALY averted in Sweden, country with very high HDI, was 1.46 times the GDP per capita, which amount to approximately SEK 720,000[1] [79, 80] (≈ EUR 72,000). This estimate is similar to the once used as threshold for a QALY gained, which is in line with research arguing that a QALY gain and a DALY averted could be used interchangeable [81, 82].

[1] Calculation based on GDP per capita in Sweden 2019 (SEK 491,300) [80].

3 ANTIBIOTIC RESISTANCE

3.1 DEVELOPMENT OF RESISTANCE

Resistance to penicillin was known already before penicillin was launched as a medical product [5, 16]. The development of resistance is a part of the evolution of the bacteria, and bacteria who mutate to be resistant to treatment survive to reproduce. This mutation is a natural phenomenon, and even before antibiotics were developed and used as medicines, resistance mechanisms were found in environmental bacteria. Nonetheless, antibiotic resistance was not common in pathogenic bacteria before the development of antibiotics [83, 84]. Even though resistance often occurs naturally, inappropriate use of antibiotics, both in humans and in the agricultural sector [85, 86], has led to the rapid growth of ABR worldwide.

ABR is a global concern with significant effects on both mortality and morbidity. Since the discovery of antibiotics, the burden of infections has markedly decreased. In addition, antibiotics have also allowed for other medical interventions such as organ transplantations, chemotherapy, advanced surgery, and care of premature babies, where a minor infection could potentially be fatal without active antibiotics [6, 14]. It has, for example, been estimated that prophylactic use of antibiotics in hip replacement surgery reduces postoperative infection rates by up to 50 percent and death due to infection by 30 percent [87].

In early 2022 the Antimicrobial Resistance Collaborators published a scientific paper in Lancet, estimating the global burden of ABR in 2019 [7]. The authors estimate deaths and burden of disease both *attributable* to ABR (i.e., the excess effects compared to infections caused by susceptible infections) and *associated* with ABR (i.e., the effects of infections caused by one of the included pathogens compared to no infection at all). According to their estimations, approximately 4.95 million deaths globally were associated with ABR in 2019, including 1.27 million deaths attributable to ABR. Estimations were based on 23 bacterial pathogens and 88 pathogen–drug combinations. The six most common pathogens accounted for more than 70 percent of all ABR attributable deaths. Similar estimations have been done for the EU/EEA area and the US, estimating

about 33,000 and 35,000 deaths in the EU/EEA in 2019 and the US in 2017, respectively, would be attributed to resistance [8, 15].

The levels of resistance, as well as the pace of development, differ between countries. For example, Sweden has relatively low resistance levels compared to many other countries worldwide [8]. Resistance levels also differ between and within different groups of bacteria. It is, however, difficult to compare cross-country data of ABR due to differences in treatment guidelines, varying use of multiple drugs, standards in testing and tracing, and methods and equipment used in different parts of the world. At the European level, European Centre for Disease Prevention and Control (ECDC) collects data on the resistance of eight different bacteria through the European Antimicrobial Resistance Surveillance Network (EARS-Net) [88].

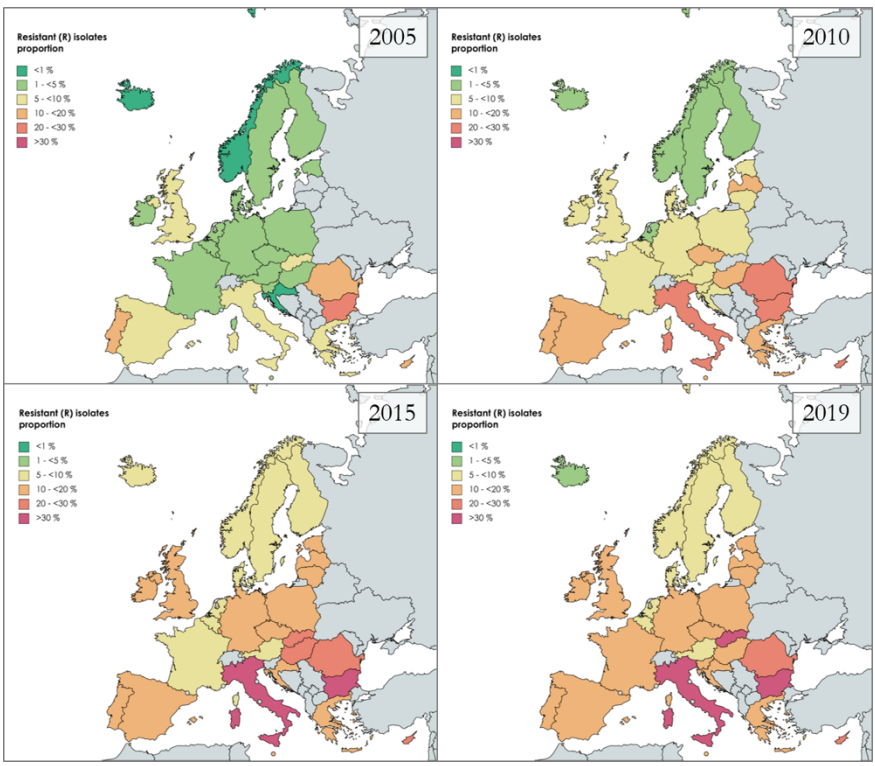

Figure 3. Development of resistance to 3rd generation cephalosporin in E.coli in Europe

Figure 3 shows the development of resistance to 3rd generation cephalosporin in E. coli from 2005 to 2019 [89]. During these years, E. coli resistant to 3rd

generation cephalosporin has increased in all countries. Between 2005 and 2015, the increase was estimated to be about 222 percent across all OECD countries [14]. Countries in Eastern and Southern Europe generally have higher proportions of resistance than the countries in Northern and Western Europe, which could be seen in the data from ECDC for resistance to 3rd generation cephalosporin in E. coli (Figure 3). Furthermore, the OECD estimated that for some antibiotic-bacterium combinations there are countries where 75-80 percent of all infections are caused by bacteria resistant to at least one antibiotic [14].

Most countries has seen both increases and decreases in resistance levels, depending on which microorganism or antimicrobial agents are considered [14]. Across the OECD countries, for example, MRSA was estimated to have an average decrease of 17 percent between 2005 and 2015 [14]. However, overall development of resistance in the OECD countries has been projected to increase by 2030. Resistance to second and third-line antibiotics, i.e., antibiotics given when initial (or second) treatment does not work anymore, are expected to be 70 percent higher in 2030, compared to resistance rates in 2005 for the same antibiotic-bacterium combinations [14].

De Kraker et al. [90] argue that global estimates of the burden of AMR are highly uncertain and not very informative. Instead, they argue that more detailed and reliable data are needed to produce accurate results. One way of doing so is through national estimations or estimations based on low-, middle- or high-income country groups. However, access to and amplitude of data differ significantly between countries. Independent of the perspective when estimating the resistance rates or development of resistance, global aspects such as traveling is important to bear in mind. International travel has been shown to significantly increase the presence of ABR genes and, hence, enhance the global spread of locally endemic resistance types [91].

There are many reasons for the increase in resistance and why the levels of ABR differ between countries. High antibiotic consumption is one factor often associated with higher resistance levels, which is true for, for example, Mexico, while in Belgium, the resistance levels are lower than expected when considering antibiotic consumption. This inconsistency suggests that the accuracy of treatment is important for effects on development of resistance. Access to healthcare services is also positively associated with the levels of some types of resistance [14], implying that easier access to antibiotics drives the development of resistance. Factors such as compliance to and duration of treatment are also crucial for the emergence and spread of ABR [92]. Furthermore, extensive use of antibiotics in livestock and food industry has also been shown to affect overall resistance rates [93].

There is a global consensus that actions need to be taken to reduce the development of ABR [94]. Several initiatives targeting different aspects of resistance have already been implemented. For example, WHO initiated the Global Antimicrobial Resistance Surveillance System (GLASS), aiming to support global surveillance and research to strengthen the evidence base on AMR and support decision-makers with evidence on interventions to reduce development [95]. There have also been national and global initiatives to create incentives for the pharma industry to develop and launch new antibiotics effective in resistant bacteria [96, 97].

3.2 INTERVENTIONS TO STEM THE DEVELOPMENT OF RESISTANCE

Developing resistance is the natural way for bacteria to survive as more and more infections are treatable. So far, antibiotics are used widely to treat all kinds of infections, and in some countries, antibiotics are even used on viral infections and not only when infections are caused by bacteria, causing a perfect ground for resistance to thrive and grow.

Several countries have developed national action plans to stem the development of resistance. For example, in 2005, the Swedish government approved the first cross-sectional national action plan for collaborative work against antibiotic resistance and healthcare-associated infections [98]. In addition, since 2012, there has been a national antibiotic forum annually in Sweden, with participants from different stakeholders, for example, from the healthcare, public health, veterinary medicine, animal health, food production, and environment sectors. The main goal of this forum is for different sectors to share information, knowledge, and experiences [99].

The Swedish government adopted the current Swedish Strategy to Combat Antibiotic Resistance in February 2020, which extends from 2020 to 2023 [100]. The overarching goal of this strategy is to "preserve the possibility of effective treatment of bacterial infections in humans and animals" [100]. The plan is divided into seven objectives, including an objective to improve awareness and understanding of antibiotic resistance and countermeasures in the general population. This being one objective out of seven in total shows the importance of a society well-informed about the consequences of ABR, not just the stakeholders directly involved, to curb the development of resistance. Furthermore, Sweden has an objective of being a leader in the work against antibiotic resistance within the EU and international cooperation.

In 2015, the World Health Assembly (the decision-making body of the WHO), the Food and Agriculture Organization of the United Nations (FAO), and the World Organisation for Animal Health (WOAH) adopted a global action plan on antimicrobial resistance [101]. The overall goal of this plan is to ensure continuity of the ability to treat and prevent infectious diseases with effective and safe medicines that are quality-assured, used responsibly, and accessible to all who need them (see Box 1 for further information on the objectives). Furthermore, it was also expected that the member states of the WHO would develop their own national action plans on antimicrobial resistance in line with the global plan. National action plans should consider national and regional aspects of resource use and priorities. In addition, it should also address relevant national and local governance arrangements.

Box 1 WHO Global Action plan

The five strategic objectives of the WHO global action plan:

1. Improve awareness and understanding of antimicrobial resistance through effective communication, education, and training.
2. Strengthen the knowledge and evidence base through surveillance and research.
3. Reduce the incidence of infection through adequate sanitation, hygiene, and infection prevention measures.
4. Optimize the use of antimicrobial medicines in human and animal health.
5. 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.

Reference: World Health Organization (2015) [101].

While access to clean water, sanitation, vaccines, and other 'basic' infection prevention measures could be the important first step for many poorer countries to prevent infections in humans, countries with more evolved healthcare systems focus mainly on appropriate antibiotic use, evolved surveillance, and vaccination programs and screening systems. Furthermore, countries such as France, Sweden, the UK, and the US also highlighted the importance of securing access, and availability, to both new and old antibiotics with an effect on bacteria with critical resistance development [100, 102-104]. To successfully implement activities within the national action plans, decision-makers need to be aware of the economic consequences and expected resource use.

The following sections will further evolve on antimicrobial stewardship programs and access to effective antibiotics.

3.2.1 Antimicrobial stewardship programs

Interventions to decrease the development of resistance, such as antimicrobial stewardship programs (ASP), aim to improve patient care and patient outcomes through optimal therapy, reduce collateral damage by reducing antimicrobial use, and reduce the cost of antibiotics. Since antibiotic use is a driving force in ABR development [14], most ASP refers to the more appropriate use of antibiotics, for example, through shortening treatment duration or a different choice of drug with a lower risk of developing resistance [17]. In many countries where antibiotics are used widely and not only for bacterial infections, appropriate use could also refer to antibiotics only being used when necessary.

In a Swedish study by Edlund et al. [105], they assessed the effects of different treatment options (temocillin vs. cefotaxime) in patients with febrile urinary tract infection (UTI). Results showed that treatments were similar regarding safety and clinical efficacy. However, patients treated with temocillin were, to a lesser extent, colonized with resistant bacteria (Enterobacterales with reduced susceptibility to third-generation cephalosporins) after initial intravenous treatment compared to cefotaxime. The authors conclude that the spread of resistant bacteria from patients into the hospital environment could diminish if treatment led to less colonization. Further, this could lead to a reduction in hospital-acquired infections caused by such resistant bacteria. However, the authors also stress that their findings might only be generalizable to healthcare settings with similar levels of multidrug resistance.

ASP could be several different interventions. However, often they are a bundle of interventions, which makes it complicated to evaluate different interventions independently [106]. When assessing the effects of ASP, they should instead be seen as a combination of measures taken to reduce or curb the development or resistance. Furthermore, it is important to consider regional or national conditions and changes in resistance levels to form ASP optimal in specific settings. Health economic analysis could further support decision-makers in situations where different interventions need to be prioritized against each other – to maximize the health output given estimated resources use and costs.

3.2.2 Access to effective antibiotics

During the last decade, 15 new antibacterial agents have been developed and brought to the market [107]. However, a recent study suggests that research and

development of new agents decrease over time [108]. As the development of resistance gets more comprehensive and new types of resistance occur, access to effective new antibiotics becomes a prerequisite for treating more and more bacterial infectious diseases.

Since the use of many antibiotics, especially novel ones, often are restricted, there are few commercial incentives for pharmaceutical companies to invest in this kind of research. By extension, this could lead to companies not making their products available on small markets since the cost of market authorization exceeds the potential income from sales. This is particularly a problem for countries with low resistance levels and well-established antibiotic stewardship programs. In addition, current compensation systems do not seem adequate to fulfill the economic incentives of marketing a new product in small markets.

The rising global health problem of antibiotic resistance and the draining pipeline of new antibiotics has been known and discussed for decades. In a recent overview, the WHO [109] concluded that the clinical pipeline and recently approved antibiotics are insufficient to tackle the emergence and spread of antimicrobial resistance. In the 2009 Council Conclusions on innovative incentives for effective antibiotics [110], the Council concludes that access to effective antibiotics is essential to ensure adequate healthcare and a high level of public health. Furthermore, they projected that the development of new therapeutic alternatives would not meet the medical need within 5 to 10 years because of a significant decline in research of new antibiotic therapies. Consequently, the Council urged all member states to examine how to secure access to effective antibiotics. Since then, many initiatives have been taken by politicians, governmental agencies, academia, interest groups, and industry globally [111].

In the UK, NICE has been commissioned to develop a new cost-effectiveness evaluation methodology that considers the broader benefits and values to society of having new effective antibiotics available, even if they are only kept as a reserve [112]. In a pilot study, based on these evaluations, NHS England will then negotiate with selected pharmaceutical companies to agree on an annual payment. Initial contracts will be for three years, with an option to extend to 10 years. Payments will be structured as a guaranteed annual fee of up to £10 million per product. Furthermore, payments should be fully delinked, meaning that the financial compensation should not be based on volume or quantity of sales [113].

A similar approach has been suggested in the US. The value of contracts has been suggested to ranges from $750 million to $3 billion in total over the contract period [114]. Furthermore, France, Germany and Sweden also suggested alternatives to national reimbursement system to account for the risk of insufficient access to some new antibiotics [111].

The EU Pharmaceutical Strategy for Europe also highlights the need for new, innovative business models to account for the problems arising around decreased demand of new antibiotics due to restrictions in use [115]. Antibiotic resistance is a global issue, and so is insufficient access to effective antibiotics. Several calls have been made to find global or, at least, the G20 countries, initiatives to solve this problem with many countries united. Some global/international models has also been suggested [116, 117]. However, on order to accurately value access to effective antibiotics, it is essential to understand the economic consequences of antibiotic resistance.

3.3 ECONOMIC ANALYSES OF ANTIBIOTIC RESISTANCE

Policy changes are necessary in healthcare, as well as in environmental and livestock areas, to decrease the development of resistance [118]. It is therefore important that decision makers have accurate estimates of the total burden of resistance, including estimates of the economic consequences of resistance. A recent study concluded that methodological assumptions need to be improved in order to capture the true costs of ABR in future studies [119]. For example, they highlight the importance of considering:

- development of resistance over time,
- using a societal perspective to include all cost of resistance,
- having a wider scope which accounts for effects also beyond the treated patient and
- using a national or global perspective instead of a local viewpoint.

Other studies, emphasize the importance of accuracy and transparency in assumptions for decision-makers to fully understand the implications, since data often are scares or uncertain [120, 121]. Still, there is no "one-way" to conduct such analyses. Instead, they need to be adjusted based on the specific circumstances relevant for the setting the analysis concern.

Previous analyses differ in execution, for example in how the contrafactual scenario is constructed, or in the perspective used. However, several analyses have been carried out to estimate the economic effects of antibiotic resistance. For example, in 2009 the ECDC estimated more than EUR 900 million in additional hospitalization costs per year, calculated from additional hospital length of stay, and out-patient costs attributable to antibiotic resistance in the EU, Iceland and Norway [13]. In addition, non-healthcare costs were estimated at about EUR 600 million, including cost due to absence from work and premature death.

In more recent research, OECD calculated the average economic burden on the healthcare system in the EU countries over the period 2015-2050 to be up to USD 1.5 billion annually [14]. However, they did not estimate the non-healthcare costs, such as cost of productivity loss in their analysis.

The O'Neill review from 2016, which is well-referred, estimated the cumulative economic consequences on global production by 2050 to be about 100 trillion dollars, leading to a significant reduction of the world's GDP [10-12]. However, the relevance of some of the estimates used in the O'Neill review have been questioned [122]. The critique is, for example, about using global trends of development of resistance, which, according to the authors, is not informative enough since it does not consider differences in development between countries. Furthermore, there is a large range of uncertainty in parameters such as incidence of infections, prevalence of resistance or the attributable mortality that is not considered in the O'Neill review [122].

Results from the different analyses depend on both which countries are included in the analysis as well as which resistance types. They also differ in whether they estimated the cost for only healthcare or if they included costs for society as well. Analyses mainly carried out in inpatient settings and in high- or middle-high income countries, means that several countries with high levels of resistance are left out and that the cases occurring in other healthcare areas are disregarded. From this perspective the total burden of resistance may be underestimated. Overall, the range of results shows the complexity of making comprehensive economic analyzes of ABR.

Recent studies have mainly focused on the disease burden from ABR to broaden the knowledge of antibiotic resistance and include less frequent resistance types as well. Studies measuring the burden of resistance as loss of DALY could further on be used to estimate the societal cost of resistance. For example, Cassini et al estimated more than 33,000 ABR attributable deaths and 874,000 DALYs lost in EU and EEA due to resistant bacteria [8].

4 AIM

The overall aim of this thesis was to increase knowledge of the health economic consequences of the development of antibiotic resistance in humans in Sweden. The analysis includes the effects on costs and health to both the healthcare sector and to society, as well as an economic evaluation of interventions to stem the development of resistance. In addition, this thesis aims to assess the implications of methodological assumptions related to measuring health in health economic analysis.

The specific aim of each study was:

Paper I To project the impact of antibiotic resistance on total healthcare consumption and associated costs over the period 2018 until 2030 and 2050, respectively, in the Swedish setting.

Paper II To estimate the additional days of production loss for infection caused by antibiotic-resistant bacteria compared to those caused by susceptible bacteria. In addition, we aimed to assess the additional costs of production loss attributable to antibiotic resistance.

Paper III To analyze the implications of different instruments and value sets on the policy of measuring health related quality of life by including different types of QALY estimations, using EQ-5D Burström, the EQ-5D Dolan, and the SF-6D Brazier value sets.

Paper IV To evaluate the cost-effectiveness of using different antibiotics (temocillin or cefotaxime) in patients with febrile UTI, while taking external effects such as development of resistance into account.

5 METHODS

Health economic analysis often requires modeling to support evaluation. The amplitude of the model used should be proportional to the research question. For example, some questions could be answered using simpler modeling techniques, while others need more comprehensive modeling. Furthermore, models should not be interpreted as they predict what *will* happen, rather that they can be used to help decision-makers understand what *might* happen in different scenarios. Additionally, models are only as good as the data or assumptions used, which indicates that if data is uncertain, sensitivity analyses are required to understand the range of possible output better, and hence, the uncertainty of the results.

In this section, I will immerse in modeling of epidemiological progression and decision-analytic modeling in general, and the statistical methods relevant for this thesis.

5.1 MODELING THE DEVELOPMENT OF RESISTANCE

Epidemiological models, or infectious disease models, are used to understand the spread of a disease through populations. Relevant aspects to study could be the pace at which a disease may spread; number of individuals infected or dead, or the number of individuals requiring treatment. Modelling is also used to analyse how diseases progress over time. Models could be conducted from an aggregated level or on a micro-simulating level [123].

In aggregated models, population-attributable probabilities are used to estimate the changes in disease outcome following an intervention. This means that the same probability of an event is induced on the entire population, often age- and sex-specific strata. In the more advanced analyses, aggregated models are divided into several subgroups depending on, for example, education level or income group, with subgroup specific risks applied simultaneous. Aggregated models could be as diversified as data allow. However, aggregated models could not account for interactions between individuals, instead events occur given populations-specific probabilities [124].

In comparison, in microsimulation models, individuals are each represented separately. The state of the individuals is updated annually according to rules and statistical models taking individual attributes and history into consideration, thereby creating dynamics. For example, a person's health state is updated annually using a statistical model that includes, among other factors, age, sex, marital status, last year's healthcare consumption, and last year's health state. A significant advantage with a microsimulation approach is that it takes the individuals' history, such as previous diseases, and healthcare consumption into account, which could be relevant for the risk of contracting resistant bacteria. Furthermore, individual behaviour, for example, how individuals respond to policies, can easily be incorporated, and finally, microsimulations enable to target policies to specific individuals based on their characteristics and history [125, 126].

In paper I, we used a microsimulation model to project the development of ABR in Sweden while taking individual risks of infection into account. After implementing risks and trends based on reported data from the SmiNet database (more information on data collection in section *6 Data*), the simulation output was the estimated annual number of cases of antibacterial resistance per type of resistance divided by infection types and carriership. Since the model has stochastic elements, we ran the model 30 times to ensure stability in results. When estimated the number of cases we used the output from the microsimulation model to estimate the total cost using a cost-of-illness analysis approach.

5.2 DECISION ANALYTIC MODELING

Decision analytical modeling is often used within health economic analysis to assess whether an intervention is cost-effective compared to an alternative strategy [127]. It aims to support decision-makers when prioritizing different interventions or treatment options by modeling potential outcomes over time. Decision modeling compares the expected costs and health consequences from one intervention with those from another intervention or strategy by combining information from multiple sources with mathematical techniques to forecast future outcomes [128].

As clinical trials often are conducted in a limited environment with many restrictions on both treatment duration and participants' characteristics, data collected from such studies hence provide data that may differ from the use in real life. Therefore, it could be necessary to extrapolate data when evaluating an intervention where the trial data does not capture the costs and effects that the intervention causes in the long run.

Decision analytic models are beneficial tools in health economic analysis and healthcare prioritization since they enable synthesizing evidence from different sources, if there is not one source containing all relevant data. It is also valuable to make estimations that stretch over a longer time horizon to account for effects that occur later in a lifetime [129].

There are different approaches to use in decision-analytic modeling. The most commonly used are the decision tree model and the Markov model [129]. A decision tree model is the simplest structural model where the outcome of an intervention is illustrated as a series of decision nodes which occurs with a given probability. The structure of this model looks like a tree where probabilities of different events are illustrated as branches. Furthermore, decision trees models assume that all events occur instantaneously in the model.

Decision tree models are helpful for simple decision problems but could rapidly grow to an unmanageable combination of probabilities and events in more complex disease dynamics or if events occur repeatedly. In addition, decision tree models are considered appropriate for short time horizons, while longer time horizons usually require the use of models a sequence of health states, such as Markov models [127].

A Markov model simulates a cohort of individuals over a finite set of health states. Transitions between the states are represented by changes in health and could only occur with fixed time intervals, called cycles. An individual can remain in one health state or move to another health state, depending on the dynamic of the health issue studied. Transitions occur based on probabilities of leaving the current health state, independent of previous health states or events, often referred to as the model has no memory. Transitions will be repeated until the appropriate time horizon has been reached or when the individuals reach an absorbing state (death). The model will run for as many cycles as is relevant for the specific disease or health issue studied. However, time horizons should be long enough to include all relevant costs and health outcomes. Figure 4 illustrates

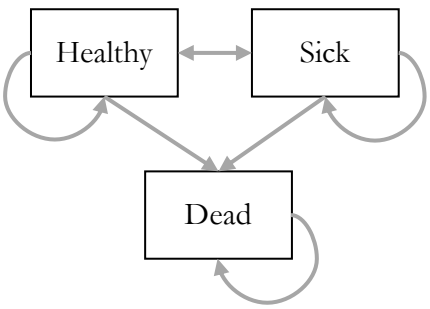

Figure 4. Illustration of a Markov model

a Markov model with three health states. Arrows illustrate the direction of possible transitions.

When conducting decision-analytic models, it is essential to consider the model's structure and complexity. A too simple model could be at the expense of validity, while a too complex model could lose transparency and, hence, be difficult to understand. Furthermore, to fully understand the impact of model choices and input parameters, it is essential to conduct sensitivity analysis on the results and validate the output from the model with the data available [129].

5.2.1 Discounting

Discounting is applied in decision-analytic modeling when time horizons exceed one year. The aim of discounting is to make costs and health effects that occur at different times comparable, which is achieved through adjusting future costs and health effects to a present value using a discount rate. Discounting is a year-to-year adjustment. For example, in Sweden, costs and health effects are usually discounted by 3 percent annually [130].

There are different ways to discount costs and health effects in economic evaluations. Discount rates could be either constant or non-constant over time (i.e., the discount rate changes over time) [131]. The rate could also differ between costs and health effects. Most national guidelines recommend a constant discount rate for both costs and health effects, as in Sweden and the UK, while, for example, the Netherlands recommend a differential discount rate of 4 percent for costs and 1.5 percent for health effects [131]. In France [33, 131], discount rates decrease over time with 4 percent during the first 30 years, which decrease to 2 percent further on.

In modeling preventive measures, discounting could have a significant impact since costs, and health effects often occur at different times. In addition, preventive intervention often has initial costs invested in avoiding illness or bad health in the future. Furthermore, it means that discounting could have a negative effect on prevention since discounting will decrease the impact and value of events in the future more than those occurring today.

However, it has been argued that there is no intrinsic reason to value a year of health as less relevant simply because it is in the future [132]. For example, the WHO uses a zero percent discount rate in their DALY estimations in the GBD study [41]. Since discount rates differ between studies and potentially have a significant impact on modeling results, sensitivity analyses that vary the discount rate and apply different discount rates to explore how results are affected are often

recommended in health economic guidelines to understand better how discount rates impact the result.

5.2.2 Sensitivity analyses

When conducting decision-analytic modeling, it is important to remember that the modelled outcome is the results of the data assigned and the chosen structure. Uncertainties around input parameters could therefore have a significant impact on the results. In order to deal with these uncertainties, sensitivity analyses are often recommended.

There are two main methods when conducting sensitivity analyses; deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) [133]. Both aim to assess parameter uncertainties and determine how sensitive the base case results are for changes in parameter values. In a DSA, parameter values vary either one at a time (one-way sensitivity analysis) or multiple variables at once (two- or multiway sensitivity analysis) and are preferred when only a few parameters are of interest. This stepwise approach makes it easy to assess if the results from the sensitivity analysis differ significantly from the ones in the base case analysis, implying that parameter values have a significant impact on the estimated results.

In a PSA, the uncertainty for individual parameters is incorporated into the model using different probability distributions. Usually the model is run several times, using different parameter estimates from the probability distributions [134]. The PSA gives multiple replicates of the model output, indicating the uncertainty in the overall results rather than the uncertainty surrounding the individual parameters [135]. PSA could be used to estimate the maximum and minimum ICER estimates, i.e., a range of probable ICER estimates. It is, however, mainly used to calculate the probability that the intervention is cost-effective at a certain threshold by analyzing the proportion of simulations that falls beneath the cost-effectiveness threshold. The results could be plotted in a cost-effectiveness acceptability curve (CEAC), presenting the probability that the intervention will be cost-effective at different cost-effectiveness thresholds.

In paper IV, we used a PSA to assess the uncertainty of the results from the base case analysis.

5.3 STATISTICAL METHODS

In paper II, regression analysis was used to estimate the effect of resistant bacteria on the long-term sick leave in in-hospital patients with an infectious disease. In

order to account for skewed data caused by most patients having none or only a few long-term sick leave days, we used a two-part model to estimate the marginal effect of resistance compared to susceptible bacteria causing the infection [136].

In the first part of the analysis, we used logistic regression to estimate the probability of more than zero sick leave days. In the second part, we estimated the proportional change in long-term sick leave days between resistant and susceptible bacteria using a Negative binomial regression. The choice of method was based on the dependent variable, long-term sick leave days, being discrete count data and over-dispersed. Negative binomial regression is a kind of Poisson regression [137].

Results from the first and second parts were combined to estimate the marginal effects of each independent variable, i.e., the average effect on sick leave days of all variables included. Furthermore, standard errors were clustered by patient ID since patients might recur in data sets several times if they had been admitted to the hospital more than once during the five years of data collection. Using clustered standard errors account for heteroscedasticity in the sample, i.e., that there could be subgroups with different variance when estimating the standard errors.

In paper III, we assessed the comparability of QALY weights estimated through two generic instruments and three value sets using different statistical methods. In addition, a combination of methods was used to account for the multidimensionality of quality of life measures.

The analysis was conducted in two parts; 1) to what degree the dimensions of EQ-5D and SF-6D were comparable, and 2) how the QALY estimates corresponded to each other depending on the instrument and value set. In the first part, we analyzed the correlation between dimensions in EQ-5D to those in SF-6D. Furthermore, to assess conformity in severity levels, we examined the distribution across dimensions and levels of responses.

To show the relationship between different QALY estimates and what variables affected the QALYs, we conducted a regression analysis with QALY estimates as the dependent variable. We specified the model with different background variables and one of the other QALY estimates as independent variables. We also examined the difference in mean QALY estimates from the different instruments and value sets using a simple t-test. QALY estimates were also plotted in different graphs to study the relationships visually.

6 DATA

6.1 DATA SOURCES

There are several registers for health data in Sweden. In Paper I and Paper II, we used data on inpatient care from the patient register and the prescribed drug register held by the Swedish National Board of Health and Welfare (NBHW) [138], and ABR status from the communicable disease database (SmiNet) held by the Public Health Agency of Sweden (PHAS) [139]. In Paper II, we also used data on long-term sick leave from the national sick leave register held by the Swedish Social Insurance Agency (SSIA) [140]. Using personal identity numbers in Sweden enabled entries in different registers to be merged and the registers linked at an individual level. Access to reliable register data is essential to conduct studies with as accurate estimation as possible.

NBHW is a government agency with responsibilities in social services, health and medical services, and patient safety. As part of their assignment, they collect data in national registers to facilitate analyses and development of Swedish healthcare and social services. The patient register contains data on every in- and out-patient healthcare visit in Sweden and data on patient age, sex, and comorbidities. Diseases are reported based on the International Classification of Diseases (ICD) system [138]. The prescribed drug register contains information on all prescription medicines obtained from pharmacies [141].

PHAS is the government agency with national responsibility for surveillance and prevention of communicable diseases and other public health threats. As part of the surveillance, PHAS collects data on all detected cases of diseases classified as notifiable according to the Communicable Disease Act in Sweden [65, 142]. In addition, information about resistance type and sample site for each case is reported by laboratories and clinicians, along with data on patient age, gender, and country of infection, in the SmiNet database [139]. According to the Communicable Disease Act, five types of resistance are notifiable: methicillin-resistant *Staphylococcus aureus* (MRSA); extended-spectrum beta-lactamase (ESBL) in Enterobacterales; carbapenemase-producing Enterobacterales (CPE);

penicillin-non-susceptible *Pneumococci* (PNSP); and vancomycin-resistant *Enterococci* (VRE) [143].

SSIA is a government agency that administers the social insurance system in Sweden, which aims to provide financial security for families with children, people with a disability or illness, and the elderly [144]. For example, compensation for sick leave or care of children is handled through the SSIA. The system is publicly funded through taxes and dues.

People of working age, independent of employment status, are insured through the social insurance system. This system assures that anyone who falls ill gets a sickness benefit during the time they are unable to work or seek work if unemployed. If the person is employed, the employer is responsible for paying the sickness benefit for the first 14 days. For the unemployed, sickness benefit is instead paid by the SSIA. Sickness benefit in Sweden is approximately 80 percent of the individual's daily salary, subject to a cap of close to EUR 80 or EUR 54 daily, depending on employment status [145]. After 14 days' sick leave, the SSIA pays this benefit irrespective of employment status, referred to as "long-term sick leave" (LTSL). Only sickness benefit paid by the SSIA is registered in the national sick leave register [140], which means that information on sickness benefit paid by the employer is lacking if the employee's total absence from work lasts less than 14 days.

6.2 DATA SAMPLES

In Paper I, we used registered data to estimate the additional healthcare costs due to resistance. Additional costs were defined as the difference between the costs of an infection caused by resistant bacteria compared to one caused by susceptible bacteria. To estimate the development of resistance data of all reported cases of ESBL, CPE, PNSP, and VRE from 2012 to 2016 and MRSA from 2012 to 2014 was collected from the communicable disease database held by PHAS. Cases were grouped into the most common clinical infections and carriership, respectively. We pooled all cases reported by gender and age into 5-year groups for all resistance types to improve representativeness in scarce data. Despite aggregation, some age and gender cohorts had zero cases, and the calculated risk would then be zero. A small but non-zero risk was used in the model instead to avoid this.

To estimate the economic consequences of resistance, we matched cases from the communicable disease database with healthcare data from the patient register and the prescribed drug register. Healthcare consumption was considered associated with the infection if it occurred during the 30 days following the sample date. Identified costs were compared with the average costs of treating infections from

the Case Costing Database held by the Swedish Association of Local Authorities and Regions [24] to estimate the additional costs due to resistance. If this information was unavailable (urinary tract infections and skin and soft tissue infections), clinical experts were consulted to provide their best estimate. To identify the on-top consumption due to resistance, we subtracted the healthcare consumption due to infections caused by susceptible bacteria.

Costs for hospital length of stay and outpatient visits were derived from the Case Costing Database [146]. Costs of personnel due to contact tracing was estimated using data on work hours associated with contact tracing, provided by Värmland and Stockholm counties, and standardized salary costs for relevant professional groups. In addition, laboratory costs for contact tracing were collected from the Region Skåne [147].

In Paper II, we use registered data on individuals' sick days at the time of infection to quantify the additional days' production loss attributable to ABR. To calculate the time associated with resistance, we estimated the additional days of long-term sick leave for cases with infection caused by antibiotic-resistant bacteria with those caused by susceptible bacteria.

To identify the study population in Paper II, we selected a number of infections reported in the patient register by ICD-10 codes [138]. Selection was made by clinical expert and given the most frequently reported infection types in SmiNet. The ICD-10 codes [148] were categorized by type of clinical infection (bloodstream infection, BSI; urinary tract infection, UTI; skin and soft tissue infection, SSI; and pneumonia). Data concerning all patients up to 65 were collected from 2011 to 2015. In addition, data on hospital admissions, visits to specialists, and all diagnoses registered at the time of the patients' visits were collected from the patient register [138].

As a second step, we ran the cases from the patient register to the SmiNet database to identify cases with an infection caused by one of the five resistance types. We also ran all cases from the patient register to the national sick leave register to add information on LTSL days for each case of infection. LTSL was defined as associated with the infection if the date of testing or other contacts with the healthcare system due to infection coincided with the period of sick leave or if the sick leave started within five days of the infection onset. We omitted all observations where the first day of sick leave occurred more than 30 days before the infection or resistance was registered, since that LTSL were not believed to be associated with the infection, and hence, not relevant for the analysis. Still, we chose a 30-day limit to include patients in hospital treatment who potentially were infected during their stay. Observations of ABR or infection not included in the SSIA register were assumed to have zero days of LTSL since the register contains all LTSL data.

Finally, to estimate comorbidities, we calculated the Charlson Index [149, 150] for each individual, using all registered ICD-10 codes in the patient register from 2011 to 2015.

Table 4. Summary of register data used in papers

Paper	Sample	Years	Sources
I	Cases with notifiable resistance	2012-2016	The communicable disease database held by the Public Health Agency of Sweden (PHAS), and the patient register held by the Swedish National Board of Health and Welfare (NBHW)
II	Cases with ICD-10-SE codes: A40, A41, A46, H66.0, H66.4, H66.9, I30, I33, J01, J13, J15, J18.9, K35, K57, K81, L02, L03, L08, L97, L98.4, N10, N11, N12, N30, O86.2, P36, T80.2, T81.4, T82.2, T82.7, T84.5, T84.6, T85.7	2011-2015	The patient register held by the Swedish National Board of Health and Welfare (NBHW), the communicable disease database held by the Public Health Agency of Sweden (PHAS), and the national sick leave register held by the Swedish Social Insurance Agency (SSIA)
III	People enrolled in the Needle Exchange program	2013-2015	Region Stockholm

Data in Paper III was initially collected within the Region Stockholm Needle Exchange program to assess the HRQoL among people enrolled in the program. Respondents were above the age of 20, and data was collected between April 2013 and April 2015. HRQoL was measured using both the EQ-5D3L and the SF-12 instruments. In addition, other demographic variables, such as age, gender, country of birth, housing conditions, education, and more, were collected simultaneously, along with information on drug use. Data was collected through face-to-face interviews with the staff at the program. We used the responses from EQ-5D and SF-6D (derived from SF-12) to compare the output in QALY estimates using different value sets. For EQ-5D, we used value sets by Dolan [56]

and Burström et al. [57], respectively. For SF-6D, we used the value set by Brazier et al. [63].

In general, this population is seldomly used for reference in research. However, since respondents responded to both questionnaires simultaneously, there is no reason to believe the health state should not be comparable because of the population. Furthermore, results from the regression analysis showed that background variables, such as age, gender, injection drug use, and the living situation had a minor or no impact on the estimated QALYs, independent of model specification. In addition, results from the comparison of dimensions showed that the respondents in our study were comparable to respondents in previous studies. Overall, these factors indicate that our results should not be affected to any great extent by the respondents' characteristics. However, personal characteristics and uncertain representativeness in the sample are essential issues to consider when using data from interviews or questionnaires. It is essential to understand the possible implications of such aspects on the results.

In paper IV, we used published data. Table 4 summarizes data used in papers I, II, and III.

6.3 ETHICAL ASPECTS

Individual-level data were used in the analyses of Paper II and Paper III. The use of personal identification numbers enabled us to merge data in different registers to ensure that several essential aspects for the development of resistance were considered. When working with individual data, it is essential to understand what possible implications such data, or results from analyses, could have on the subjects included. It is critical to assure that no back-tracing or other identification of subjects is possible. In Paper II and III, we received data where anonymous observation numbers replaced the personal identification numbers before the data were delivered to the research group.

Furthermore, permission to access Swedish register data requires that data is used for scientific purposes and results are intended for publication. The Ethical Review Board in Stockholm approved the merging of registers and the analysis plans for Paper I (dnr. 2013/1840-31/2), Paper II (dnr. 2016/2166-31/5), and Paper III (dnr. 2013/495-31/3). In addition, in Paper III, participants were given written and oral information about the study and signed a form consenting to participation. No ethical review was necessary for Paper IV, as this study did not include any individual-level data.

7 RESULTS

7.1 HEALTHCARE COSTS DUE TO ANTIBIOTIC RESISTANCE

The economic model used in paper I combine the microsimulation model's output (i.e., the number of cases with antibiotic resistance) with additional resource use and healthcare costs, depending on resistance type and infection type. None of the included ABR are expected to decrease in our projections, see Figure 5. Annual cases of ESBL, which is currently the most frequently reported type of resistance in Sweden (about 70 percent of all notified cases), are expected to almost double (1.97 times) by 2030 and more than 4-fold (4.52 times) by 2050.

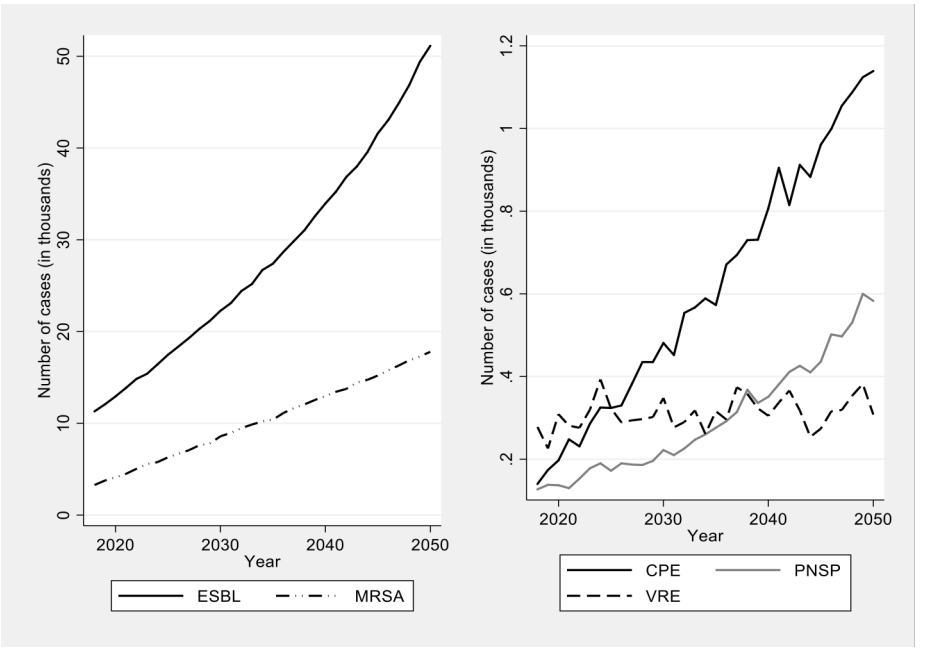

Figure 5. Projections of development of notifiable ABR in Sweden until 2050

The resistance with the greatest expected increase is CPE, with a growth rate of 8.14 between 2018 and 2050 [151].

In order to estimate the costs attributable to resistance until 2050, we estimated the "on top" costs, i.e., the difference in costs between infections caused by bacteria resistant or susceptible to antibiotics. This method means that we have only estimated the additional cost from resistance and not the total cost of treating infections.

Estimations included the cost of hospital stay, outpatient visits, primary care visits, and contact tracing. We discounted future costs by 3 percent annually to calculate the present value. However, we did not take an increase in healthcare costs in the future into account. Furthermore, as shown in Figure 1, the average growth of healthcare expenditure has been approximately four percentage points from 1990 to 2019. If this increase in health expenditure continues, it is reasonable to believe that using today's costs to estimate the total cost in 2050 would probably lead to underestimating the total costs.

Table 5. Healthcare costs due to antibiotic resistance (in thousand EUR)

Year	Inpatient care cost	Outpatient care costs	Prime care costs	Cost of contact tracing	Total costs
2018	14,230	2,000	1,340	5,860	23,430
2030	22,600	3,090	2,280	10,990	38,960
2050	52,810	3,740	2,940	15,110	74,600

If antibiotic resistance increases as projected in the microsimulation model, it is possible that the demand for healthcare will change over time. For example, if outbreaks of antibiotic resistant bacteria were more common in the hospitals, people with less severe health issues would perhaps avoid seeking hospital care and instead visit the primary care. Furthermore, if infections caused by resistant bacteria were more common, other treatments such as cancer treatment or transplants might lead to severe, hard-to-treat infections. No cost for such scenarios has been assessed in this thesis.

7.2 PRODUCTION LOSS AND SICK LEAVE CAUSED BY ANTIBIOTIC RESISTANCE

In paper II, we estimated the impact of morbidity associated with resistance on long-term sick leave days. Results showed that patients with an infection caused by resistant bacteria, on average, had 8.19 long-term sick leave days more than patients with an infection caused by susceptible bacteria. Estimations were based on hospitalized patients with one of the five notifiable types of resistance in Sweden.

Production loss due to morbidity caused by antibiotic resistance was estimated at approximately EUR 1.3 million annually[2]. Calculations were based on the number of hospitalized patients aged 20-64 with an infection caused by resistant bacteria between 2011 and 2015 [154]. As average annual healthcare costs due to resistance from 2012 to 2015 amounted to approximately EUR 19 million [155]. By that means, EUR 1.3 million in production losses would correspond to about 6.8 percent of the estimated annual healthcare costs.

In addition, if the estimation of sick leave is extrapolated to calculate production loss from parents caring for their sick child or pensioners, the total cost of production loss will increase further. In Table 6, costs of production loss due to children or pensioners with an infection caused by resistant bacteria are included. Calculations are based on the number of cases of bloodstream infection, urinary tract infection, or pneumonia from the microsimulation model, which are further divided into three groups; children aged 0 to 14 years, people of working age, and pensioners aged 65 and above. However, for the two groups of adults, an adjustment factor based on the number of patients treated in the hospital, from registered data in paper II, has been used to account for not all urinary tract infections being equally severe. The number of long-term sick leave days from paper II is used in all three groups. The cost of production loss for parents caring for their sick child and working-age people was based on the average wage and social security contributions [152, 153], while the cost of leisure was used to estimate the cost of production loss for pensioners. Costs have been discounted by 3 percent annually to estimate the present value of future costs.

[2] 8.19 LTSL days x number of annual infections x 122.5 EUR/day in cost of production loss (average wage and social security contributions [152, 153]).

Table 6. Production loss costs due to antibiotic resistance (in thousand EUR)

Year	Childcare	Absence from the workforce	Lost leisure time for pensioners	Total cost of production loss
2018	610	1,490	740	2,840
2030	930	2,060	860	3,850
2050	1,060	2,620	1,350	5,030

Production loss costs for those not of working age are more uncertain since these are based on extrapolations rather than actual data and should be interpreted cautiously. However, since infections caused by resistant bacteria are more common in young children (infants) and older adults [8], fully dismissing these costs would be a considerable underestimation of the total production loss due to antibiotic resistance.

Furthermore, the production loss due to premature deaths has been estimated to account for 30 to 43 percent of the total cost of ABR [10-12, 156]. According to estimations by Cassini et al., 167 deaths per year, and about 4,390 DALY lost, are attributable to antibiotic resistance in Sweden [8]. Thus, using these estimations and a monetary value for one DALY of EUR 72,000 would indicate a total cost of production loss due to ABR attributable deaths of about EUR 316 million.

7.3 VALUATION OF HEALTH MEASURES

Besides costs, the value of health effects is essential to understanding antibiotic resistance's overall consequences. However, the estimation of health effects depends heavily on how these effects are measured. For example, as seen in previous literature, generic health measures could be estimated using both QALY and DALY. Furthermore, as shown in paper III, the uncertainty in QALY estimates could further depend on the instrument used to measure.

In paper III, we analyzed the QALY estimates of two different instruments, with one or two value sets each. Results showed that estimated QALY could differ significantly depending on the choice of instrument and value set. Differences were especially pronounced in the most severe health states. Figure 6 illustrates the estimated QALY using the value sets by Dolan [56] and Burström et al. [57] for EQ-5D and the value set by Brazier [63] for SF-6D.

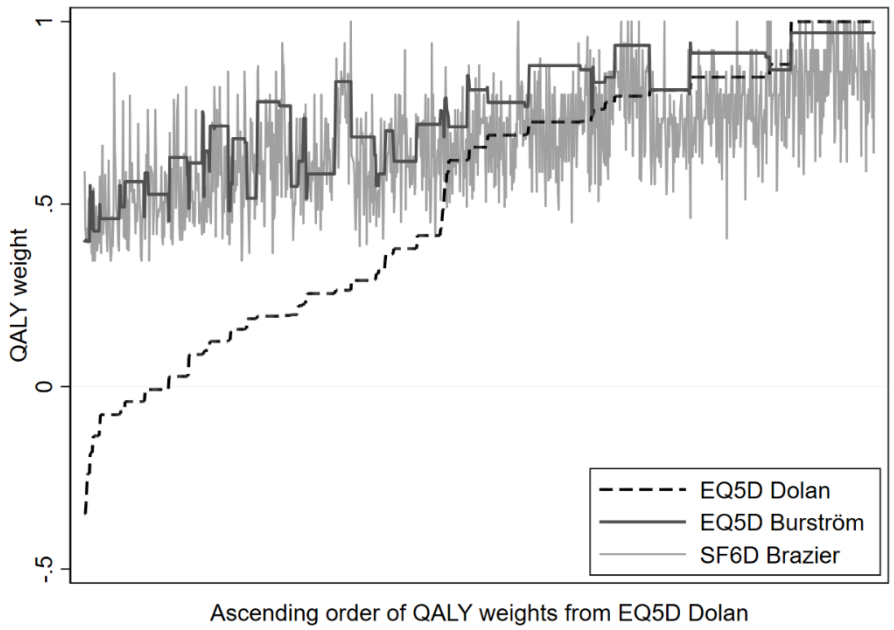

Figure 6. Illustration of estimated QALY using different instrument and value sets

The results from paper III show the importance of transparency in assumptions of health effects used in health economic analyses and the potential effect on decision making. In order to make accurate cost-effectiveness analyses, the influence of potential bias due to the choice of measurements needs to be considered.

The effects of antibiotic resistance on quality of life have not been widely measured. Since antibiotic resistance is not a health state but rather a factor affecting a health state, i.e., an infection, it is hard to estimate the additional effect of resistance and not only from the infection. Studies using QALY to estimate the health effects of antibiotic resistance have not found any difference in the quality of life based on if the infection is caused by resistant or susceptible bacteria [157, 158]. Instead, the calculations have been made based on the length of the

disease, which usually differs depending on if it is resistant or susceptible bacteria causing the infection.

Researchers have also conducted qualitative studies reporting that individuals who are carriers of resistant bacteria feel stigmatized and afraid to infect others [159]. However, no research has been done to quantify the magnitude of these effects, and to the author's knowledge, stigma is rarely included in the cost-effectiveness analysis of different antibiotic resistance intervention studies.

7.4 COST AND HEALTH EFFECTS OF AN INTERVENTION

In paper IV, we used a Markov model to estimate the health economic impact of using temocillin, instead of cefotaxime, in febrile UTI patients. In the analysis, we took indirect effects such as the development of resistance into account and used antibiotic prices based on the average Belgian and UK prices, two countries where both antibiotics were available in hospitals.

This analysis showed that temocillin treatment in febrile UTI patients led to increased costs and a gain in QALY compared to cefotaxime. Furthermore, the analysis resulted in an ICER of about 38,500 EUR per QALY, which was considered cost-effective from a societal perspective with a cost-effectiveness threshold of 50,000 EUR per QALY gained.

To analyze the uncertainties of the results, we used both a PSA and a DSA. The PSA, which took parameter uncertainties into account, found a 63 percent probability that temocillin was cost-effective at current prices compared to cefotaxime. Furthermore, the DSA showed that a longer time horizon and price of drugs had a significant impact on the results.

At the time of this study, temocillin was not marked in Sweden and, hence, only used with a special license procedure that allows the pharmaceutical company to negotiate the antibiotic price at each request. The average price paid by Swedish hospitals in 2018 for temocillin was about 3.7 times higher than the average price in UK and Belgium due to this procedure. At such price levels, temocillin would not be considered cost-effective in Sweden.

8 DISCUSSION

The aim of this thesis has been to assess the economic consequences of antibiotic resistance in Sweden, with regards to the effects on both the healthcare system and society as a whole. Knowledge of these consequences are important to further evolve the ongoing work to stem the development of resistance.

Infections caused by antibiotic resistant bacteria is known to induce costs in several sectors. However, knowledge is less extensive on the additional costs attributable to the resistance mechanism compared to the infection it causes [92]. The difference between the two depends on if the aim of the evaluation is to assess the consequences of resistance only, i.e., that the alternative was an infection caused by susceptible bacteria, or if the aim of the evaluation is to assess an alternative where there were no additional infections at all.

The discussion in this thesis begins with a thorough discussion of how the findings from the thesis can be interpreted and understood in relation to the previous literature and suggested policy to stem the development of resistance. Thereafter, the use of economic analysis as an instrument in the combat of resistance will be discussed. The chapter will end with a wider perspective on resistance, the *one health perspective*, and the role of antibiotic resistance in humans.

8.1 ECONOMIC CONSEQUENCES OF RESISTANCE

Antibiotics has been one of the most essential innovations to evolve modern healthcare to today's standard. As a result, the development of antibiotic resistance could be one of the largest threats to this establishment. Besides the contributions to safer infection care, antibiotics also enables other treatments, such as in cancer care and other immunosuppressive care. Treatments that would be associated with more uncertainty and risks if antibiotics was not available as prophylaxis to avoid serious co-infections.

If antibiotic resistance would evolve to unmanageable levels, it would cause great suffering among patients, but also large economic consequences to both the healthcare sector and to society. To support prioritization and decision-making, and, by extension, to reach the goal of stemming the development of resistance,

more thorough information on the consequences on both global and national level is needed.

Previous research has shown that an uncontrolled development of resistance could significantly reduce the world's GDP [10-12]. In a recent study [7] of the health burden of ABR it was estimated that about 4.95 million deaths worldwide were attributable to ABR in 2019. The authors did not discuss the economic consequences that follows. However, the ECDC estimated in 2009 that ABR contributed to 25,000 deaths, which amounted for more than EUR 1.5 billion in hospital care and production loss costs per year in the EU countries [13]. In a more recent study [8], the ABR attributable deaths were estimated to be 33,000 in the EU and EEA. This study did not include an economic perspective, it is, however, reasonable to believe that cost would have increased at the same pace. In general, mortality and morbidity due to resistance is more extensive in developing countries than in developed countries [7].

A global, or multi-national, perspective is essential when assessing the health economic consequences of resistance, since bacteria easily transfer across national borders. However, even though there are a lot of common actions to be taken, a national perspective is important since healthcare systems, as well as resistance types and levels, differ between countries. To develop effective strategies to combat development of resistance, countries need to base their action plan on the national circumstances. For example, the relevance of using global trends of development of resistance to predict future prevalence, such as in the O'Neill review [10], has been questioned as not informative enough, since it does not consider differences in development between countries [122].

Results from analyses conducted in this thesis aim to support decision-makers in Sweden to better understand the implications of resistance. The microsimulation model used in paper I projects the development of resistance in Sweden. Results could be used to identify resistance types with more aggressive developments, and hence, highlight which types it is most important to affect the course of development for. Furthermore, since costs used in the analysis are depending on a specific infection type and resistance type, it is also possible to assess the development on them separately.

Unlike most other studies we assessed the *additional* resource use associated with resistance, depending on the infection being caused by resistant bacteria or susceptible bacteria. This approach assumes that an increase in the number of infections caused by resistance would not affect the total number of infections but rather the share caused by resistance. This assumption was made based on historical data of the number of bacterial infections per 100 000 inhabitants treated in hospitals in Sweden in 1998 to 2019 [154]. Data showed that the number of infections in total was stable over time, even though the number of

infections caused by resistant bacteria had increased in the same period [160]. Assessing the impact of resistance as the total cost of an infection caused by resistant bacteria, compared to no infection at all, assumes that combating resistance would lead to a significant decrease in infections overall. Such assumption does not seem adequate for the Swedish situation given current infection data. However, it is important to remember that using only the additional consumption related to resistance could lead to too modest estimations of the economic burden, as it harder to account for all relevant costs due to resistance, for example: cost of postponed surgery and associated events [87].

Previous analyses of the economic consequences of resistance have divided costs into healthcare costs and cost of lost productivity. Production loss has been estimated to account for about 30–40 percent of the total cost of ABR [10-12, 156]. Healthcare costs were estimated to be about 23.4 million EUR in 2018 in Sweden and production loss was estimated to be about 318.8 million EUR (2.8+316), a total of 343.2 million EUR. Hence, this suggest that production loss accounts for more than 90 percent on the total costs associated with ABR.

However, the estimations of production loss due to DALYs lost should be interpreted with caution. These estimations greatly exceed previous calculations. The driving force for the discrepancy is presumably the estimated production loss using a GDP-based DALY threshold. Uncertainties in estimates come from both the estimations of DALYs and the value of the threshold. DALYs were estimated in a study with wider perspective than Sweden alone, which could have affected the outcome if assumptions were used from other health care settings not perfectly matching Sweden's. Furthermore, no discounting was done for DALYs lost in the future, which could lead to an overestimation of the production loss.

The OECD has projected the development of AMR between 2015 and 2050, assuming that there are no changes to current trends [14]. In contrast, the O'Neill review, authors assumed a significant increase of resistance, and infections overall, estimating that AMR could lead to an average of 10 million deaths worldwide by 2050 [10]. These analyses differ regarding which countries and which microbes are included. However, De Kraker et al. [122] raise concern on, for example, how attributable mortality data is taken out of context in the original research, applied in a non-transparent way, and then assumed to be static over time to estimate the future scenarios. In accordance with these concerns, it is important to validate and further study these aspects in future research. Furthermore, De Kraker et al. argue that the transparency of the assumptions used in the O'Neill review overall is inadequate, and that it is not fully explained how the uncertainty in input parameters affects the results. Overall, the results of production loss illustrate that methodological choices and assumptions matter for the outcome of the estimations.

In paper IV on the cost-effectiveness of temocillin compared to cefotaxime, no cost due to premature deaths were included. Given the above discussion, this could lead to an underestimation of the actual benefits of temocillin, since a higher number of individuals died from secondary infections in the cefotaxime case. Since health economic analyses aim to support decision-makers it is important to be aware of and transparent about the potential limitations in methods or assumptions used.

Overall, the economic consequences of resistance are significant for society. However, the magnitude and potential future impact is hard to fully grasp. A transparent method to assess the economic consequences of resistance is an important first step to understand the scope and to further support the efforts taken to combat resistance.

8.1.1 Methodological considerations

Methodological choices and assumptions used in modelling could have great impact on the outcome and comparability of analyses. In the estimates presented in this thesis, measures of production loss will have a great impact on the overall costs of resistance. However, as the study on Swedish data was limited to estimating the production loss from work absence only, it is not clear to what extent the societal costs are fully reflected.

This thesis has been limited to only include the consequences of five types of resistance, those notifiable according to the Communicable Diseases Act [65]. Even though the most severe forms of antibiotic resistance are notifiable, there are a range of other variants (for example, Carbapenem resistant *Pseudomonas aeruginosa* (excluding those resistant to colistin)), with clinical significance and, hence, potential consequences for the healthcare sector and society. According to calculations used by Cassini et al. [8], based on data from EARS-net, 90 percent of cases in Sweden are caused by one of the notifiable resistance types. Since other variants are not reported in the same way it is difficult to estimate the economic impact of these resistance types. If the cost of excluded resistance types was assumed to be the same as the average of notifiable types, the total costs would be about 10 percent higher than estimated in this analysis.

Furthermore, in this thesis I have not been able to include the cost of potential effects arising from a scenario where the healthcare system does not have access to effective antibiotics. These costs have been excluded as data to interpret the effects of no more effective antibiotics are lacking. A dystopic scenario where all healthcare would be annulled is, however, not probable. Rather, healthcare will remain but with changes in routines and with an increased risk of adverse events from treatment. Irrespective of the magnitude of such secondary effects of

resistance, it is reasonable to believe that as resistance increase, the healthcare sector will be negatively impacted and the cost and burden on health will be noticeable. Excluding these effects from the health economic analyses would be to underestimate the full impact and is hence a limitation of this study.

Lack of data could also impose other limitations to the estimations of economic consequences. In a recent study by the Antimicrobial Resistance Collaborators [7], the authors highlight the potential limitation of possible selection bias in microbial surveillance data if cultures are made only if a patient does not respond to initial antibiotic therapy, and not by routine. This kind of surveillance data is usually used to estimate the prevalence of a resistant bacteria by using the proportion of resistant bacteria found in all cultures conducted. If a selection bias exists, i.e., it is more common to draw a culture if there are strong reasons to believe there is a resistant bacterium, then using this surveillance data could lead to an overestimation of the prevalence of resistance. If estimations of prevalence are later used to estimate the economic consequences, this kind of bias would potentially indirectly affect also that analysis.

A strength with the estimations made in paper I and II is that they are based on registered data on actual cases. The possibility to link data in different registers through personal identification numbers is a great advantage when using Swedish data in research. Few other countries have this possibility and, hence, even though a lot of different data about cases with resistant bacteria are collected it is not always possible to use it in the same way if all relevant variables were not collected at once.

8.2 THE USE OF ECONOMIC ANALYSES

As previously stated, the use of economic analyses is essential to fully understand the impact of resistance on society. However, projections and modeling are just results of the assumptions and choices made by the individual researcher, and hence imposed with uncertainties. Results from economic analyses are reliant on the choices of models, input data and potential assumptions needed to form an adequate analysis. In this section I will evolve on the methodology used in this thesis and the use and potential limitations of economic analyses as a tool to assess the health economic consequences of resistance.

8.2.1 Estimating costs

One of the base assumptions to make when conducting a health economic analysis is to choose the perspective of the analysis. When conducting an analysis

in a Swedish setting the two most relevant approaches are the healthcare perspective, focusing on the effects on the healthcare system, and the societal perspective, accounting for all effects and cost arising from a disease or treatment independent of who is affected [22]. In this thesis, I applied a societal perspective as antibiotic resistance is a health issue that goes beyond the health care sector.

The healthcare perspective is a narrower perspective since it mainly accounts for the *direct* effects and costs associated with a health state. The advantage of a healthcare perspective is that, as long as a health state is treated alike in different countries, analyses are comparable between countries and possible to use also outside of the country where analysis was conducted. The societal perspective, on the other hand, is more dependent on national structures of, for example, sick leave benefits and other compensations systems, which could affect to what extent an individual could be absent from work because of their current health state. This kind of national considerations complicates transferability of results and analyses across countries.

In previous research about the economic consequences of resistance, healthcare costs have been estimated using similar approaches, for example, length of stay in hospitals or the number of GP visits needed for each case of resistance. Methods to estimate production loss, on the other hand, differ between studies. For example, in the O'Neill review, production loss was estimated as the change in GDP from AMR attributable deaths among people of working age [10]. In the ECDC report production loss was on the other hand based on the number of cases times the number of extra hospital days due to infection (used as a proxy for the number of days absent from work since this information was missing) [13]. Production loss due to premature deaths was estimated using likely earnings of a patient who died from ABR. When methods to estimate production loss are so diverse as they are in these two cases, comparability between studies is hard. Additionally, as different methods are used, results get less transparent and harder to communicate to people less familiar with the subject. However, using different methods to estimate the societal costs is still important. As shown in the previous section, the estimations suggested in this analysis differ significantly from previous studies. However, as the societal costs are intangible costs, i.e., not possible to actually measure, different approaches are needed to understand the uncertainties in estimates.

The different methods used by O'Neill and ECDC can be seen as top-down and bottom-up approaches, respectively. Top-down, which O'Neill uses, refers to a method that uses total health expenditures and disease-specific rates to demonstrate disease-specific costs, while bottom-up, used by ECDC, refers to a method that uses unit costs per case to calculate the sum of cost on an illness or health state [161]. Since healthcare cost in CEAs usually are measured using a

bottom-up perspective, the same perspective should be preferred also when estimating the production loss costs. In paper II, we used Swedish registered data on hospitalized cases with an infection caused by either resistant or susceptible bacteria to estimate the additional days of sick leave due to resistance. This estimate could be used to estimate the costs of production loss, using a bottom-up method. The advantage of using a micro perspective, as in the papers included in this thesis, is that at a micro level one can see more exactly what affects the outcome and thus make adjustments based on it. A top-down approach is more difficult to use as a basis for decision-making, when changes are needed in, for example, the care structures or treatment guidelines.

Furthermore, we used the human capital method to estimate the cost of production loss due to morbidity since it is not probable that absence due to an infection is long enough for a worker to be replaced, which is the main assumption in the friction cost method. This was similar to the ECDC approach [13]. The human capital method is suitable when time with a specific disease is short and relatively temporary. The friction cost method is, instead, more suitable when the disease leads to permanently decreased ability to work, and thereby, the probability of being partially or fully replaced is higher.

8.2.2 Estimating health effects

Health economic analyses are used to account for both costs and consequences in health. Besides information about costs, this requires information about the health due to a disease or intervention in the population of interest. As described earlier health could be measured in different ways. In cost-of-illness studies, the most relevant factors are the size of health issues in a population, which groups are at risk, and the trends in development of health states over time. In cost-effectiveness analyses, not only the prevalence or incidence of mortality and morbidity are of interest, but also the effects on the HRQoL [22]. Moreover, prioritizing healthcare aims not only for an extended life expectancy, living these extra years in good health is just as important [162].

Previous studies on antibiotic resistance have used DALY to measure overall health effects. However, since antibiotic resistance is not a health state, but rather a factor affecting health, quality of life of infections has been used for estimating the effects of resistance. As mentioned earlier, different approaches have been used to estimate the incremental effects of resistance. Studies where the counterfactual scenario to resistance is no infections at all uses the total health effect from infection, whilst studies focusing on the difference between infections caused by resistant and susceptible bacteria uses the additional effect. The first

method requires information on quality of life of infections only, while the second also need information on the impact of resistance on the infection.

Measuring the impact of resistance on infections is difficult. Previous studies have assessed the difference in time, i.e., that a patient with resistant bacteria in general is hospitalized for a longer time period than patients with susceptible bacteria. To the author's knowledge there is no research on the difference in quality of life during the time of infection, associated with resistant or susceptible bacteria. A probable reason for this lack of knowledge is that methods to measure quality in life are not sensitive enough to capture small changes in quality of life when duration of illness is relatively short, as is the case with severe infections.

When using QALY to estimate the quality of life, different instruments are variously sensitive to measure small changes in health. SF-6D has, for example, been shown to be more sensitive than EQ-5D-3L [163]. The EQ-5D-5L has been developed to account for this drawback in the previous version. However, until recently, the value set developed for the 3L version was still used to estimate a QALY from the 5L version, which most probably removed the positive effects of more diverse levels. In order to get accurate estimates, value sets are as important as the instrument used to measure health. In paper III, we assessed the QALY outcome form EQ-5D and SF-6D using two different value sets for EQ-5D. As previous studies have shown [163, 164], QALY estimates differ greatly in the more severe health states, depending on instrument and value set. However, our study showed that the experience-based value set by Burström et al. rendered more comparable estimates to QALY estimated using the SF-6D Brazier instrument and value set, over the entire range of health state severity. Since it is not possible to know which instrument and value set that estimates the most truthful values, it is not possible to decide on one that is always the preferred one. It is therefore important to enhance knowledge of how various instruments and value sets affect health-related output and, to some extent, the cost-effectiveness analyses. Moreover, researchers and decision-makers should be aware of the implications of different methods for economic analyses that support decision-making and prioritization. For example, since temocillin, evaluated in paper IV, is primary life enhancing, using QALY estimates from another instrument or value set could affect the cost-effectiveness result. Future research validating he results from the CEA in paper IV should consider using different QALY estimates to assess the impact of the method used on the results.

Another aspect of quality of life in persons affected by resistance is that of stigmatization due to carriership of resistance. It has been argued that some individuals feel stigmatized due to the feeling of being seen as contagious [159]. However, studies of possible stigmatizations are qualitative, meaning that the magnitude of such health effects is unknown. Inaccurate or lacking information

on the effect on quality of life from resistance could potentially lead to lower prioritizing of interventions aimed at reducing development of resistance. Focus only on the monetary costs, while not being able to include the value of health effects, could lead to decision-makers allocating resource to other areas, only because there is more evidence in those areas, independent of the actual effects on health, and by extension on society.

As shown in this theses, health related outcomes could be measured using different methodologies. Not only difference in measuring QALY is of importance, but also differences between DALY and QALY, in relation to ABR. Since DALYs are estimated using a specific weight for infectious diseases, the advantage of DALY is that it is directly related to the infectious disease. In contrast, QALY is measured using a (generic) weight dependent on different dimensions of health, but unrelated to infectious disease. However, the advantage of QALY is that since it is generic and disengaged from the type of condition, and rather focusing on the health state, it is more objective to use when comparing outcomes of different health conditions.

8.2.3 Economic analyses of preventive measures

Health economic analyses, particularly CEA, are important tools to support decision-making and prioritization in healthcare and the public health area since it takes both costs and health effects into account. The output is, however, as previous stated, to a high degree dependent on the methodological considerations and assumptions made. Traditionally when CEA is used to analyze the outcome of different treatments within healthcare, costs and health effects are assumed to have occurred in about the same time. For example, when treating a patient in the hospital, most healthcare costs occur immediately and, at least some, health effects occur in relative proximity. However, as it comes to preventive measures, such as interventions to stem the development of resistance, a large part of the costs comes early while the health effects might be delayed several years. Healthcare and public health interventions are usually evaluated using similar approaches and methods. However, similar methods applied on interventions with differences in time horizons could affect the cost-effectiveness outcome in unforeseen ways.

Discounting is rational when costs invested return a health effect roughly simultaneously, regardless of them happening today or in a few years. However, when money is invested early, while health effects occur much later, there will be an imbalance in the analysis, as the actual discount rate will differ between the cost (lower, due to shorter time to occurrence) and the health effect (higher, because longer time to occurrence of event) caused by that cost. When

considering economic analyses as a support of prioritization between interventions to decrease the development of resistance it is important to consider the potential effect of discounting on the results.

Arguments in favor of using discounting refer to *time of event* being an important parameter to consider. However, in the case of prevention with delayed effects on health, discounting could cause a problem to the interpretation of results and potentially mislead decision-makers. Consider the following example:

Example Assume the following two alternatives, with 3 percent discount rate:

1) a *treatment* of an infectious disease, used for infection where costs and health effects occur at the same time (year 8). ICER is calculated as:

$$ICER = \frac{\Delta costs\ x\ discounting}{\Delta effects\ x\ discounting} = \frac{\Delta costs}{\Delta effects} \text{ x } 1$$

The relative effect of discounting on the ICER is, thus, equal to 1.

2) a *preventive* measure to avoid future infection, used to prevent an infection that would have occurred in 8 years. However, investments are made today (year 0). ICER is calculated as:

$$ICER = \frac{\Delta costs\ x\ discounting}{\Delta effects\ x\ discounting} = \frac{\Delta costs\ x\ 1}{\Delta effects\ x\ 1/(1+0.03)^8}$$

The relative effect of discounting on the ICER is, thus,

$$\frac{1}{1/(1+0.03)^8=} = 1.267$$

In total the ICER of prevention will be 1.267 higher than the ICER for treatment. This example illustrates that the discount rate has a negative effect on the ICER for prevention even though it is the same health state with health outcome happening at the same time. However, outcomes will differ only because costs occurred at different times. Thus, discounting could potentially be a disadvantage for preventive treatments, such as stewardship programs or other interventions to stem resistance over time, which needs to be considered when analyzing the cost-effectiveness of preventive interventions. Hence, it is essential to fully understand the impact of discounting when analyzing prevention and to be aware that the cost-effectiveness of prevention is often affected by a methodological assumption.

Another methodological limitation for antibiotic clinical research is that studies on the effect of antibiotics are limited to only being non-inferiority studies because of ethical considerations. Meaning that potential benefits from one antibiotic treatment compared to another is not possible to estimate even though it has been shown in pre-clinical research. This shortcoming in methodology due to ethical considerations further impact the cost-effectiveness analysis since comparative studies between antibiotic treatment could be insufficient.

8.2.4 Ethical considerations

When conducting research using personal data, researchers need to consider the potential risk the research could have on individuals' safety and integrity. Potential risk should be weighed against the potential benefits of gaining new knowledge from the research conducted. In the case of my thesis and the papers included, there are no direct benefits for the research subjects themselves. Instead, the main benefit comes from increased knowledge of the effects of resistance overall. By extension, increased knowledge of consequences could be beneficial to further evolve on interventions to stem the development of resistance, which could lead to an increase in population health.

The main risk with the studies conducted in this thesis is that individual level register data contains personal and sensitive (health-related) information about a large number of individuals. To minimize the risk of identifying specific individuals, we used anonymized data with reference numbers instead of personal identification number. Since anonymization was carried out by register holders, and since we used large datasets, the risk of back-tracing should be minimal, and integrity should therefore not be jeopardized.

Furthermore, to protect individual integrity, it is important for researchers to only request the data specifically needed for the proposed analysis and to store data in a safe space. It is essential to ensure that individual data is not accessible for people outside of the research group and that no data is collected only for the sake of having more data. On another note, one could also argue that it would be unethical, and a waste of resources, *not* to use the data collected in registers for purposeful research with benefits to society.

8.3 ONE HEALTH – BEYOND THE HUMAN PERSPECTIVE

The focus of this thesis has been on the human perspective of antibiotic resistance. However, the effect on humans is only one part of the total effects of resistance. Most sectors intervene with each other and effects on the human side

could have potential side effects that also impact animal and environmental health, and vice versa.

The One Health perspective aims to include all sectors with potential effects on the development of resistance. One health action plans have been developed with focus on how to deal with bacteria that transmit between humans, animals and the environment [165]. Additionally, a one health framework to estimate the cost of antibiotic resistance has been suggested by the Global Antimicrobial Resistance Platform for ONE-Burden Estimates (GAP-ON€) network [166]. This structure uses a bottom-up approach to estimate the total costs from a societal perspective.

Sweden has a relatively favorable situation regarding antibiotic resistance from an international perspective. One contributing factor is the responsible use of antibiotics in both human and animal care. As a comparison, the antibiotic sales per kg estimated biomass in Swedish human and veterinary medicine in 2018 were 112.1 and 12.5 mg active substance, respectively. Compared to an average of 133.3 and 104.6 mg for human and animal medicine, respectively, in the EU countries [167].

The context of antibiotic resistance differs between countries, which postulate different interventions to combat development of resistance on a national level. The GAP-ON€ framework, developed to be used in most countries, is a good start to better understand the consequences overall. However, to tackle the national challenges of resistance, and given national circumstances of antibiotic consumption or stewardship programs, specific analyses are needed on a national level. For example, analyses in paper I and II are essential from a Swedish perspective to better understand the economic consequences based on the actual impact on Swedish healthcare and productivity. The GAP-ON€ framework is more useful for countries who lack the capacity to develop country-specific models on their own. Furthermore, as stewardship programs in countries with low levels of resistance focus on more appropriate antibiotic use in human and animal health in order to stem development of resistance, interventions in low- and middle-income countries instead need to focus on environmental interventions such as access to clean water, sanitation, or food hygiene and safety.

9 CONCLUSION

> "Given that the dangers of resistance are widely acknowledged, why isn't more being done? One reason is that antibiotic resistance has fallen victim to evidence based policy making, which prioritises health problems by economic burden and cost effectiveness of interventions. Health economists have been unable to show that antibiotic resistance costs enough to be a health priority."
>
> Smith & Coast 2013, *The true cost of antimicrobial resistance*, BMJ [87]

This statement was given by Smith and Cost in 2013. Since then, several economic analyses have been conducted to increase the knowledge of the economic consequences of resistance. However, as shown in this thesis it is not a straightforward estimation. Different approaches and methods have been used, and different estimates of consequences have been suggested. Difficulties illustrated above still give legitimacy to the statement by Smith and Coast. One of the main goals for health economists is to improve knowledge about health economic consequences, but the potential negative consequences in prioritization when data is scarce, or contradictory, need to be further addressed.

In the case of antibiotic resistance, most people agree that it is a global health concern that needs to be considered. Many governmental leaders all over the world have stressed the fact that antibiotic resistance needs to be tackled rapidly in order to avoid a pandemic situation without effective antibiotics. The more antibiotics we use, the faster the antibiotic resistance increases. With increased antibiotic resistance, infections become more difficult or impossible to cure, which in turn causes great suffering and high costs for healthcare.

The results from this thesis, and the studies included, suggest a significant health economic impact of antibiotic resistance in Sweden even though the effects from animal and environmental health is not yet included. Even accounting for potential shortcomings in using health economic analysis, it is an essential tool to understand a serious health problem in the light of limited resources. Furthermore, in order to achieve progress against the development of resistance, it is important to allocate resources to the interventions believed to contribute the most to reaching that goal.

10 FUTURE PERSPECTIVES

Future research on the health economic effects of antibiotic resistance should touch upon the non-healthcare costs of resistance. Primarily the societal consequences of ABR attributable deaths and quality of life losses. Furthermore, the results in paper II could be reproduced in other countries where the sick leave benefit system differs from the Swedish setting. Comparing such results with those from paper II could add information on production loss independent of national structures of social security systems.

Another important aspect, to facilitate better cost-effectiveness analyses of interventions, is assessing the direct effect of resistance on QALY estimates. In this work, researchers should consider the impact of different methods used to estimate health effects, and preferably use different estimates in sensitivity analyses to fully understand the impact of health on the cost-effectiveness result.

Furthermore, future research needs to include more types of resistance if they have a significant impact on the healthcare system or population health. Also, accurate studies on the secondary effects of resistance are essential to understand the entire impact of resistance on human health. Analyses should be constructed to be reasonable scenarios and not only worst-case scenarios where no antibiotics are effective.

Finally, as mentioned before, future study needs to take a One Health perspective to fully grasp the societal consequences of antibiotic resistance, to enable interventions to be directed towards other sectors besides the human sector as well.

ACKNOWLEDGEMENT

I'd like to take the opportunity to express my gratitude to everyone who has supported me through this process, and to **Folkhälsomyndigheten** for giving me this opportunity. Thank you to all my **colleagues** at the agency who shared their unlimited knowledge and gilded my days at work even when it was stressful.

Thank you to my supervisors – **Mikael** and **Josefine** – for your guidance, support and feedback throughout the project. Thank you, **Lisa**, for being a fantastic leader, supported me and pushed me to evolve as a health economist. Thank you, **Anders,** for being a great colleague and co-supervisor. I really appreciate the times we worked together, and the support you have given me – through your knowledge and with pep talks in the Ph.D. project.

To my **friends** – thank you for supporting me when it felt hard to go on with this project. Thank you for making me ease my mind when we are together and do the fun things in life. A special thanks to **Sara** who always been there for me, undoubtedly supporting and cheering me in every aspect of life. Thank you to **Ida** and **Hanna R** for being the most amazing friends, always by my side (even though we are miles apart). Thank you to **Hanna FW**, for being a great friend and for all your support and advice in both work and personal life.

A special thank you to **Ellen**, my friend and forever colleague no matter where we work! Thank you for all the time we spent together, for all the fun we had at work, but mainly for all the fun we have had in our spare time. It is a privilege to have a close friend as your closest colleague. Thank you for all your sharp insights in this work and in life overall.

To my family – **Mamma**, **pappa**, **Elin** och **Hanna** – Jag är så tacksam för att ni alltid finns nära mig och stöttar mig i allt jag tar mig för. Tack för att ni alltid ställt upp för mig – in sickness and in health. Tack för er omtanke när jag kämpat ända in i slutet av detta projekt, och tack för att ni har förstått och accepterat att jag inte haft så mycket tid över till annat.

Lastly, thank you **Jakob** for supporting me and encouraging me to finalize this project. Your support has been invaluable. Thank you for cheering me and for listening to me babbling about this thesis for such a long time. I'm so grateful for all the things you've done (and do) for me. Thank you for the time we spend together – I love you.

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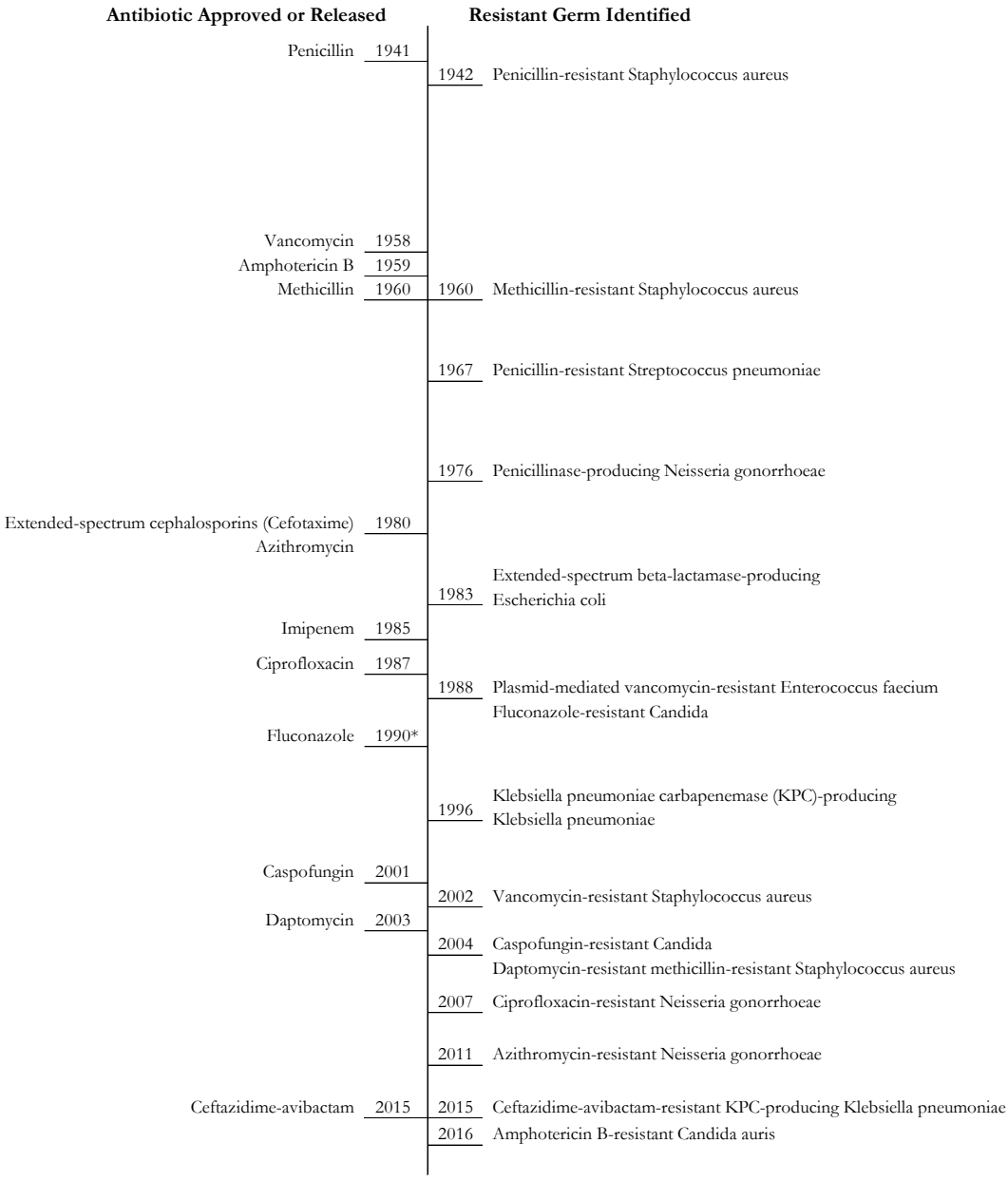
APPENDIX

Timeline over the approval of antibiotics and the development of resistance.



* FDA approved

Ref: https://www.cdc.gov/drugresistance/about.html