

MAKING INFORMED DECISIONS

THE VALUE OF TESTING STRATEGIES IN HEALTHCARE

SIMON VAN DER POL

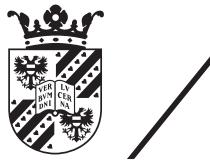
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Making Informed Decisions

The Value of Testing Strategies in Healthcare

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CHAPTER

1

General Introduction

After March 2020, a novel coronavirus (SARS-CoV-2) spread globally from South-East China, causing millions of deaths and hundreds of millions of cases globally¹. As the transmission of this new virus was unknown, and no vaccine or curative treatment was available yet, governments worldwide severely limited mobility and social life by imposing lockdowns. Health systems were not equipped to deal with the enormous number of cases if the virus could run its course, hence, governments aimed to “flatten the curve”². Especially in the early stages of the pandemic, decisions had to be made under great uncertainty: the modes of transmission were not clear³ and due to a shortage of tests the incidence of new COVID-19 cases was unknown⁴. In the Netherlands, the testing infrastructure was reported to be ready to be used for all citizens with COVID-19-related symptoms towards the end of the Summer of 2020. However, as soon as the second wave hit the country in the Fall, the testing capacity was insufficient; resulting in long waiting times for people with symptoms, delayed contact tracing and an inadequate overview of the outbreak. Eventually, this led to a second lockdown, which would last well into 2021. The lockdowns saved many lives, but came at great economic costs^{5,6}: the Dutch Gross Domestic Product (GDP) for 2020 dropped by 3.8%⁷ and is expected to be structurally reduced with € 12 billion⁸. The way out of these lockdowns consisted of continued social distancing measures, increased testing and, eventually, rapidly developed vaccines. When considering the initial public health response to the outbreak of any infectious disease, testing and tracing is crucial; hence, having an adequate testing infrastructure is essential.

COVID-19 has shown the world what devastating effects an infectious disease can have on individuals and society, especially when there is no cure available. Experts have warned of a similar threat, which is the emergence of antimicrobial resistance (AMR). Towards the end of the 1920s, penicillin, discovered by Alexander Fleming⁹, caused a revolution in medicine: enabling doctors to cure infections that would previously have been fatal and to safely perform increasingly invasive surgeries. Medicine worldwide has come to depend on antibiotics, used both curatively against acute infections as well as prophylactically against likely infections: common procedures such as a hip replacement, performed 38.000 times annually in the Netherlands, would be very dangerous without antibiotics¹⁰. Unfortunately, bacteria can become resistant to antibiotics through natural selection, resulting in reduced effectiveness of treatments. Currently, AMR is estimated to cause over 30.000 deaths annually¹¹ and AMR is expected to rise in the years to come¹². Considering the reliance on antibiotics in the healthcare system and rising AMR rates, experts have warned of a post-antibiotic era, where high resistance rates require a complete restructuring of modern health systems^{13,14}. This post-antibiotic world may be very similar to the COVID-19 lockdowns: with society needing to be constantly aware of the dangers of infection, strict infection preventive measures in place and mobility severely restricted. New antibiotics may solve the issue of AMR, however, few have been developed in recent years, probably due to a lack of economic incentives. To prevent resistance, novel antibiotics are used only as a last resort¹⁵. Various governments are looking to new funding models to incentivize the development of novel antibiotics, such as a subscription model in the United Kingdom¹⁵. Such a subscription enables developers of new antibiotics to get paid for making antibiotics available, whether they are used or not. This is different from the traditional payment model, where the income of drug companies is based on the number of tablets, vials or tubes sold. However, developing new treatment requires a lot of time. Preventing AMR from occurring may be more feasible on the short term; this requires a reduction in antibiotic use, as AMR and antibiotic consumption are tightly connected¹⁶. Vaccines can play an important role here: if infections and related disease are prevented,

there is no need to consult a doctor and initiate antibiotic treatment. Vaccination will not prevent all illness, and when a patient does get ill and seeks care, he should get the appropriate treatment. In many cases however, antibiotics are inappropriately prescribed, for example when a patient's disease is caused by a viral infection¹⁷. Knowing when to prescribe an antibiotic, and if so, which one, can reduce unnecessary antibiotic prescriptions. Various diagnostic tests are available which can aid in this decision: to prevent AMR, having an adequate testing infrastructure is essential.

A global health approach to combat antimicrobial resistance

Governments worldwide have made it a priority to counter AMR, covered in the global action plan on AMR from the World Health Organization, covering five objectives¹⁸:

1. Improving the awareness and understanding of AMR, by educating the public from a young age, but also improving AMR-related education for professionals in healthcare and the veterinary sector.
2. Strengthening surveillance and research, including more epidemiological data on AMR, but also more economic research on the costs of AMR and cost-effectiveness of AMR-reducing interventions.
3. Reducing the number of infections, both in healthcare, in the community and in the veterinary sector, through infection prevention, education and vaccines.
4. Optimizing the use of antimicrobial medicines, by collecting more data on antibiotic use, introducing effective diagnostics and improving the rational use of antibiotics.
5. Developing an economic case for sustainable investment in new medicines, affordable diagnostics and vaccines, including analysing the costs of the burden of AMR.

Collaboration across disciplines is important to reach these goals: medicine, microbiology, economics, sociology and agriculture, but also, collaboration across governments, both locally and globally; and across the public and the private sector. Within the health sector, this translates to various stewardship models¹⁹. Antimicrobial stewardship entails a collaboration between physicians, pharmacists and microbiologists on appropriate and timely diagnostics, empirical therapy based on up-to-date local epidemiology and streamlined personalized therapy. In addition, infection prevention stewardship considers hygienic measures to prevent the spread of resistant bacteria and surveillance. In healthcare settings, patients carrying a resistant bug should be identified in an early stage and isolated to protect other patients. Finally, diagnostic stewardship makes sure the right diagnostic is performed at the right time. Rapid diagnostics can enable a theragnostic approach for antibiotic prescriptions, where targeted antibiotics are prescribed to patients within hours. Containing the spread of resistant organisms, preventing the use of unnecessary antibiotics and more targeted antibiotic treatment are required to combat AMR, and in all these processes, microbiological tests play a vital role.

In economic terms, AMR can be regarded as a negative externality associated with the consumption of antimicrobials^{20,21}. When taking an antibiotic, patients (understandably) prioritize their own health as opposed to the long-term effects on society. For a clinician, it usually is more important to treat the currently-consulting patient than to prevent potential (and highly uncertain) health losses caused by AMR in the future. AMR is an interpersonal issue, as it affects not only the individual taking antibiotics, but also surrounding people²⁰. In many ways, it is similar to the issue of climate change, where individuals

responsible for carbon emissions do not bear the cost of climate change in the future¹⁴. Both AMR and climate change are global issues, where nations responsible for antibiotic consumption or carbon emissions may not be hit hardest by the outcomes. Both issues are also inter-generational in nature, as the potential effects of AMR and climate change are long-term problems²⁰.

The value of tests to counter AMR is a clear focus of this thesis: although there is broad support from clinicians²², researchers^{11,14}, companies²³, and policy makers¹⁸ alike, it remains difficult to assess the value of AMR-reducing interventions. In this process, lessons learned outside the clinical field of infectious diseases are also considered.

Screening, diagnosing, and monitoring: the right tool for the job

Tests can have various aims; three are considered in this thesis: screening, diagnosing and monitoring. Screening tests are applied to a broad population, for example screening all school-going children for growth defects, breast cancer screening for all women from the age of 50, or screening all patients for vancomycin-resistant *Enterococcus* on the gastro-enterology ward. The aim is to find disease in a defined population, in people without, or unaware of, symptoms²⁴. Especially for diseases with better outcomes if treatment is started at an early stage, screening can be beneficial. A common example is cardiovascular risk management, which aims to place patients in a risk category based on a combination characteristics, such as sex, age and smoking behaviour, and simple diagnostic tests: blood pressure and cholesterol tests²⁵. Lifestyle advice and treatment to lower cholesterol levels and blood pressure are aimed to prevent, among others, future cardiovascular disease, diabetes and chronic obstructive pulmonary disease (COPD).

With diagnostics the aim is to identify the most likely cause of, and optionally optimal treatment for, a previously undetected disease in a clinically-suspect patients who is seeking care^{26,27}. This concerns patients that experience complaints and consult a clinician who can hopefully prescribe a cure. This could be a person with a persistent cough, or a patient with shortness of breath after exercise. In the Netherlands and other countries where the general practitioner (GP) acts as a gatekeeper to the health system, the GP has an important role in determining whether a patient requires immediate treatment, should be referred to specialist care, or can wait for the complaints to fade without treatment. Next to clinical experience, GPs can use clinical rules and diagnostic tests to aid in this decision process. An example of a test commonly used to diagnose patients is a C-reactive protein (CRP) test, which can be used in the GP office for patients consulting for respiratory complaints. The CRP test can be used to discriminate between a viral and a bacterial infection and can inform the GP and patient on the decision to prescribe an antibiotic. An example of a clinical score, is a scoring system for deep-vein thrombosis (DVT) developed by Wells *et al.*, during clinical assessment, patients can be stratified in three risk categories during clinical assessment: low, moderate and high²⁸. Patients in the high-risk group have an 85% risk of DVT, compared to 5% for the low-risk group. In the case of personalized medicine, having diagnosed a disease may not be sufficient to initiate treatment; especially if the treatment can cause severe adverse reactions or is very expensive, as is often the case in oncology for example. Companion diagnostics are used to predict whether a specific treatment option will be beneficial for an individual patient²⁹. For example, a test to check whether a mutation is present in a tumour so that this can be targeted by antibody treatment.

Finally, there is monitoring, where a patient is tested periodically to assess a certain bio-

marker. A classic example is the monitoring of blood glucose levels for diabetes patients or international normalized ratios (INR) for patients on anticoagulation therapy. An extreme example would be a patient admitted to the intensive care unit, who is monitored for countless vital signs. As many diseases are chronic in nature, monitoring systems are important in treatment optimization and disease management³⁰.

Currently, the majority of clinical tests are performed in hospitals and diagnostic laboratories, although the exact setting varies between countries³¹. In some countries, centralized, external laboratories have focussed on scale: by improving efficiency, the costs per test can be reduced. In the Netherlands, hospital laboratories and regional laboratories play an important role in the testing capacity; although some laboratories have merged in recent years, the laboratories are relatively small compared to, for example, the German labs³². However, this system was a major point of criticism at the start of the COVID-19 pandemic, as the testing capacity initially was inadequate for the demands during the pandemic⁴. Although the large-scale laboratories place the tests further away from patients, there is also an opposite trend: point-of-care (POC) tests and self-tests bring the tests closer. These tests can provide information on the cause of disease or the effectiveness of medication within minutes and immediately inform the shared decision-making process of the clinician and patient. This knowledge can lead to improved treatment decisions and also to better adherence³⁰. Although these POC tests are more expensive than the equivalent tests performed in large-scale laboratories, these patient-level improvements may make them a worthwhile investment: to make this decision, health technology assessment (HTA) can play an important role. Part I of this thesis illustrates various settings where tests are conducted, but also different types of tests: from simply measuring the weight of a school-going pupil to custom-developed polymerase chain reaction (PCR) tests which can identify resistant bacteria at the genetic level.

Health technology assessment

Since the thalidomide affair in the early 1960s, a drug that had a severe teratogenic effect, it has been clear that new medicines should be subject to rigorous safety regulations³³. In the Netherlands, the *College ter Beoordeling van Geneesmiddelen* (CBG) was launched in 1963 and safety, effectiveness and quality became important requirements for new drugs entering the market³⁴. As costs related to the delivery of care have been rising in the past decades³⁵, governments worldwide have come with measures to curb increasing costs. This led to the rise of the field of pharmaco-economics, a field that relates the costs of drugs to the clinical outcomes experienced by patients³⁶. Although this field has its roots in the assessment of medication, this can be applied to all health technologies. These economic evaluations usually relate the costs related to the implementation of a health technology to a generalizable patient outcome, such as quality-adjusted life years (QALYs). Increasingly, other factors have also received attention regarding the implementation of health technologies, such as patient preferences, organization of the healthcare system and ethics; all these factors that can either promote or restrain a new intervention from being implemented, are assessed in an HTA.

HTA has been defined as a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle, with the purpose to inform decision-making in order to promote an equitable, efficient and high-quality health system³⁷. This is an interdisciplinary field which has increasingly become important in making decisions related to interventions in healthcare and ensuring a sustainable health system. Globally, there are many guidelines on how to perform an HTA; for

Europe the HTA Core Model has been developed which covers nine domains³⁸. Table 1.1 shows how these domains are relevant for the assessment of tests. Through HTA, the use and reimbursement of tests in clinical practice can be evaluated. However, the HTA process for tests has been lacking behind, for example, pharmaceuticals³⁹. Tests, and in particular diagnostics, are more complex to assess as the clinical outcomes will depend on the treatment options following the test results. The main focus of this thesis are economic evaluations – below, some concepts which explain the difficulties in assessing the cost effectiveness of novel diagnostics are introduced. Although also important and sometimes referenced in this thesis, the focus of this thesis is not on issues related to safety, patient and social preferences and law.

Health-economic analyses

In most economic evaluations in healthcare, the costs of a new medical technology are compared to the clinical effects, usually expressed as QALYs. QALYs combine the length of life, i.e., life years gained, and the quality of life. The quality of life usually is between 1 and 0, ranging from perfect health to death. The most-used outcome in cost-effectiveness analyses (CEAs) is the incremental cost-effectiveness ratio (ICER), the costs divided by the clinical effects. The ICER can then be related to a willingness to pay, which ranges from €20,000 to €80,000 per QALY in the Netherlands, depending on the disease burden. A strength of these analyses is that the effects of the intervention can be extrapolated beyond the time horizon usually captured within a clinical trial. Short-term clinical outcomes, such as the disease duration and effectiveness of treatment, usually can be captured in clinical trials, while long-term outcomes, such as life years gained, can be captured in post-market surveillance, or extrapolated using health-economic methods. For this purpose, health-economic models, in which individual patients or patient cohorts are followed for a certain period, are used. The Dutch guidelines recommend a lifetime horizon, where patients are simulated for the remainder of their life⁴⁰. Various costs should be considered, of course the costs directly related to the intervention, but in some countries also productivity losses or costs accrued elsewhere in the healthcare system.

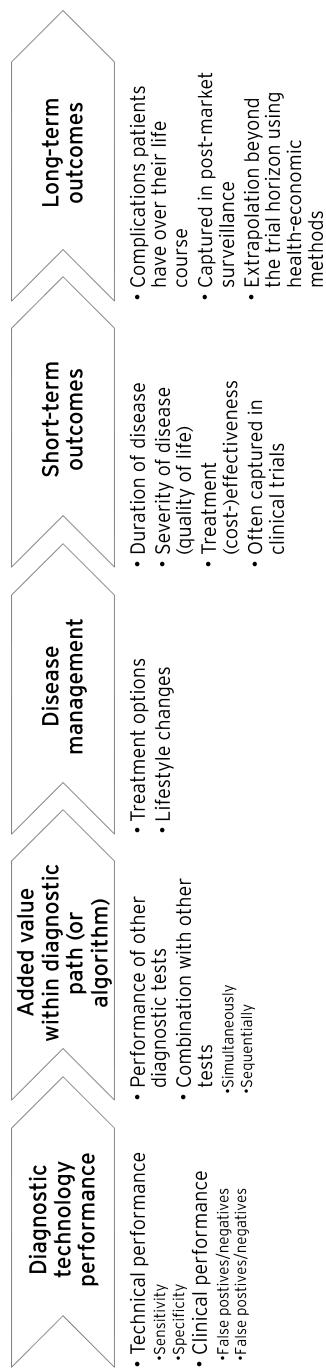
Considerations for health-economic analyses for diagnostics

Compared to pharmaceuticals there are major differences when assessing the clinical value of a diagnostic strategy. The accuracy (i.e. sensitivity and specificity) of a diagnostic needs to be adequate, but more important for its cost-effectiveness is the clinical utility⁴¹. The added value of the diagnostic in clinical practice will depend on the background incidence in the population that is tested, affecting metrics such as false positives and negatives. Additionally, it is important to consider how the diagnostic can be combined with other tests in diagnostic algorithms, either sequentially or simultaneously⁴². Finally, while pharmaceuticals directly influence patient outcomes, most diagnostics do not^{42,43}; hence, the cost-effectiveness of a diagnostic is highly dependent on the cost-effectiveness of the treatment that follows and any lifestyle changes a patient may make. For example, a relatively expensive test to inform the prescribing of inexpensive treatment, as is often the case with antibiotics, has a negative effect on the cost-effectiveness. Additionally, screening for resistant bacteria may seem even worse considering the cost-effectiveness: many patients carrying a resistant bacterium do not experience any negative effect, but if a resistant bug is found in a hospitalized patient, this patient needs to be placed in costly patient isolation⁴⁴. For an overview of some important determinants of the cost-effectiveness of diagnostics, see figure 1.1. Part II of this thesis is dedicated to the health-economic assessment of diagnostics, including practical solutions to the difficulties described above.

Table 1.1. Health technology assessment domains in relation to tests

Domain ³⁸	Test characteristics	Example in this thesis
Health problem and current use of technology	Explanation of disease related to the biomarker that should be detected	For respiratory diseases, C-reactive protein (CRP) as a biomarker can be used to discern viral and bacterial infections (chapter 7)
Description and technical characteristics	Use of the test (by a lab technician, clinician, or patient) and characteristics such as sensitivity and specificity	A test to detect resistant bacteria, such as vancomycin-resistant <i>Enterococci</i> , should not yield too many false positives and negatives (chapter 3)
Safety	Safety of performing the test	A CRP blood test should be safe for patients (chapter 7)
Clinical effectiveness	The effects on patient outcomes	An improvement in Quality-adjusted life years caused by more tailored treatment (chapter 5)
Costs and economic evaluation	The cost-effectiveness of the test	The costs associated with the tests and subsequent treatment options, related to the clinical benefits (chapter 6)
Ethical analysis	Ethical considerations can vary, depending on the disease area and group that should be tested	Providing tests for sexually transmitted diseases at school, outside of the reach of their parents (chapter 2)
Organizational aspects	The full pathway from taking a test sample to communicating and acting on the test result	The <i>Trombosedienst</i> in the Netherlands, a specialized service to monitor anticoagulation treatment (chapter 4)
Patient and social aspects	Patient preferences, also in relation to their environment	Diagnostics for respiratory infections and changes to prescribing behaviour may change patient expectations and the tendency to seek care (chapter 7)
Legal aspects	Laws and regulations	In Vitro Diagnostic Regulation (IVDR) and Medical Device Regulations (MDR) (chapter 5)

Figure 1.1. Determinants of cost-effectiveness of diagnostics



Public health economics

As mentioned before, improved diagnostics may play an important role in preparing for an outbreak of infectious disease or in preventing AMR. Although these are relevant scenarios to prepare for, certainly now that the pandemic is still fresh on the minds of politicians, policy makers and the public, they are difficult to predict and difficult to express in an ICER. Who knows what the costs and QALY losses will be of a future pandemic; or whether the post-antibiotic world will become a reality and what this will mean for modern healthcare? Considerable uncertainty stems from the fact that estimating the costs related to changes in resistance levels is complex¹⁴. Additionally, the costs per QALY paradigm works well when thinking of a specific disease but is more complicated when thinking about broad public health investments, where it is impossible to *a priori* identify the benefits associated with the intervention. Within the framework of CEAs the goal is to maximize the total health gains, without regarding the distribution of these gains; for example globally or inter-generationally²⁰. Investments made from this public health perspective may need to be assessed differently from the investments we make in the health of individual patients. The health-economic toolset to determine which investments to make, may need to be adapted. In part III of this thesis, various improvements to this toolset to assess and reimburse the value of interventions in the healthcare system are considered.

A new regulatory framework

In recent years, several examples of medical devices causing severe damage to patients have reached the public attention^{45,46}. A striking example is from the Dutch television programme Radar, which managed to get a mandarin bag approved as a vaginal implant⁴⁵. To improve patient safety, two European regulations have launched in recent years: the medical device regulation (MDR) and in-vitro diagnostics regulation (IVDR). Especially for products that are qualified as high-risk products, such as pacemakers or diagnostic tests for severe diseases, stricter safety requirements for gaining market entry are implemented and post-market surveillance is required. Also, more elaborate evidence on the clinical effectiveness of these health technologies will be required⁴⁷. Under the previous legislation, there was a focus on technical standards, for diagnostics this may concern the sensitivity and specificity of a test⁴⁸. Under the new regulations, clinical data needs to be collected, meaning that the relevance to the patient of the test result needs to be assessed. Especially for high-risk devices, more data will be available on the effectiveness of new medical devices and in-vitro diagnostics. This all brings these devices more in line with regulations introduced for pharmaceutical products in the 1960s.

Aims of the thesis and thesis outline

This thesis consists of three parts, in part I various health-economic aspects of tests used in the health system are considered. In part II the focus is on economic analyses of diagnostics. In part III, potential solutions to improve development, assessment and reimbursement are assessed.

Part I: aspects of tests in practice

Tests are used in various settings in society, from the community to specialized hospitals. In the first part of the thesis, the health-economic aspects of three different examples are the focus. First, in chapter 2, the organizational aspects of an important setting to screen for and diagnose health-related problems at an early stage are assessed: the school health system. Various tests are part of this system, from measuring the height and weight of chil-

dren to sexually transmitted disease diagnostics. Additionally, schools play an important role in promoting hygiene and thereby preventing the spread of communicable diseases. This chapter provides an estimation of spending on the school health workforce across five European countries. In chapter 3 the costs and benefits of screenings for vancomycin-resistant *Enterococci* (VRE) in the hospital setting are assessed. Following a VRE outbreak, the University Medical Center Groningen increased VRE screening for high-risk patients, however, this is a costly intervention. In chapter 4, patients treated with vitamin K antagonists in need of a surgical procedure are considered. The INR of these patients is monitored frequently, and a simulated INR is combined with clinical prediction algorithms for their bleeding and stroke risks, to identify patients in need of periprocedural bridging anticoagulation.

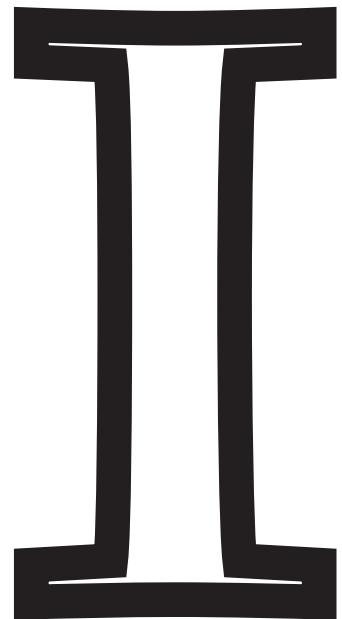
Part II: methods to assess the value of diagnostics

The focus of part II is completely on the value of diagnostics, with a special focus on the role of diagnostics to reduce AMR. In chapter 5, I review current methods to assess the value of diagnostics for respiratory tract infections, including 70 cost-effectiveness studies from the year 2000 onwards, also considering the inclusion of AMR. Using the gaps in economic assessments of diagnostics identified in chapter 5, in chapter 6 I provide eight recommendations for economic analyses of diagnostics linked to the often-used consolidated health economic evaluation reporting standards (CHEERS)⁴⁹ and reference case for health-economic evaluations⁵⁰. Chapter 7 concerns a cost-effectiveness analysis of the use of a hypothetical diagnostic algorithm for respiratory tract infections that reduces antibiotic prescribing in Dutch primary care. Instead of an effect on QALYs, this research incorporates an effect on long-term AMR levels.

Part III: improving development, assessment and financing

Part III aims to provide recommendations to improve the development, assessment and reimbursement of tests. Here, three innovative solutions are included which are not all directly related to tests, but very applicable to this field. Chapter 8 concerns a memorandum of initiative which was submitted in Dutch parliament to use real option value to improve the development and availability of vaccines and antibiotics. This memorandum discusses the economic difficulties when investing in infectious disease prevention, considering the high degree of uncertainty, and presents solutions that can be applied by the national government to better prepare for pandemics and the emergence of AMR. Tests are seldom used individually, and several tests can be performed sequentially or simultaneously. Also, tests can be offered at different locations: from a laboratory, at POC in a GP office or even in a pharmacy. This quickly introduces many different possibilities that can be described as diagnostic algorithms. However, the cost-effectiveness results of the various possible algorithms can be difficult to communicate. Chapter 9 applies the efficiency frontier methodology, identified in chapter 6 as a helpful method to overcome this problem, to a model of a new heart failure drug: sacubitril/valsartan. In chapter 10, the tripartite insurance model is proposed which aims to incentivize hospitals, laboratories, and casualty insurers to improve the use of tests and prevent outbreaks of resistant organisms.

PART



**Aspects of
Tests in Practice**

CHAPTER

2

School Health in Europe A Review of Workforce Expenditure Across Five Countries

Simon van der Pol
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Abstract

Background: Most European countries have implemented a form of school health services (SHS) to provide young children and adolescents with various types of healthcare. No estimations on SHS expenditure for European countries have been published until now. We estimated SHS workforce expenditure in Europe, expected to serve as the main driver of school healthcare costs.

Methods: Using two networks of experts on healthcare provision for children we contacted various country representatives to provide data on the number of professionals working in SHS and salaries. These data were used, together with publicly available data, to estimate annual SHS workforce expenditure on the national level.

Results: We received sufficient data for five European countries, and estimated the SHS workforce expenditure. Nurses were the most widely reported professionals working in this field, followed by doctors and psychologists. Our SHS expenditure estimations ranged from €43,000 for Estonia to €195,300 in Norway (per 1,000 pupils). For Norway, Estonia, Finland and Iceland, school nurses were the main drivers of SHS expenditure, mainly due to their large numbers, while in Austria, school doctors played the largest role in SHS expenditure.

Conclusions: We estimated the spending on SHS workforce for five European countries, which comprises relatively minor parts of total healthcare spending (0.16% to 0.69%). Many questions regarding SHS spending in Europe remain, due to a general lack of data on national levels.

Background

Children's happiness and health are known to be important societal values^{51,52}. It is generally considered that lifetime health outcomes and socioeconomic status are largely determined by an appropriate and stable environment at the start of life⁵³. This highlights the importance for society to invest in health equity in life's early stages, that may very well result in increased health and socioeconomic status. Not only should international human rights incentivise countries to invest in the health of children, but also this economic principle^{54,55}. School Health Services (SHS), offered in most European countries, educate children from a young age regarding the importance of their health, screen them for various illnesses and provide care for those in need⁵⁶. Recently, SHS care was researched within the Horizon 2020 funded Models of Child Health Appraised (MOCHA) project⁵⁶⁻⁵⁸. The organization and composition and content of SHS were explored by sending out questionnaires to country agents, local experts in child and adolescent healthcare, across 30 European countries, of which 28 countries provided school healthcare⁵⁶. In many European countries, direct medical care was found to be a part of SHS, including tasks like the management of chronically ill children and emergency care. In almost all countries, SHS comprised screenings, with a focus on height and weight, as well as vision, hearing and dental tests. Another focus in most countries was mental health promotion. Key components of most SHS included preventative care, with a particular focus on communicable diseases with vaccinations, infection control and hygiene surveillance. Preventive measures included vaccinations (21/28), referrals to other health professionals (22/28), infection control (19/28) and surveillance of the school's hygiene (18/28)⁵⁶. Education was a key area within SHS in many countries as well, such as sex education and the promotion of a healthy lifestyle⁵⁶.

Although the urgency for investing in prevention within the healthcare sector is obvious, in European countries expenditure on prevention programmes only accounted for 1-5% of total healthcare spending in 2016⁵⁹. SHS expenditure data in general are unknown and its workforce has not been mapped in many countries. For example, the Organisation for Economic Co-operation and Development (OECD), which collects data on national healthcare expenditure, does not report data on SHS spending⁶⁰. One factor of this incompleteness is that some parts of SHS are paid through healthcare budgets and others through education budgets; also, in many countries the responsibility of SHS lies with both local and national governments⁵⁶. Although data on the costs and cost-effectiveness are available for specific interventions in specific countries, the evidence for the costs and cost-effectiveness of the general SHS is limited⁶¹, including the most basic interventions offered (such as screening programmes, education on hygiene and infection prevention).

No studies have been published detailing the costs on a system-wide level for European countries. For the United States, studies determining the cost-effectiveness of running a school-based health centre have been published⁶²⁻⁶⁴. For specific interventions within schools, European cost-effectiveness studies are available, considering topics like: obesity prevention^{65,66}, healthy food programmes⁶⁷, dental care programmes⁶⁸, attention deficit hyperactivity disorder education⁶⁹, smoking cessation⁷⁰, sexually transmitted infections prevention⁷¹ and school-based immunisation programmes^{72,73}. Many of these interventions are considered to be cost-effective with relatively low budgetary investments⁶⁵⁻⁷³.

As part of our investigations within the context of MOCHA, we examined SHS expenditure and system-wide health effects and concluded data on this topic was lacking⁵⁶. We therefore aim to further investigate SHS expenditure in Europe by estimating the money

spent on the SHS workforce, which we expect to be the main driver of SHS costs. With this research, we estimate SHS workforce spending on the national level in countries which are able to provide the necessary data. Additionally, we identify gaps in current knowledge. Better insights into the costs of SHS allow valid cost-effectiveness analyses of SHS in the future, potentially further supporting its attractiveness.

Methods

Questionnaire

Building on the country agent network initiated for MOCHA⁵⁷ and the economic data collected in work package 3 of the project^{56,58}, we sent out a questionnaire by email, focusing on the workforce and gross salary of the SHS workforce. This included all countries within the European Economic Area, except for Liechtenstein. The country agents were experts in the field of child healthcare in their respective countries and used indigenous sources to collect data within the MOCHA project. They were selected using a mixed-methods approach and trained by the lead researchers of MOCHA⁵⁷. In case the country agent did not respond, we also contacted the contact listed on the European Union for School and University Health and Medicine (EUSUHM) website⁷⁴. The responses were visualized using a flow chart. Informed consent to use the responses for this research project was acquired from the country agents in writing.

In the questionnaire (see supplementary file 2.1), we asked the workforce (numbers) and remuneration estimates of the following SHS professionals (which were identified in previous research⁵⁸):

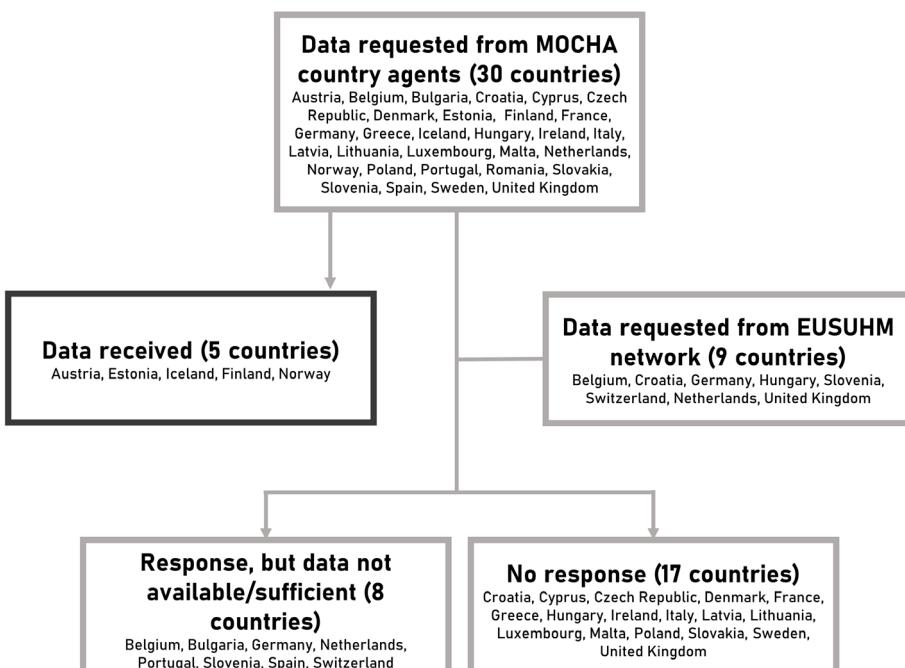


Figure 2.1. flow chart of responding countries

MOCHA: Models of Child Health Appraised; EUSUHM: European Union for School and University Health and Medicine

- School nurses
- School doctors
- Psychologists
- Social workers
- Dentists
- Physical therapists
- Healthcare assistants
- Supportive staff
- Others

For the workforce, questions were asked on the fulltime equivalents (FTEs), the total number of professionals and their type of employment (salaried and/or self-employed). We asked the average gross salary; if this was unknown, we asked the general salary of a professional with 10 years of working experience in the field of SHS.

External data sources

From the MOCHA project, we knew which SHS professionals were working in which countries: if no numbers were reported in the questionnaire, but the professionals were reported to be working in SHS in previous research^{56,58}, we considered data to be missing.

To be able to compare the data between countries, all financial data were converted into 2018 euros and corrected for the number of pupils within each country. From Eurostat we acquired the number of pupils (4-18-year olds) for each of the included countries⁷⁵. The consumer price indexes of the various countries were used to incorporate inflation and we corrected differences in currency and purchasing power using purchasing power parities (PPPs)^{76,77}. Labour costs other than wages and salaries were estimated using country-specific averages⁷⁸ as a percentage of the SHS workforce gross income. Total healthcare expenditure for the included countries was used from the OECD⁵⁹.

Calculation model design

Using the collected inputs, we estimated the number of people working in school healthcare and the total salaries. To be able to compare countries, totals were converted to numbers per 1,000 pupils and corrected for differences in purchasing power, lastly, all amounts were rounded to the nearest hundreds of euros. The calculation steps for both workforce and expenditure are listed in supplementary figure 2.1; external data used for the analyses are reported in supplementary table 2.1. These calculations were performed using Microsoft Excel⁷⁹.

Results

Response rate

Subsequent to sending out the questionnaire to the MOCHA country agents, we received completed questionnaires from Austria, Estonia, Finland, Iceland and Norway. The results and calculations are listed in supplementary tables 2.2 and 2.3. For many countries no or insufficient data were available on the national level; this was the case for: Belgium, Bulgaria, Germany, the Netherlands, Portugal, Slovenia, Spain and Switzerland. From the other country agents, no response was received. Additionally, no complete data were received after contacting the EUSUHM network. The results are displayed in figure 2.1, all acquired data are displayed in supplementary table 2.2.

Workforce

In figure 2.2, the number of health care professionals per 1,000 pupils are displayed. Norway reports numbers on social workers, dentists, physical therapists, healthcare assistants and other SHS personnel. School nurses are reported for all included countries, except Austria. Both Norway and Estonia report around 1.4 school nurses on average per 1,000 pupils; Finland 1.2 and Iceland reports 0.9. Data are missing for certain countries; no numbers are reported for certain professionals although they are part of a country's SHS⁵⁶: school doctors for Iceland; social workers for Finland and Austria; dentists for Austria; and others for Austria. Salaries of SHS professionals are reported in figure 2.3. In addition to the salaries displayed in figure 2.3, Norway reports salaries of €39,900 for social workers; €58,600 for dentists; €38,100 for physical therapists; €35,800 for healthcare assistants and €50,300 for others (administrators/leaders). The salary of school doctors is missing for Iceland⁵⁶.

Expenditure

The total estimated expenditure on salaries per 1,000 pupils is displayed in figure 2.4, as well as the total SHS expenditure as a percentage of the national health budget on the secondary y-axis. Norway, which reports most types of SHS staff, also spends most on SHS: around €195,000 per 1,000 pupils. Finland is estimated to spend around €85,000; Austria around €56,000; and for Estonia and Iceland we calculate around €45,000 per 1,000 pupils. These estimations of SHS workforce expenditure range from 0.16% to 0.69% of total health expenditure for the included countries. All respondents indicate that SHS staff have a salary paid by the government.

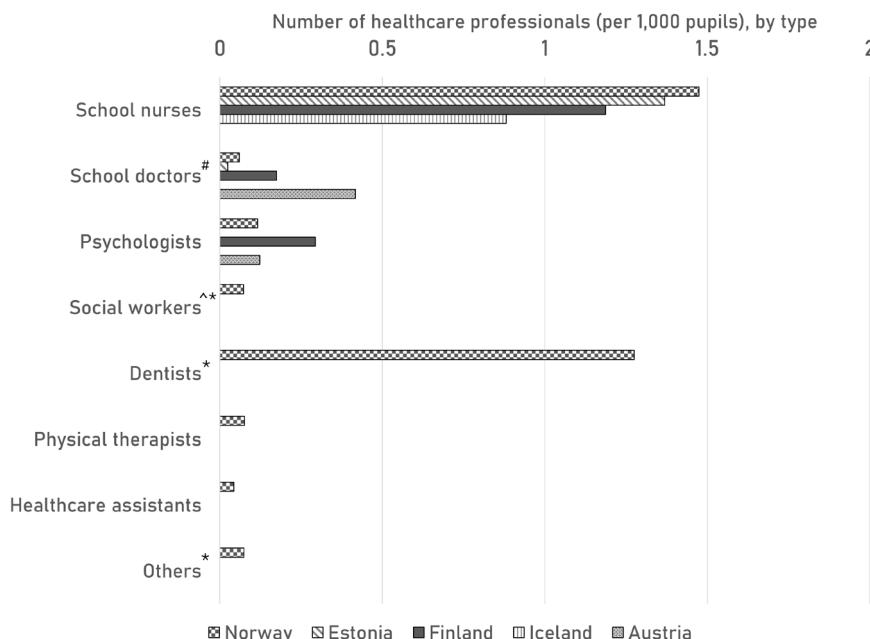


Figure 2.2. Number of school health professionals by type, per 1,000 pupils

[^]: indicates missing data from Finland; [#]: indicates missing data from Iceland; ^{*}: indicates missing data from Austria.



Figure 2.3. Annual salaries per school health professional function
Only included are school nurses, school doctors and psychologists; #: indicates missing data from Iceland.

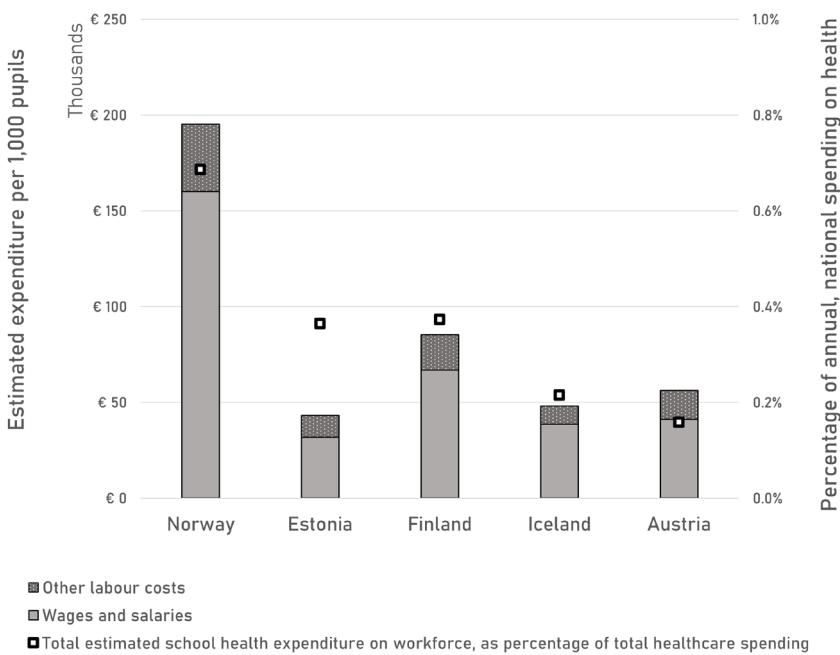


Figure 2.4. School health workforce expenditure per 1,000 pupils and as a percentage of national health expenditure

Discussion

Our results show estimated SHS workforce costs for five European countries, ranging from €43,100 for Estonia to €195,300 in Norway (per 1,000 pupils). For Norway, Estonia, Finland and Iceland, school nurses are the main drivers of SHS expenditure, mainly due to their large numbers. In Austria, school doctors' salaries contribute to most of SHS workforce spending, with school psychologists playing a relatively minor role due to their modest numbers.

For most countries that are included in our analysis, more health professionals are working indirectly in SHS, making it more difficult to provide estimates of SHS workforce. Examples include nurses in Austria or various health professionals collaborating closely with school nurses in health centres in Iceland. Their work description may include a role in advancing public health for children, however, they are not formally employed in school healthcare. For health systems which are tightly integrated on various levels, it may be difficult to separate the various functions and settings within the system. Many services may be provided to children which are considered a part of SHS in one country yet not in another. For example, dental care in Iceland, which is free for all children, is not considered part of SHS; or social workers who are employed by the municipality in Austria. Frequently, these differences between countries are cultural and historical; the overarching effectiveness of delivering healthcare within school services, as opposed to an alternative primary care setting, remains to be investigated further⁸⁰.

As mentioned in the introduction, we hypothesise that workforce spending is the most important driver of school health expenses. No expensive materials are needed, such as expensive medicine or advanced diagnostics⁵⁶. Facility costs are limited, a room inside a school or first-line care facility will suffice. We tried to estimate some of the overhead costs by including supportive staff in the questionnaire, however, no numbers were reported by any of the country agents. Part of the overhead costs is included in the *other labour costs*, which are reported in figure 2.4. Another possible limitation of this study is the reliance on country agents to report SHS professionals and salaries, however, all country agents have experience with this type of research through the MOCHA project and were trained within this project to provide reliable information⁵⁷.

This is the first research project which examines the spending on workforce and wages of SHS personnel in European countries. We estimate this for five countries and find large differences in both workforce and workforce expenditure. However, we are careful in making policy recommendations based on these data, as the aim of this study is not to compare the functioning of SHS between different countries and the full picture regarding child health is missing, as still some data are not available. For most European countries, data on the workforce and associated expenditure remain unknown. Here, we identify a major gap in knowledge on how an important part of European health systems is financed.

From a policy perspective, we believe this lack of data may be a threat to the maintenance and further development of European school health. Within MOCHA, almost all countries indicated a shortage of staff in SHS⁵⁶, however, no data seems to be available to support this claim. Although school healthcare is considered an important part of our health systems as an entry point to target almost all children and adolescents⁵⁸, increasingly, there is a focus on quantifying healthcare decisions, e.g. by performing multi-criteria decision analyses^{81,82}. This requires standardized data on the total SHS workforce and expenditure, to place specific interventions within school healthcare in perspective and

estimate the impact on the overall SHS budget. For certain activities within the health system, such as caesarean sections, MRI exams or length-of-stay for myocardial infarction, rather exact data are available, allowing healthcare professionals, researchers and policy makers to compare different regions and countries⁸³.

For the future, more accurate measurements of the SHS workforce, performance and expenditure need to be made. We recommend a bottom-up approach; starting on the regional level and working up from there. Consecutively, spending for specific functions (screenings, vaccination, hygienic measures etc.) within SHS can be identified and prioritized for further (cost-)effectiveness analyses. This may provide decision makers with the necessary tools to decide where to invest within healthcare provision for children with the aim of improving health for all.

Conclusions

We estimate the spending on SHS workforce for five European countries, which is a relatively minor part of total healthcare spending (0.16% to 0.69%) in these countries. Many questions regarding SHS spending in Europe remain, due to a general lack of data on the national level.

Acknowledgements

We would like to thank our contacts within the included countries: Reli Mechtler (Austria), Kädi Lepp (Estonia), Mika Gissler (Finland), Geir Gunnlaugsson (Iceland), Ingrid Sperre Saunes (Norway).

CHAPTER

3

Costs of Two Vancomycin-resistant Enterococci Outbreaks in a Dutch Academic Hospital

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Submitted

Abstract

Introduction: In early 2017, the University Medical Center Groningen, the Netherlands, had an outbreak of two strains of vancomycin-resistant Enterococci (VRE) which spread to various wards. In the Summer of 2018, the hospital was again hit by a VRE outbreak, which was detected and controlled early, because of aggressive screening. During these outbreaks various costs were incurred by the hospital, such as the costs of cleaning, personnel costs, laboratory costs and lost costs due to closed beds. This study aimed to quantify the costs of the 2017 and 2018 VRE outbreaks.

Methods: Using data from various sources in the hospital and interviews, we identified and quantified the costs of the two outbreaks, resulting from tests, closed beds (opportunity costs), cleaning, additional personnel, and patient isolation.

Results: The total costs associated with the 2017 outbreak were estimated at €352,070, or €8,383 per day; the total costs associated with the 2018 outbreak were estimated at €157,474 or €8,288 per day.

Discussion: The main drivers of the costs were the opportunity costs due to the reduction in admitted patients, tests, and cleaning. Although the second outbreak was considerably shorter, the costs per day were similar to the first outbreak. This paper shows that there are major investments associated with the VRE control measures. From this study, we can conclude that an outbreak of VRE can lead to considerable costs for a hospital: hitting hard and early may reduce the total costs and improve the continuity of care within the hospital.

Introduction

Enterococci are bacteria normally present in the human gastrointestinal system. Especially in healthcare settings, Enterococci resistant to certain antibiotics are transmitted, most importantly vancomycin-resistant Enterococci (VRE)⁸⁴. The number of resistant isolates varies by country: in continental Europe low resistance generally is found in Northern and Western countries, while high resistance is found towards the East and South⁸⁵. In the Netherlands, the prevalence of VRE is low compared to most European countries, ranging from 0 to 2% of clinical isolates⁸⁵. VRE is mainly transmitted through contaminated surfaces and the hands of healthcare workers^{86,87}, hence VRE transmission can be reduced by strictly isolating patients carrying the resistant bacterium and by adhering to hygiene guidelines, such as frequent handwashing⁸⁸. An important tool to adequately isolate VRE carrying patients concerns the screening of high-risk patients, such as patients suffering from gastrointestinal diseases or patients who have been admitted to hospitals in regions with a high prevalence of VRE.

Early in 2017, the University Medical Center Groningen (UMCG) in the Netherlands had an outbreak of VRE⁸⁹. Due to an incidental finding from a patient that was hospitalized for about 10 days, patients that shared the same hospital room were screened. Several patients tested positive for VRE causing an extensive screening with many additional patients testing positive. Due to typing with Next Generation Sequencing (NGS) it was found that not one strain, but two strains were causing the outbreak. One of these strains was isolated first from a patient who had previously been admitted to a German hospital and was tested positive in November 2016. Despite isolation measures, the VRE strain could spread during December 2016 and the first weeks of January 2017. Due to the movements of patient to various wards and intensive care units, the VRE could spread to several locations.

Two wards with many positive patients closed completely and the patients had to be moved to a temporary ward which was only used for VRE positive or high-risk patients, for example patients who tested negative at the initial sampling but shared rooms or facilities with positive patients. A patient-stop was initiated in the UMCG, to prevent further transmission, and to ensure adequate capacity at the intensive care unit for acute care. A total of 38 patients were tested positive for VRE during this outbreak, with two separate strains. During the Summer of 2018, 27 patients tested positive in another outbreak, who could all be traced back to a single VRE-carrying patient. Again, despite isolation measures, the VRE could spread. Because of an early and aggressive screening, the outbreak was detected in an early stage and quickly controlled. To contain the spread of VRE, new patients were temporarily rejected, current patients were moved to an outbreak ward and the original ward was completely disinfected using hydrogen peroxide vapour decontamination.

During these outbreaks various costs were incurred by the hospital, such as the costs of cleaning, personnel costs, laboratory costs and lost costs due to closed beds. This research aims to quantify the costs of the 2017 and 2018 VRE outbreaks in the UMCG.

Methods

In a prior study, in which costs associated with several outbreaks in the UMCG were quantified, five main categories of costs were identified: diagnostics, closed beds, cleaning, additional personnel and patient isolation⁴⁴, these were also assessed in this study. To calculate the costs associated with each category, we estimated volumes of the various categories

and multiplied them with the unit costs. To estimate the volumes of the various items, we used clinical data and data collected during interviews with representatives of various departments that were affected by the outbreaks.

The first outbreak started 10 January 2017 and ended 21 February 2017, while the second outbreak started 21 August 2018 and ended 8 September 2018. For both outbreaks, transmission occurred before the starting date; in this study only the time periods were considered where the hospital staff was aware of the outbreak.

For the analyses, the VRE-status of patients is important. For this paper, we used three categories of patients:

- VRE-positive, for patients confirmed to carry VRE, having positive results in both a polymerase chain reaction (PCR) test and a culture;
- VRE-suspect, for patients at high risk to carry VRE; and
- VRE-negative, for patients not suspected to carry VRE.

Data sources

Interviews

Eight interviews with representatives of relevant departments were conducted to get an overview of the relevant costs. We interviewed staff from the infection prevention unit, the microbiological and viral laboratories, the most severely affected department (the gastrointestinal unit), facility services, procurement, and business intelligence. These interviews were used to get an expert opinion on various costs, but interviewees were also requested to provide data sources where available.

Data sources

Various sources of clinical input data were used to assess the unit volumes used for the cost analysis. Patient movement data were used to estimate the number of times a room had to be cleaned. Cleaning staff was estimated to need one to two hours per room in which a VRE-positive patient was admitted to completely clean the room. Some patients were admitted to rooms where more than one VRE-positive patient was admitted, we therefore assumed that the cleaning time per VRE-positive patient was one hour. Patient isolation data were used to estimate the number of days VRE-positive or VRE-suspect patients were put in isolation, with the aim to prevent further spread through the hospital. Ward occupancy data were used to estimate the opportunity costs due to closed beds⁹⁰. Laboratory data were used to estimate the volume of VRE tests performed, both patient and environmental samples.

To estimate the unit costs, Dutch reference prices⁹¹ were used where possible, otherwise data from previously-published literature were used, table 3.1 provides an overview of the various unit costs, including references. All costs were converted to 2020 euros using the health-related consumer price index, as published by statistics Netherlands⁹². Internal cost calculations from the microbiology department were used for the unit prices of the various tests: these are the costs that are offset to the clinical departments, they include staff costs but do not reflect commercial prices as all tests were performed by the internal laboratory of the UMCG. Cleaning costs per hour were used as published in previous research⁴⁴. For the 2018 outbreak, the affected ward was cleaned using hydrogen peroxide, which amounted to almost €35.000.

Table 3.1. Unit prices, expressed in 2020 euros

Item	Price	Reference
Ward stay (academic hospital), per day	€662.87	91
Intensive care unit stay, per day	€1,224.55	91
Contact isolation, per patient per day	€26.27	44
Cleaning costs (weekday), per hour	€26.52	44
Hourly labour costs: infection and prevention specialist	€39.28	93
Hourly labour costs: nurse during regular hours	€36.36	93
Hourly labour costs: nurse during night shifts and on Saturday	€53.45	93

3

Opportunity costs due to closed beds

During both outbreaks, there was a patient stop in the UMCG, making it likely that there was missed revenue. To estimate the missed revenue for both outbreaks, we used occupancy rates of the patient wards in the hospital, and we compared the real occupancy from the start of the outbreak up till two weeks after the outbreak with the expected occupancy. This expected occupancy was estimated using autoregressive integrated moving average (ARIMA) models⁹⁴. For each ward, the best fitting ARIMA model was automatically determined using the Hyndman-Khandakar algorithm⁹⁵. To estimate the opportunity costs, we used the difference between the measured occupancy and the bootstrapped 95% prediction interval of the forecast occupancy⁹⁴. (For example, if the lower bound of the ARIMA model predicted an occupancy of 10, but only 6 patients were admitted to a ward, the difference $10 - 6 = 4$ was used to calculate the opportunity costs due to closed beds.) The result was then multiplied by the ward stay costs (see table 3.1) to estimate the opportunity costs. The various fit models, including the prediction intervals and the measured values, are displayed in supplementary figures 3.1 and 3.2.

During both outbreaks, there was a transfer ward, which was established to isolate VRE-positive patients. To prevent the double counting of outbreak-related costs, we did not include the hospitalization costs of this transfer department in the analysis, as they are counted using the ARIMA models.

Cleaning and patient isolation costs

For all VRE-positive patients, we assumed one hour of cleaning for every movement through the hospital, from the moment at which the VRE infection was confirmed. For all VRE-suspect patients, we also assumed one hour of cleaning for every movement through the hospital, until they were confirmed to be VRE-negative; if this exact point of time was unknown in the patient isolation records, we assumed a period of 48 hours between the start of the suspicion of VRE and the confirmation of the VRE status, either positive or negative. Patient isolation costs were applied to all patients, for each isolation day⁴⁴.

Test costs

Test costs were calculated by multiplying the number of tests performed with the costs per test. After the 2017 outbreak, an inhouse PCR test was developed, resulting in a less expensive test used in the 2018 outbreak, compared to the 2017 outbreak, where the Cepheid GeneXpert® was used. All positive tests were sequenced using NGS. VRE tests are per-

formed regularly in the UMCG. To correct for the baseline level of VRE tests, we used the average daily number of VRE tests from the preceding four months and subtracted this number from the total tests during the outbreaks.

Analyses

All analyses were performed using R 4.1.0 and the package dplyr for data transformation^{96,97}. For time series analyses, the fable package was used⁹⁸. In addition to the total costs of both outbreaks, the outbreak costs per day were calculated.

Results

The total costs associated with the 2017 outbreak are estimated at €352,070, or €8,383 per day; the total costs associated with the 2018 outbreak are estimated at €157,474 or €8,288 per day. Table 3.2 summarizes the costs associated with the 2017 and 2018 outbreaks, which are graphically displayed in figure 3.1. The main

driver of the costs in the 2017 outbreak are the diagnostics, followed by the opportunity costs due to closed beds. For the 2018 outbreak, the opportunity costs are the main driver, followed by the cleaning costs. A large proportion of the costs in 2018 concerns the hydrogen peroxide cleaning costs, which amounted for over a quarter of the total costs during this outbreak.

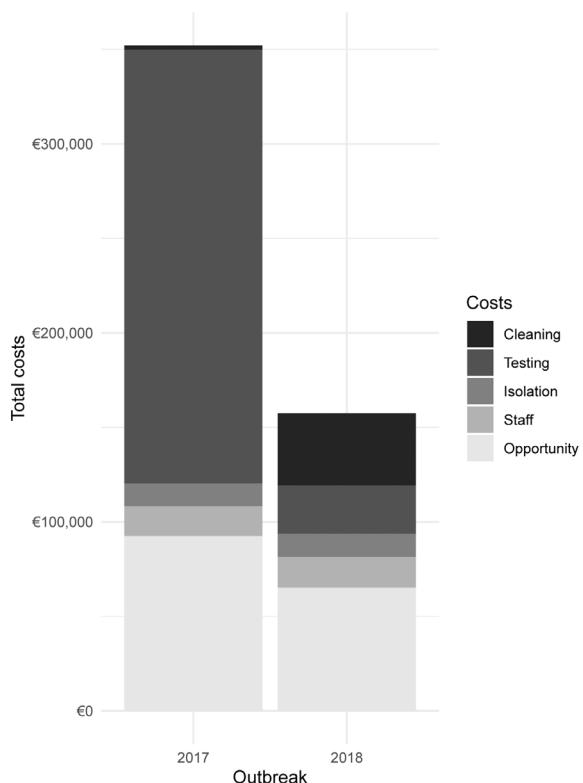


Figure 3.1. Schematic overview of costs related to VRE outbreaks in 2017 and 2018

Table 3.2. Costs associated with 2017 and 2018 VRE outbreaks, total costs and percentage of total outbreak costs

	2017		2018	
Cleaning	€2,175	1%	€38,222	24%
Testing	€229,526	65%	€25,516	16%
Isolation	€11,981	3%	€12,217	8%
Staff	€15,789	4%	€16,260	10%
Opportunity	€92,600	26%	€65,258	41%
Total	€352,070	100%	€157,474	100%

Discussion

In this study, we assessed the outbreak costs of two VRE outbreaks in the UMCG (Groningen, The Netherlands). The total costs of the 2017 outbreak were estimated at €352,070 and the total costs of the 2018 outbreak were estimated at €157,474. The main drivers of the costs were the opportunity costs, additional diagnostics, and cleaning costs. Although the second outbreak was considerably shorter, the costs per day were similar to the first outbreak.

There are few studies published on the costs associated with VRE outbreaks in hospitals. A VRE outbreak in the UMCG in 2013 was estimated to cost around €3800 per day⁴⁴, which is considerably less than the outbreaks considered in the current study. However, this outbreak was smaller, as 19 patients were involved and affected only one ward. As in the 2017 and 2018 outbreaks, the major drivers of these costs were those of diagnostics and opportunity costs due to closed beds⁴⁴. A study in a French university hospital estimated the total costs of a VRE outbreak amongst 13 patients at €171,439 (2008 euros), where the opportunity costs were also a major driver⁹⁹. A difference in this study with ours concerns the inclusion of costs of antibiotics, which was the second most important driver of costs. We also considered the inclusion of antibiotics, however, considering the alternative for VRE patients would be teicoplanin and the price differences between vancomycin and teicoplanin in the Netherlands are negligible, we decided to not include these as extra costs¹⁰⁰.

Our analysis has some limitations. It is complex to accurately estimate the opportunity costs due to closed beds, as patients are exchanged between the various wards in the hospital, and it is unknown exactly how many patients went to other hospitals during the patient stop. We tried to estimate this using various ARIMA models and considered the measured occupancy outside the 95% prediction intervals to be caused by the outbreaks. This is a conservative approach, as the prediction intervals are rather wide due to the variability in the data; hence we may underestimate the opportunity costs due to closed beds. In December 2017, the UMCG switched the computer system used to measure the ward occupancy and movements of patients through the hospital, resulting in poorly comparable data for the two periods. We trained the time series model on the four months preceding both outbreaks to make sure the data cut caused by the new system did not affect the analysis, but this prevented us from fitting more advanced predictive models.

Another limitation is related to the cleaning costs. While the cleaning procedures for patients in contact isolation are rather strict, there were no data available on increased staff expenditure and cleaning materials. Instead, an approximation was used where we counted one hour of cleaning time per isolated patient. The cleaning costs in the 2018 outbreak are higher compared to the 2017 outbreak: in the 2018 outbreak hydrogen peroxide vapour decontamination was used to ensure a rapid reopening of the ward. This was very precisely accounted for in this analysis as the invoice was available. The limitations concerning data collection raise an important opportunity to improve the registration and findability of data, as even for directly involved staff, high-quality data was difficult, and in many cases impossible to find.

This study did not consider clinical consequences of VRE-positive patients. A meta-analysis including 12 cohort studies found increased mortality for patients with a VRE bacteraemia and increased length-of-stay, compared to vancomycin susceptible Enterococci (VSE)¹⁰¹. A case-control study from a German hospital compared nosocomial infections of VRE to VSE and found significantly higher costs for VRE-infected patients, but found no

statistically significant differences in the hospital length of stay and mortality¹⁰². A recent review of economic analyses of VRE infection prevention and control interventions included nine studies, six of which recommended the (continued) implementation of VRE control practices, while three concluded that VRE control practices were not cost-effective¹⁰³. However, the quality of the included studies was considered to be low¹⁰³. A cost-effectiveness analysis not included in this review, considered VRE screening and isolation in Ontario, Canada using a dynamic transmission model and concluded that this was cost-effective, albeit with considerable uncertainty¹⁰⁴. Another aspect to consider is the hospital's reputation and patient opinions: patients expect their health to be improved when hospitalized, they should not fear contagion with resistant bacteria¹⁰⁵. Hospitals with high rates of resistant organisms or frequent outbreaks may suffer from a loss in reputation¹⁰⁶ and, eventually, patient trust.

Currently, the incidence of VRE is low in the Netherlands⁸⁵ and the stringent VRE control measures may have played a role in that. This paper shows that there are major investments associated with the VRE control measures. However, the containment of VRE may result in lower healthcare costs overall due to a shorter length-of-stay and decreased mortality. Estimations from previous research show that annually there are around 16,000 VRE infections in Europe, causing over 1,000 deaths, but that the burden of VRE-related morbidity and mortality in the Netherlands is very low¹¹. However, for such a study, it is important to consider that VRE rates are likely to rise if these measures are not implemented, negatively affecting patient outcomes.

From this study, we can conclude that an outbreak of VRE can lead to considerable costs for a hospital. Although no outbreak will be the same, hitting hard and early can reduce the total costs and improve the continuity of care within the hospital.

Acknowledgements

We thank the interviewed staff members, Tjibbe Hoogstins, Irene Niestijl-Cusiel, Peter Lenselink, Marijke Hanania and Lilli Rurenga-Gard for their input in identifying the relevant costs for this research project.

CHAPTER

4

Perioperative Bridging of Vitamin K Antagonist Treatment in Patients with Atrial Fibrillation Only a Very Small Group of Patients Benefits

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Abstract

Aims: Bridging anticoagulation in atrial fibrillation patients who need to interrupt vitamin K antagonists for procedures is a clinical dilemma. Currently, guidelines recommend clinicians to take the stroke and bleeding risk into consideration, but no clear thresholds are advised. To aid clinical decision making, we aimed to develop a model in which periprocedural bridging therapy is compared to withholding anticoagulation in atrial fibrillation patients, for several bleeding and stroke risk groups.

Methods: A model was developed to simulate both a bridge and a non-bridge cohort, using simulated INR values for patients on warfarin, acenocoumarol and phenprocoumon. For both clinical strategies, stroke and bleeding risks were included and outcomes were stratified by CHA₂DS₂-VASc or CHADS₂ and HAS-BLED groups. Quality-adjusted life expectancy was the main outcome considered.

Results: Our analyses show bridging to only be beneficial for patients with HAS-BLED scores equal or lower to 2 and with CHA₂DS₂-VASc scores of 6 or higher. For patients using acenocoumarol bridging may be beneficial starting at a CHA₂DS₂-VASc score of 7. Post-procedural time to therapeutic INR has a significant influence on the results: no significant benefit of bridging was found for patients reaching therapeutic INR values within 5 days.

Conclusion: When deciding whether to bridge anticoagulation, clinicians should consider the patient's individual stroke and bleeding risk, while also considering the patient's post-procedural INR management. In practice, only a small subset of patients is expected to benefit from bridging anticoagulation treatment.

Introduction

Anticoagulant treatment reduces the risk of stroke in patients diagnosed with atrial fibrillation (AF)¹⁰⁷. As they increase the risk of bleeding, anticoagulants have to be interrupted prior to a procedure if the risk of bleeding is considered high¹⁰⁸. Oral vitamin K antagonists (VKAs) are discontinued around five days prior to planned surgery; if the stroke risk is expected to be high, low-molecular-weight heparins (LMWHs) or unfractionated heparin can be administered to bridge this short “unprotected” period, referred to as bridging anticoagulation.² However, perioperative bridging is known to significantly increase the bleeding risk, enhancing discussion on the appropriateness of bridging¹⁰⁹. Notably, the recent BRIDGE trial (Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation) by Douketis et al. showed no added value of bridging therapy in AF patients¹⁰⁹. However, the BRIDGE trial included patients with a low average stroke risk (average CHADS₂ score of 2.3 and 2.4, for the nonbridging and bridging arms, respectively) and might therefore have limited clinical validity¹⁰⁹.

According to current guidelines, VKAs need to be interrupted if the procedural bleed risk or the patient bleed risk is increased and perioperative bridging anticoagulation should be considered if the annualized thrombotic risk is 5% or higher¹⁰⁸. These recommendations are mainly based on expert opinion: there is no clear clinical evidence to substantiate these claims¹⁰⁸. The CHA₂DS₂-VASc and CHADS₂ scores can be used to determine the stroke risk. Bleeding risk mainly depends on the type of procedure, though bleeding risk will also vary per patient as expressed in their individual HAS-BLED score^{108,110,111}. A previous modelling study showed that perioperative anticoagulation is superior to non-bridging if a patient’s annual stroke rate exceeds 5.6% or there is a less than 2.0% increase in bleeding risk caused by heparin¹¹². More recently, outcomes of bridging vs. non-bridging were simulated in a Monte Carlo simulation model and it was concluded that patients at highest risk of ischemic complications will benefit from bridging anticoagulation¹¹³.

We aimed to develop a model that compares perioperative VKA bridging to withholding anticoagulation for different stroke and bleeding risk subgroups considering different VKAs and procedures, resulting in straightforward clinical outcomes that can be used in medical decision making.

Methods

Model design

A Markov model (figure 4.1) was developed to compare a bridge and a non-bridge cohort. The model starts with 1,000 patients with two main stages being defined:

- Pre-procedural stage: five-day period before the procedure, since warfarin is usually interrupted four to six days prior to the procedure¹⁰⁸. Stroke and bleeding rates were based on AF population parameters.
- Post-procedural stage: the 30-day follow-up period after the procedure, which is an often-used period for both bleeding and stroke in clinical studies¹⁰⁹. Stroke risk was based on either the CHADS₂ or CHA₂DS₂-VASc population parameters, bleeding rates were derived from the BRIDGE trial^{109–111}.

In line with the above, patients can undergo three events in the model:

- Procedure: a surgical procedure, with intraprocedural events not being specifically included in the model, as the 24-hour period around the procedure is as-

sumed to have the same probabilities for specific events and complications as the pre-procedural period. All patients without a pre-procedural stroke or bleeding underwent surgery.

- Stroke: an ischemic stroke, stratified in mild (modified Rankin Scale 0-3), severe (4-5) and fatal (6). Stroke survivors entered the post-stroke state.
- Major bleeding: as defined by the International Society on Thrombosis and Haemostasis and as used in the BRIDGE trial, including fatal bleeding^{109,114}. Patients surviving a bleeding event entered the post-bleeding state.

The model was build using R and several packages (see supplementary table 4.1, for a complete list)¹¹⁵.

Transition probabilities

Supplementary tables 4.2-4.7 list all parameters that were used as model input. The stroke risk for both cohorts was simulated using international normalized ratio (INR) values and the odds ratios for stroke as reported in a trial, using a method previously described¹¹³. We assumed non-bridging patients gradually moved from an INR value of 2.5 to 1.0 pre-operatively and back to 2.5 post-operatively, using a normal logarithmic function. For the bridging cohort, a LMWH was administered during this period, up to 24h prior to the procedure; post-operatively LMWH administration started 24h after the procedure and was assumed discontinued when the INR reached 2.5. In the 48h-period around the procedure, the INR was assumed to be 1.0, thus increasing the stroke risk.

The post-procedural period to reach an INR of 2.5 was assumed to vary between 5 and 15 days. Post-procedurally, the stroke risk was tripled as compared to the pre-procedural probabilities, based on the stroke rates of the BRIDGE trial^{109,116}. Since this parameter estimate was uncertain and not stratified for the CHADS₂ or CHA₂DS₂-VASc subgroups, a wide beta-PERT distribution was applied in the probabilistic analysis. Regarding the bleeding risk, the bleeding rate reported in the BRIDGE study was used for the non-bridge cohort and the corresponding relative risk was applied to the bridge group¹⁰⁹. Low and high bleeding rates were differentiated using data from Omran et al., assuming the populations to be comparable^{109,117}. We considered patients with a HAS-BLED score of 0-2 to have a low bleeding risk and a score of 3 or higher to have a high risk¹¹⁷.

Health outcomes and utilities

The clinical outcomes we looked at, stroke (mild and severe) and bleeding events, are not of an equal magnitude: stroke often has a permanent impact on the quality of life, bleeding events usually are restricted to short-term complications. To account for these differences, the declining exponential approximation of life expectancy was calculated to approximate the life expectancy, using the population parameters as reported by Statistics Netherlands and the AF incidence as reported in literature¹¹⁸. The effect of the modified Rankin Scale score on the life expectancy was derived from Chiu et al.¹¹⁹ As a base-case, data for 75-80 year-old women was applied.

Calculated life expectancies were converted into Quality Adjusted Life Expectancies using utility values. For the stroke survivors, long-term utility values were used to differentiate the mild (modified Rankin Scale 0-3) and severe (4-5) groups. The impact on the quality of life of major bleeding was assumed to be negligible. Death was set to a quality of life of 0.

Simulation of INR

Warfarin is usually interrupted five days prior to the procedure¹⁰⁸. This INR course has

been modelled using a natural exponential function (see Equation 1), where the constant factor p was set to -0.18 /day to gradually reach an INR of 1 in five days.

$$\text{Equation 1: } 2.5e^{pt}$$

$$\text{Equation 2: } e^{qt}$$

The INR course after the procedure has been modelled using Equation 2. For the base-case, all patients are assumed to reach an INR of 2.5 in 10 days, thus Equation 2 is capped after this period. This is a conservative estimate, though not unrealistic, in clinical practice. The uncertainty of the INR trajectory was modelled by varying the variable q , with a mean of 0.092 (normally distributed, 95% Confidence Interval (CI): 0.069 - 0.18). The impact of the INR trajectory was explored using separate scenarios where a post-operative therapeutic INR of 2.5 was reached post-operatively in 5, 10 or 15 days (fixed).

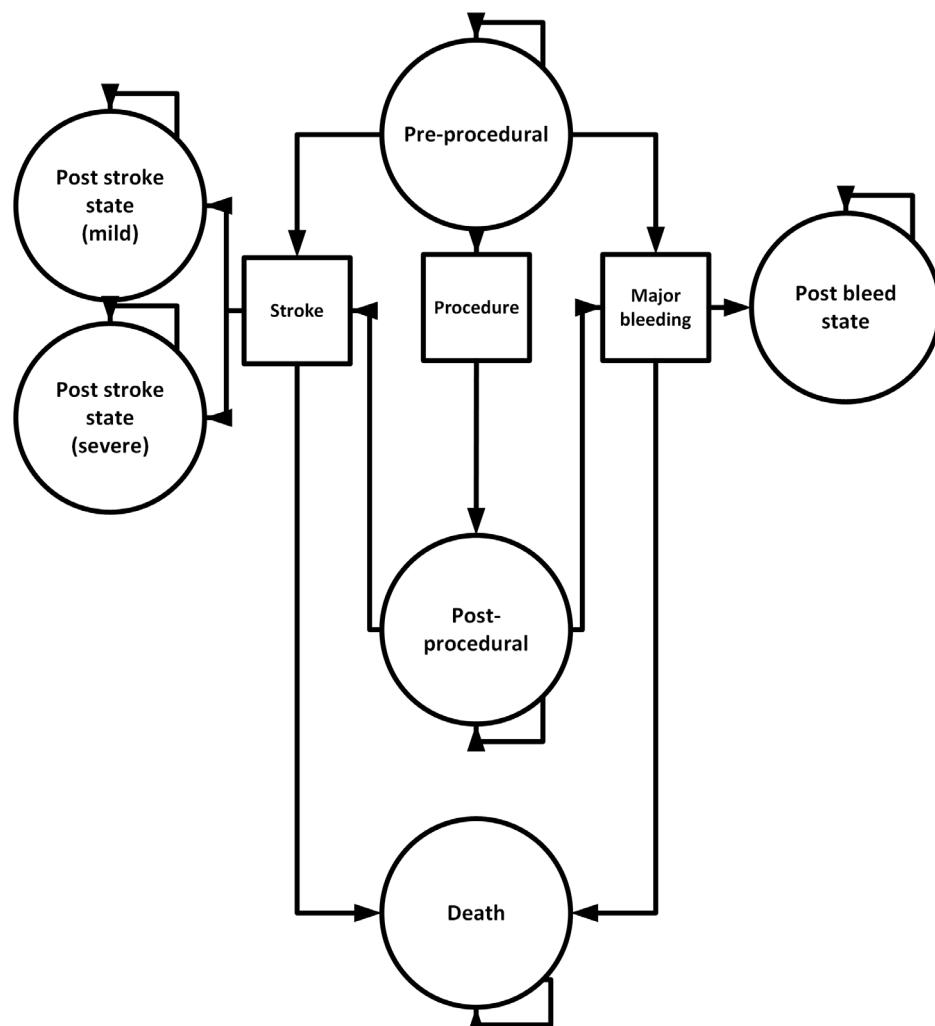


Figure 4.1. Markov model. The schematic representation of the Markov model used to simulate the perioperative period for atrial fibrillation patients on vitamin K antagonists. Circles represent health states, squares represent events, and arrows indicate transitions.

Sensitivity analyses

Random samples of the distribution for the model parameters were used in a Monte Carlo simulation consisting of 10,000 calculations. The results were recorded and used to calculate the mean and both the 2.5th and 97.5th percentile score, to approach the 95% CI of the mean. Results were considered statistically significant at the conventional cut-off at p=0.05. As a base case warfarin was considered, being the most used VKA in Europe¹²⁰. Acenocoumarol and phenprocoumon were considered as alternatives, where the preprocedural period was changed to three and seven days respectively, to account for the different half-lives of these VKAs¹²¹.

Results

In figure 4.2 the stroke and bleeding rates are displayed for the base case. The rates of strokes ranged from less than 0.02% to almost 10% for the non- bridging group and less than 0.01% to almost 6% for the bridging group for the different CHA₂DS₂-VASC scores; bleeding rates varied from 0.03% to over 4% for low and high HAS-BLED scores for the non-bridging group and almost 1% to almost 10% for the bridging cohort. For the outcomes using the CHADS₂ scores, see supplementary figure 4.1.

Figure 4.3 shows whether our simulation support bridging or not and whether the result was significant for the various age categories and both women and men, the results are stratified by CHA₂DS₂-VASC and HAS-BLED scores. As an example, for a female patient, aged 76, with a CHA₂DS₂-VASC score of 4 and a HAS-BLED score of 3 we do not expect

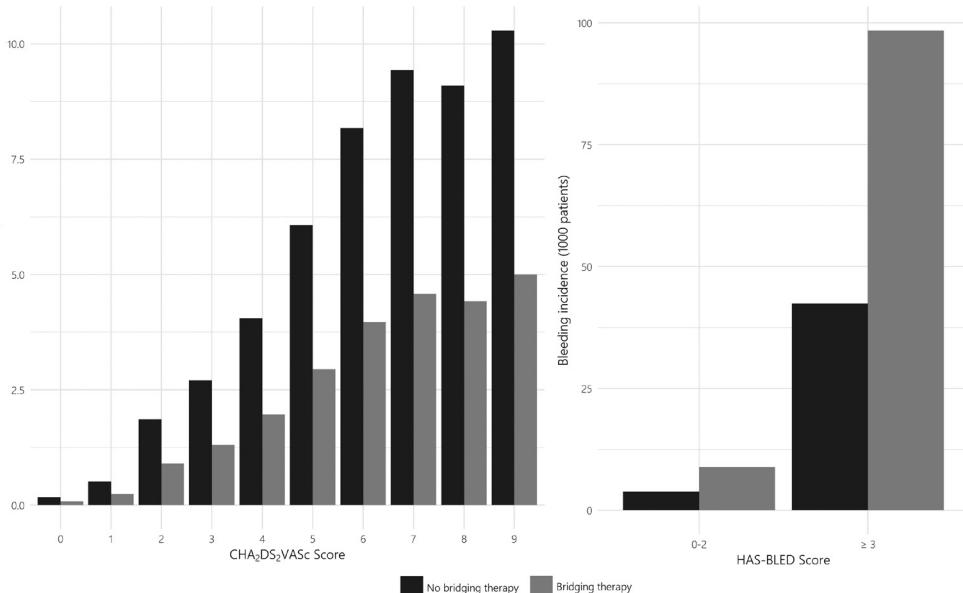


Figure 4.2. Stroke and bleeding outcomes in the simulation. Outcomes reported are for women of 75–80 years old. Left: stratified by CHA₂DS₂-VASC score as a percentage of the population. Right: stratified by HAS-BLED score as a percentage of the population.

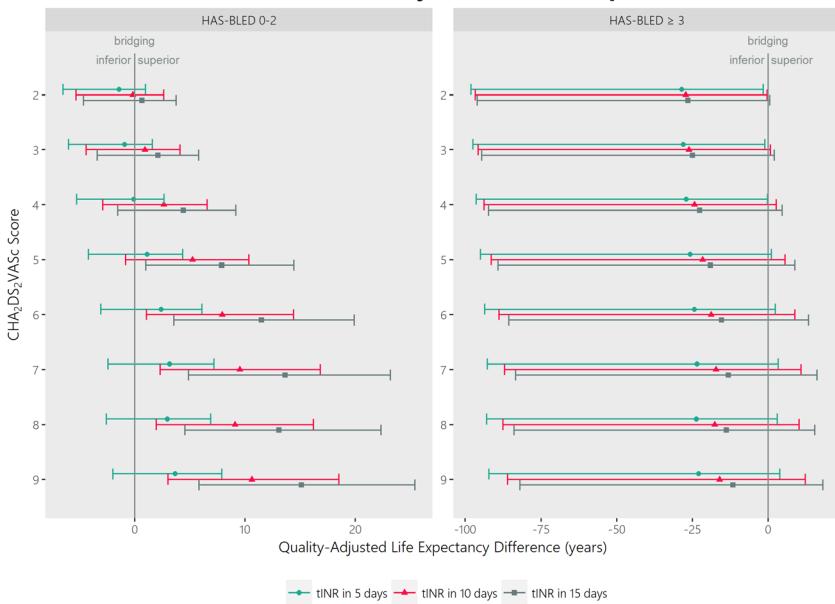
CHA₂DS₂-VASC, congestive heart failure, hypertension, age, diabetes, stroke, transient ischaemic attack or thromboembolism, vascular disease, age and sex; HAS-BLED, hypertension, abnormal renal and liver function, stroke, bleeding, labile INR, elderly, drugs/alcohol.



Figure 4.3. Bridging benefit decision matrix. Stratified by CHA₂DS₂-VASc and HAS-BLED scores, for various age categories and both sexes.

CHA₂DS₂-VASc, congestive heart failure, hypertension, age, diabetes, stroke, transient ischaemic attack or thromboembolism, vascular disease, age and sex; HAS-BLED, hypertension, abnormal renal and liver function, stroke, bleeding, labile INR, elderly, drugs/alcohol.

Effect of number of days to reach therapeutic INR



Different vitamin K antagonists

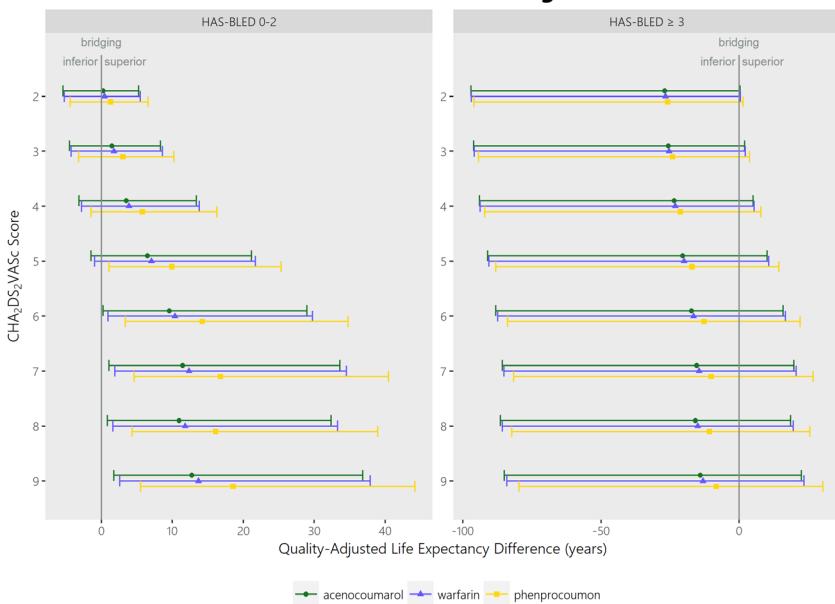


Figure 4.4. Effect of various vitamin K antagonists and time to reach therapeutic INR on quality-adjusted life expectancy difference of bridging.

Stratified by CHA₂DS₂-VASc and HAS-BLED scores, results are for the base case, women of 75–80 years old, including the 95% confidence interval of the probabilistic sensitivity analysis. CHA₂DS₂-VASc, congestive heart failure, hypertension, age, diabetes, stroke, transient ischaemic attack orthromboembolism, vascular disease, age and sex; HAS-BLED, hypertension, abnormal renal and liver function, stroke, bleeding, labile INR, elderly, drugs/alcohol.

a benefit if she is bridged. In general, the benefit of bridging was greater in younger patients and at higher CHA₂DS₂-VASc scores. For HAS-BLED scores of 3 and higher, no statistically significant benefit of bridging was found, regardless of the stroke risk. Figure 4.3 is based on the Monte Carlo simulation, which is displayed in more detail in supplementary figures 4.2 and 4.3; the equivalents using the CHADS₂ stroke risk scores are displayed in the supplementary figures 4.4 and 4.5.

For the base case (women 75-80 years old), figure 4.4 displays the effect of the amount of days it takes to reach therapeutic INR values and the three different VKAs (warfarin, acenocoumarol and phenprocoumon). Small differences were found between the three VKAs: at low risks of bleeding, bridging likely to be beneficial for patients on phenprocoumon from a CHA₂DS₂-VASc score of 5 compared to a score of 7 for patients on acenocoumarol. The benefit of bridging gets more pronounced when it takes longer to reach an INR of 2.5. If an INR of 2.5 was reached within 5 days, periprocedural bridging was never significantly beneficial, for both low and high bleeding risk patients. Reaching a therapeutic INR within 10 or 15 days marked the difference between having a significant benefit of periprocedural bridging at a CHA₂DS₂-VASc score of 5 or 4 respectively. The CHADS₂ equivalents of figure 4.4 are displayed in supplementary figure 4.6.

Discussion

The results of the base case analysis showed that stroke risk, bleeding risk, type of VKA and time to reach therapeutic INR are important factors to consider while deciding whether to apply periprocedural bridging anticoagulation. According to our evaluation, patients at a high risk of bleeding (HAS-BLED ≥3) are very unlikely to ever benefit from periprocedural bridging: the mean shows a decreased life expectancy in all cases, although usually not significant.

Patients with lower HAS-BLED scores may benefit if they have an elevated risk of stroke (CHA₂DS₂-VASc 6 or higher, CHADS₂ 4 or higher, 3 or higher for the age categories 55-65). Within the total AF population, around 18% of patients would have a sufficiently high stroke risk as defined by our calculated threshold value¹¹⁶. Since the HAS-BLED score is not reported per CHA₂DS₂-VASc group, we do not know which proportion of this group would have a low HAS-BLED. The bleeding risk and stroke risk scores have corresponding predictors and consequently it is expected that only a very small number of patients with a high stroke risk would have a low bleeding risk. Therefore, we speculate that the patient group that could benefit from bridging anticoagulation according to our calculations, will be very small.

We found only slight differences between acenocoumarol, phenprocoumon and warfarin. For patients with a low bleeding risk, bridging acenocoumarol is significantly beneficial from a CHA₂DS₂-VASc of 7 and higher, as opposed to a CHA₂DS₂-VASc of 6 and higher for warfarin and phenprocoumon. Our calculations stress the importance of post-procedural INR management: if patients reach a therapeutic INR within five days, strokes will occur less frequently, thus reducing the potential benefit of bridging. For patients in which it takes 10 or 15 days to reach an INR of 2.5, periprocedural bridging is only likely to be beneficial at higher CHA₂DS₂-VASc or CHADS₂ scores. We expect the time to reach therapeutic INR will mainly depend on the patient-specific INR management, but it might also depend on the used VKA: e.g. for patients on phenprocoumon it may take longer to reach therapeutic INR¹²². In clinical settings, the VKA used and the individual patient's history regarding INR management could be taken into account when deciding whether

to bridge or not.

Our results show a lot of uncertainty around the calculated means, especially for patients with high HAS-BLED scores. This is a result of the limited number of events, especially strokes, found within clinical studies. More real-life data could enhance the reliability of the results, for example within the context of a large multi-centre registry. The stroke risks in the model are calculated using the risk stratification schemes from the clinical setting to determine the necessity of anticoagulation, which may not be valid to use as a decision tool in surgical settings. Regarding the post-procedural stroke risk for AF patients, it would be preferable to use specific stratified stroke rates from the surgical setting, however, these numbers are not available.

The included strokes in the model are ischaemic, since most perioperative strokes are ischemic instead of haemorrhagic, and data reliably differentiating ischemic and haemorrhagic strokes is rare¹²³. Transient ischemic attacks were not included in the model, because their relative risk with warfarin treatment vs. non-treatment is not significant¹²⁴. Systemic embolisms were also not included, as the odds ratio of warfarin vs. placebo is not significant¹²⁵.

The evidence for post-operative bleeding rates that incorporates both the HAS-BLED score and the effect of LMWHs is not available. This obstacle was tackled by using the effect of periprocedural bridging from the BRIDGE trial and the effect of the HAS-BLED score from Omran et al^{109,117}. Procedure-specific bleeding rates were not incorporated in the model, as the necessary data that could support this analysis, was not available in literature. The patient-specific bleeding rate, which we have included using HAS-BLED scores, can be used to approximate the procedure-specific bleeding rates: for procedures with high bleeding risks, bridging will be highly unlikely to be beneficial, while we may underestimate the benefit of bridging for low-risk procedures. However, for procedures with low bleeding risks, interrupting VKA treatment is not indicated, making our model superfluous¹⁰⁸. Thrombotic risk was not included in the model, since this is equal in both treatment arms.

The BRIDGE trial previously concluded that forgoing anticoagulation bridging is not inferior to perioperative bridging with low-molecular-weight heparin for the prevention of arterial thromboembolism and decreased the risk of major bleeding¹⁰⁹. This evaluation demonstrated that for specific AF patients, bridging is expected to be beneficial. Within the BRIDGE trial, patients with relatively low stroke risks were included: CHADS₂ 2.3 (± 1.03) and 2.4 (± 1.07) for the non-bridging and bridging groups respectively¹⁰⁹. These patients also do not benefit from periprocedural bridging in the base case of our simulation.

Dunn et al. previously found that bridging anticoagulation was preferred at an annual stroke rate of >5.6%, which would correspond to a CHADS₂ score between 2 and 3^{110,112}. This outcome is comparable to our results, though in our model the difference is only significant from a CHADS₂ score of 2 (age 55-65) or 4 (age 65-85). Compared to the article by Dunn et al., we were able to incorporate more recent evidence to support the model, such as the BRIDGE trial.^{3,6} A more recent simulation study by Pappas et al. simulated net clinical benefit using population parameters for stroke and bleeding¹¹³. As we used the quality adjusted life expectancy as the main outcome, we were able to take the long-term effects of strokes into account. Another difference is that we have incorporated increased risks, as compared to the population parameters, for bleeding and stroke post-procedurally^{109,117}.

Current guidelines already advice to consider the risk of stroke, the patient-related bleeding risk and the bleeding risk of the procedure¹⁰⁸. The results of our model confirm this and, additionally, make it possible to identify more specific patient groups where bridging may be beneficial.

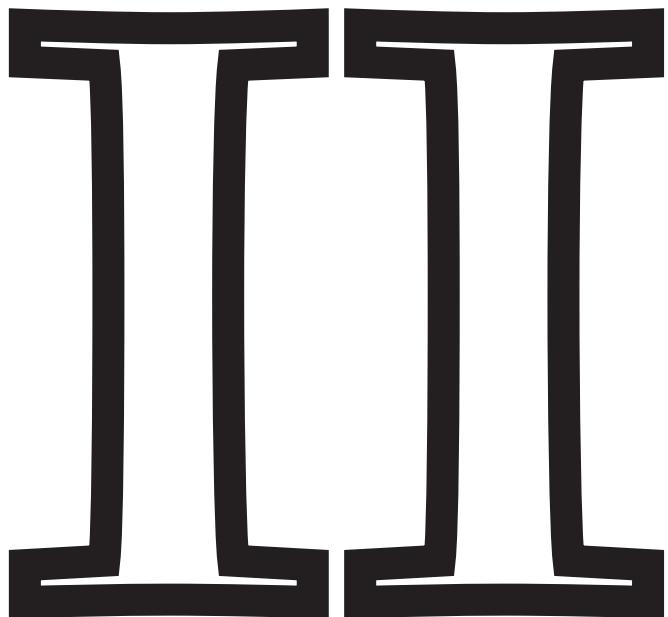
Our analysis stresses the importance of the post-procedural time to therapeutic INR. Limited research is available that focusses on the time it takes for AF patients to reach therapeutic INR levels after interrupting a VKA in the clinical setting. Frequent monitoring of the INR and tailored post-procedural VKA usage schemes seems to have a critical role in minimizing the risk of stroke. Currently, it is recommended that VKAs are reinitiated at the previous dose, however, there may be an opportunity to develop individualized dosing regimens to improve the time to reach therapeutic INR. Specifically, in the clinical setting, focussing on the optimal organization of post-procedural INR management for all VKA users may yield greater benefits than bridging the small subpopulation of VKA users that we identified may benefit from this.

In conclusion, our results show that only a small subset of AF patients is expected to benefit from bridging anticoagulation: those at a high risk of stroke ($\text{CHA}_2\text{DS}_2\text{-VASc} \geq 6$, $\text{CHADS}_2 \geq 4$) and also at a low risk of bleeding ($\text{HAS-BLED} \leq 2$).

Acknowledgements

The authors would like to thank the Regional Coagulation Roundtable of the Provinces Groningen and Drenthe (The Netherlands) and the Martini Hospital Coagulation Committee for their input during the development of the model.

PART



**Methods to Assess the
Value of Diagnostics**

CHAPTER

5

Economic Analyses of Respiratory Tract Infection Diagnostics A Systematic Review

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Abstract

Background: Diagnostic testing for respiratory tract infections is a tool to manage the current COVID-19 pandemic, as well as the rising incidence of antimicrobial resistance (AMR). At the same time, new European regulations for market entry of in vitro diagnostics, in the form of the in vitro diagnostic regulation (IVDR), may lead to more clinical evidence supporting health-economic analyses.

Objective: To systematically review the methods used in economic evaluations of applied diagnostic techniques, for all patients seeking care for infectious diseases of the respiratory tract (such as pneumonia, pulmonary tuberculosis, influenza, sinusitis, pharyngitis, sore throats and general respiratory tract infections).

Methods: Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, articles from three large databases of scientific literature were included (Scopus, Web of Science and PubMed) for the period January 2000 - May 2020.

Results: A total of 70 economic analyses are included, most of which use decision tree modelling for diagnostic testing for respiratory tract infections in the community-care setting. Many studies do not incorporate a generally comparable clinical outcome in their cost-effectiveness analysis: fewer than half the studies (33/70) used generalisable outcomes such as quality-adjusted life years (QALYs). Other papers consider outcomes related to the accuracy of the test or outcomes related to the prescribed treatment. The time horizons of the studies generally are limited.

Conclusion: The methods to economically assess diagnostic tests for respiratory tract infections vary and would benefit from clear recommendations from policy makers on the assessed time horizon and outcomes used.

Introduction

When diagnosing a patient with common symptoms with various possible pathologies, such as respiratory infections, clinicians historically had to either rely on clinical judgement and empirical therapy, or wait for the results of diagnostics performed in specialized laboratories¹²⁶. Recent developments have brought diagnostic tests to the point of care (POC): these novel diagnostics enable clinicians to rapidly and more accurately diagnose patients and to prescribe more appropriate treatment¹²⁷, which in turn improve understanding of the patient's condition and monitoring of the patient's clinical course¹²⁸.

In light of the COVID-19 pandemic, rapid diagnostic tests are regarded as a fundamental instrument in combating the spread of SARS-CoV-2^{129,130} and, consequently, have received a lot of attention. While societies worldwide are vaccinated at an unprecedented rate, rapid COVID-19 tests are expected to play an important role in reopening the economy. Since the start of the pandemic, many diagnostics have been developed and are entering the market^{131–133}.

The pandemic is a major risk to public health and economies worldwide, but infectious disease poses another threat as well: in 2018, the World Health Organisation (WHO) declared antimicrobial resistance (AMR) to be one of the ten greatest threats to public health¹³⁴. In Europe, there are estimated to be over 650,000 infections with resistant bacteria every year, causing over 30,000 attributable deaths¹³⁵. Innovative POC testing may have an important role in combating AMR, as it enables clinicians to prescribe antibiotics more accurately^{136,137}. Antibiotic prescriptions related to respiratory infections are especially relevant because this type of infection represents a third of total visits to primary care centres¹³⁸ and generate difficulties for medical professionals when diagnosing, as they tend to overestimate the proportion of patients presenting with bacterial infections and, consequently, overprescribe antibiotics¹³⁹.

5

In the field of pharmaceuticals, health technology assessment (HTA) plays an important role in assessing the value for money of new drugs¹⁴⁰, but in the case of diagnostic technologies, this is not as established. A complicating factor here is that, unlike pharmaceuticals, which directly influence a patient's health status, the impact of diagnostic technologies is indirect and only takes effect when diagnostic results change downstream clinical interventions¹⁴¹. Until now, the assessment of new diagnostic techniques often focused on technical capabilities, such as the test's sensitivity and specificity. However, starting in 2022, the European “in vitro diagnostic regulation” (IVDR) law will come into effect, making it mandatory for companies to prove the clinical effectiveness of new diagnostics before they enter the market with aligned data evidencing this¹⁴². These data will enable policy makers, payers and healthcare providers to better estimate the added clinical value of novel diagnostics and can be incorporated in HTA.

Considering the public health relevance of diagnostics of respiratory infections and the policy changes that may increase the focus on the HTA of diagnostics, we systematically reviewed the methods used in economic evaluations of applied diagnostic techniques, for all patients seeking care for infectious diseases of the respiratory tract (such as pneumonia, pulmonary tuberculosis (TB), influenza, bronchitis, bronchiolitis, sinusitis, pharyngitis, sore throats, group A beta-haemolytic streptococcal infections (GABHS) and general respiratory tract infections). Specifically, we report on the types of economic models used to assess current practices for implementing development diagnostic technologies so that the results generated would facilitate the identification of areas for improvement in economic evaluation of diagnostics. Finally, considering the evidence of increasing societal

costs of AMR¹³⁵ we evaluate how authors have modelled the influence of AMR and under which circumstances diagnostic tools would help reduce antibiotic prescription.

Methods

Search strategy

We conducted a systematic review of articles contained in PubMed, Scopus and Web of Science. The search syntax was constructed to include economic evaluations of diagnostic strategies of infectious diseases, see supplementary table 5.1 for the specific search syntax. The results were not limited to certain countries but, with the purpose of reflecting recent clinical practice, we only included articles published between January 2000 and May 2020.

Eligibility criteria

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines¹⁴³ were used for this study. Economic evaluations of diagnostics strategies for all respiratory tract infections were considered for inclusion. Articles meeting the eligibility criteria performed an economic analysis comparing both costs and effects, including Cost-Effectiveness Analyses (CEA), Cost-Utility Analyses (CUA) and Cost-Minimization Analyses (CMA) that incorporated clinical effects. Studies assessing only the test characteristics from a technical (laboratory) point of view were not considered in this review. Patient-relevant outcomes had to be included, such as Quality-Adjusted Life Years (QALYs), Disability-Adjusted Life Years (DALYs), life years gained or the proportion of correct diagnoses. An inclusion criterium was also utilised that at least two diagnostic strategies for respiratory tract infections were compared. Diagnostic strategies were defined as: “identifying the most likely cause of, and optionally optimal treatment for, a previously undetected disease in a clinically suspect patient who is seeking care”²⁶. Population screening, disease monitoring or genotyping of genetic material from patients were therefore explicitly not considered to be diagnostic strategies. Other exclusion criteria were studies focusing on animals, review articles, study protocols, comments on articles or individual case reports, and languages other than English, Spanish, Dutch, German or French.

Study selection

Phase one consisted of two reviewers independently screening the titles and abstracts (PRG & SvdP). In case of not reaching an agreement, a third person (ADIVa) was asked. The full-text screening phase was performed by the same two reviewers, applying the same criteria. This phase was also used to separate the diagnostic and screening strategies, as this distinction was often not clear from the abstract, and to assess whether the article concerned respiratory tract infections.

Data extraction

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist⁴⁹, was used as a basis to create a standardised digital (Google) form to extract the relevant data from the articles. Various items relevant to diagnostics were added to this extraction tool. See supplementary file 5.1 for an overview of the items included. The data extraction was divided between three reviewers (PRG, SvdP and ADIVa); 10% of extractions was duplicated to check for consistency between authors. Furthermore, the reviewers reached consensus with continuous discussions on the extracted data and repeating the extraction if necessary. To analyse the reporting quality of the studies, a score was calculated based on the presence of the items as reported in CHEERS⁴⁹.

In the general and introduction parts of the extraction tool, the research question, specific

disease area and pathogens considered were included. In the methodology, we emphasised the type of model developed and its characteristics in terms of perspective, time horizon, setting, population included and incorporation of uncertainty analysis in parameter values (stochastic or deterministic). A section was included to assess whether the model included AMR and, if so, how. In the results sections, we paid attention to the incremental costs and outcomes and techniques for reporting uncertainty in the model. Finally, for the discussion, the focus was on the main findings, limitations, specific limitations in the assessment of diagnostics, and advantages/disadvantages of the modelling technique discussed by the authors.

Data analysis

The data extracted from the articles were analysed using R 3.6.3¹⁴⁴, categorising the data by the considered pathogens (influenza, streptococcus) and the type of models (decision tree, Markov). For data transformation and table creation, the packages Dplyr 1.0.0¹⁴⁵ and gt 0.2.2¹⁴⁶ were used. The code was made available on GitHub.

Results

Figure 5.1 shows the included and excluded studies in a PRISMA flow diagram. 70 papers were included in this review. Most studies were a CEA or CUA, comparing the standard of care, mostly consisting of empirical therapy, clinical judgement or traditional diagnostics (e.g. cultures or microscopy), to the use of rapid diagnostic tests. The most common

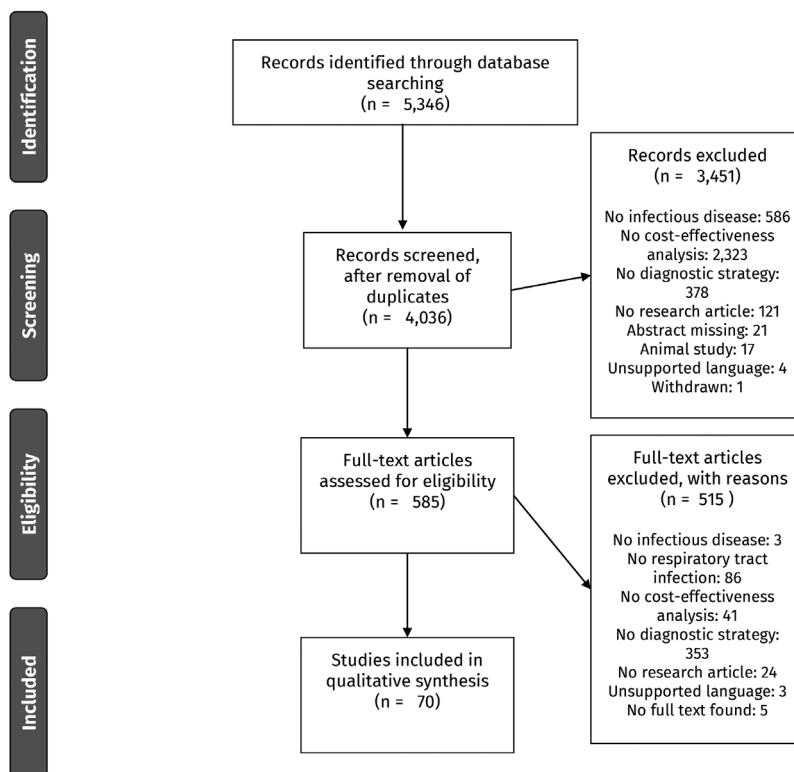


Figure 5.1. PRISMA flow diagram of inclusion and exclusion

rapid tests included are: Xpert for TB, influenza-specific POC tests, C-reactive protein (CRP) POC tests and procalcitonin (PCT) tests. Other diagnostics included are Polymerase Chain Reaction (PCR), microscopy, X-ray and clinical scoring algorithms. No tests for coronaviruses were included in this review. Most studies (46) included a decision tree model, two included a Markov model in addition to a decision tree, 12 were trial-based analyses, seven were categorised as a dynamic model, and three papers were categorised as 'other'. Table 5.1. provides an overview of the settings and tests assessed in the studies, while table 5.2. provides an overview of the methods used. Key characteristics and results of all studies can be found in supplementary tables 5.1 and 5.2.

The reporting quality, in the form of a CHEERS score, can also be found in the supplementary table 5.2. Most items were included by most studies. All articles reported comparators, model assumptions and incremental costs and outcomes of the model. Background and objectives were items included in all Markov model but only included in a 90% of trial-based analyses and 93% of decision tree models. The target population was included in all trial-based analyses, decision trees and Markov models but in 86% of all dynamic models.

Table 5.1. Overview of included studies

	Trial-based analysis (n = 12)^{147–158}	Decision tree model (n = 46)^{161–182,184–193,193–207}	Markov model (n = 2)^{209,210}	Dynamic model (n = 7)^{212–218}	Other (n = 3)^{219–221}
Income²					
High income	6 (50%) ^{147–151,153}	32 (70%) 162,163,165, 170–177,179, 180,182,184– 186,188–193,195– 197,199–201,203– 205	1 (50%) ²¹⁰	2 (29%) ^{212,213}	1 (33%) ²²¹
Middle income	5 (42%) ^{152,155–158}	9 (20%) ^{161, 166,178,181,187,1 94,198,202,207}	0 (0%)	2 (29%) ^{215,217}	2 (67%) ^{219,220}
Low income	1 (8%) ¹⁵⁸	5 (11%) ^{161,167–169,206}	0 (0%)	4 (57%) ^{215–218}	0 (0%)
Population					
Children and adolescents	1 (8%) ¹⁵⁸	11 (24%) 174,177,184–186, 189,194, 201–203,207	1 (50%) ²⁰⁹	1 (14%) ²¹³	2 (67%) ^{219,221}
Elderly	0 (0%)	4 (9%) ^{171,189,204,205}	1 (50%) ²⁰⁹	0 (0%)	0 (0%)
Setting					
Primary care	5 (42%) ^{148–150,152,154}	26 (57%) 161,166– 169,175,176,178, 179,181,184– 186,189,190,193– 197,199,201–205	2 (100%) ^{209,210}	1 (14%) ²¹⁶	1 (33%) ²¹⁹
Hospital	4 (33%) ^{147,153,155,158}	18 (39%) 161–165, 169–172, 177, 180–182, 187,190,192, 206,207	0 (0%)	3 (43%) ^{212,213,215}	3 (100%) ^{219–221}
Emergency department	1 (8%) ¹⁵¹	5 (11%) ^{173,174, 177,181,198}	0 (0%)	1 (14%) ²¹²	0 (0%)

Table 5.1. Overview of included studies (continued)

	Trial-based analysis (n = 12) ^{147–158}	Decision tree model (n = 46) ^{161–182,184–193,193–207}	Markov model (n = 2) ^{209,210}	Dynamic model (n = 7) ^{212–218}	Other (n = 3) ^{219–221}
Clinical indication					
Tuberculosis	6 (50%) 152,154–158	11 (24%) ^{161–171}	0 (0%)	6 (86%) ^{213–218}	2 (67%) ^{219,220}
Influenza	0 (0%)	14 (30%) ^{172–174,194–198,200–205}	0 (0%)	1 (14%) ²¹²	0 (0%)
Pneumonia	2 (17%) 151,153	3 (7%) 178,191,192	0 (0%)	0 (0%)	0 (0%)
Other ³	4 (33%) 147–150	18 (39%) ^{175–177,} 179–182,184,185, 186,187–190, 193,199,206,207	2 (100%) ^{209,210}	0 (0%)	1 (33%) ²²¹
Diagnostic strategies					
Rapid diagnostic test ⁴	3 (25%) ¹ 47–149	19 (41%) 172,175–177,179–182,194–198,200–203,205,207	1 (50%) ²¹⁰	0 (0%)	0 (0%)
Traditional diagnostic ⁵	6 (50%) 147,152, 154,156–158	15 (33%) 161–164, 166–169,184–187,191,192,199	0 (0%)	3 (43%) ^{215,216,218}	2 (67%) ^{219,220}
Xpert ⁶	5 (42%) 152,154–157	8 (17%) ^{162–169}	0 (0%)	5 (71%) ^{214–216,217,218}	1 (33%) ²¹⁹
Clinical rule	2 (17%) 153,158	6 (13%) 180,184,186, 189,194,198	0 (0%)	0 (0%)	1 (33%) ²²¹
Perspective					
Societal	0 (0%)	12 (26%) 173,177, 180,184,195,196, 198–201,203,205	1 (50%) ²⁰⁹	3 (43%) ^{212,213,215}	1 (33%) ²²⁰
System ⁷	2 (17%) 149,156	18 (39%) 163,164,168–171, 175,176,178,179, 182,185–188, 196,197,202	1 (50%) ²¹⁰	4 (57%) ^{213,214,217,218}	2 (67%) ^{219,220}
Provider ⁸	8 (67%) ¹⁴⁷ ,148,150,151,153 ,154,157,158	18 (39%) 161–163,165, 167,172,174, 180,181,189–194, 204,206,207	0 (0%)	1 (14%) ²¹⁶	1 (33%) ²²¹

Table 5.1. Overview of included studies (continued)

	Trial-based analysis (n = 12)^{147–158}	Decision tree model (n = 46)^{161–182,184–193,193–207}	Markov model (n = 2)^{209,210}	Dynamic model (n = 7)^{212–218}	Other (n = 3)^{219–221}
Type of analysis					
Cost-utility analysis	3 (25%) ^{147–149}	22 (48%) ^{163–165,} 169–174,176,177, 179,184,187,197, 199–205	2 (100%) ^{209,210}	6 (86%) ^{213–218}	0 (0%)
Cost-effectiveness analysis	9 (75%) ^{150–158}	20 (43%) ^{161,162,166–168,175,} 178,180,185,186, 189–194, 196,198, 206,207	0 (0%)	1 (14%) ²¹²	2 (67%) ^{219,221}
Cost-minimization analysis	0 (0%)	2 (4%) ^{177,188}	0 (0%)	0 (0%)	1 (33%) ²²⁰

5

Note that not all items are reported by all articles; hence not all columns sum to the total included articles

¹ Including a microsimulation and two database studies

² According to World Bank definitions

³ Including sinusitis, pharyngitis, sore throat, general respiratory infections

⁴ Includes rapid influenza tests, C-reactive protein tests and procalcitonin tests

⁵ Including microscopy and microbiological cultures

⁶ GeneXpert tuberculosis and rifampicin resistance test

⁷ Includes the healthcare system's and healthcare payer's perspective

⁸ Includes analyses from the perspective of a health centre, a laboratory or other provider of care

Table 5.2. Methods of included studies

	Trial-based analysis (n = 12) ¹⁴⁷⁻¹⁵⁸	Decision tree model (n = 46)	Markov model (n = 2) ^{209,210}	Dynamic model (n = 7) ²¹²⁻²¹⁸	Other (n = 3) ²¹⁹⁻²²¹
<hr/>					
Time horizon					
Less than 1 year	4 (33%) ¹⁴⁷⁻ 149,153	16 (35%) 168,171,175, 176,179-182,190- 193,195,196, 198,200	1 (50%) ²⁰⁹	0 (0%)	1 (33%) ²²⁰
One year or more ^j	0 (0%)	7 (15%) ^{170,} 177,178,185,199,2 01,207	1 (50%) ²¹⁰	6 (86%) ²¹²⁻ 214,216-218	0 (0%)
Lifetime	0 (0%)	7 (15%) ¹⁷²⁻ 169,172-174, 200,203,204	0 (0%)	1 (14%) ²¹⁵	1 (33%) ²¹⁹
Unknown	8 (67%) ¹⁵⁰⁻ 152,154-158	16 (35%) 161-167,184, 186-189, 194,197,202,206	0 (0%)	0 (0%)	1 (33%) ²²¹
<hr/>					
Measurement of effectiveness					
Single-study based	10 (83%) ¹⁴⁹⁻ 158	7 (15%) ^{161,} 162,169,170,174,1 75,177	1 (50%) ²¹⁰	0 (0%)	2 (67%) ^{220,221}
Synthesis	2 (17%) ^{147,148}	38 (83%) ¹⁶⁴⁻ 168,171- 173,176,178- 182,184-207	1 (50%) ²⁰⁹	7 (100%) ²¹²⁻²¹⁸	1 (33%) ²¹⁹
<hr/>					
Clinical outcomes reported					
QALYs or DALYs	3 (25%) ¹⁴⁷⁻ 149	22 (48%) 163-165,169-174, 176,177,179,184, 187,197,199-205	2 (100%) 209,210	6 (86%) ²¹³⁻ 218	0 (0%)
Treatment-related ²	1 (8%) ¹⁵¹	7 (15%) ¹ 75,180,181,185 ,189,190,198	0 (0%)	0 (0%)	0 (0%)
Based on diagnostic performance	5 (42%) ¹⁵⁴⁻¹⁵⁸	5 (11%) 161,162, 166,192,206	0 (0%)	0 (0%)	0 (0%)
Time-related ³	1 (8%) ¹⁵³	6 (13%) 167,191,194- 196,207	0 (0%)	0 (0%)	2 (67%) ^{220,221}
Resistance included in analysis	4 (33%) 149,155-157	9 (20%) 164,176,179- 182,191,198,201	1 (50%) ²⁰⁹	4 (57%) 214,215,217,218	2 (67%) ^{219,220}

Table 5.2. Methods of included studies (continued)

	Trial-based analysis (n = 12) ^{147–158}	Decision tree model (n = 46)	Markov model (n = 2) ^{209,210}	Dynamic model (n = 7) ^{212–218}	Other (n = 3) ^{219–221}
<hr/>					
Sensitivity analyses					
Univariate	5 (42%) 147,149, 154,156,158	40 (87%) ^{161–} 168,170,172– 174,176–178,180– 182,184,186– 193,195–206	2 (100%) ^{209,210}	6 (86%) ^{212–} 216,218	3 (100%) ^{219–} 221
Multivariate	0 (0%)	8 (17%) ^{162,} 164,166,172,185,1 91,193,200	0 (0%)	1 (14%) ²¹⁴	1 (33%) ²¹⁹
Probabilistic	5 (42%) 147–149,154,156	31 (67%) 162–166,168–176, 179,180,184, 187,191,192,194, 196–204,207	1 (50%) ²¹⁰	6 (86%) ^{212,214–218}	1 (33%) ²¹⁹

Note that not all items are reported by all articles; hence not all columns sum to the total included articles
 QALY: Quality-Adjusted Life Year; DALY: Disability-Adjusted Life Year; CEAC: Cost-Effectiveness Acceptability Curve

¹ Excluding lifetime horizons

² Includes number of correct diagnoses (for example true positives) and time to correct diagnosis

³ Includes time to correct diagnosis, hospital length-of-stay and disease duration

Regression models and trial-based analyses

When cost and effectiveness data obtained from a trial are directly used to analyse the costs and clinical effects of a new intervention using standard statistical methods, this is regarded as a regression model or trial-based analyses.

Several studies examined cost-effectiveness based upon (mostly) a single trial¹⁴⁷⁻¹⁵⁸, without the use of a health-economic model. Four studies assessed diagnostics for general respiratory tract infections¹⁴⁷⁻¹⁵⁰, two studies assessed diagnostics for pneumonia^{151,153} and three assessed diagnostics for tuberculosis (TB)^{152,154,155}.

Two studies by Oppong et al. assessed the cost-effectiveness of POC CRP testing^{148,149} and internet-based training for primary care clinicians¹⁴⁹ using regression models. The first study used data from an observational study in Norway and Sweden¹⁴⁸, while the second one used data from a multinational, cluster-randomised, factorial controlled trial in Belgium, the Netherlands, Poland, Spain and the United Kingdom (UK)¹⁴⁹. Both studies incorporated resource use, EQ-5D scores and antibiotic prescribing from the trials^{148,149}. Multilevel modelling was used to model the outcomes of interest: QALYs, antibiotic prescriptions and costs. Both studies found antibiotic prescribing to be less prevalent when a POC CRP test was performed and found no significant differences in health outcomes. The cost-effectiveness of POC CRP testing largely depended on the country, even when similar methods were used: while it was a dominant strategy in the Netherlands; in Spain, it was dominated by usual care^{148,149}. In the analysis where communication training was considered, this was considered to be the overall dominant strategy¹⁴⁹. Cost-effectiveness acceptability curves (CEAC) were included in both articles^{148,149}, using the net benefit regression framework¹⁵⁹. The reduction in antibiotic prescriptions was expressed in monetary terms as additional costs per patient prescription avoided¹⁴⁸ or additional costs per percentage reduction in antibiotic prescriptions¹⁴⁹.

Nicholson et al. conducted an RCT and health-economic evaluation of diagnostic tests for influenza, RSV and *Streptococcus pneumoniae* in adults hospitalised for chronic or acute cardiopulmonary illness in the UK¹⁴⁷. Three strategies were included in the analysis: POC tests, PCR and traditional, conventional laboratory diagnostic assessment. The clinical characteristics of the various diagnostic strategies were compared, and the cost-effectiveness was assessed using a bivariate model, mainly incorporating costs and QALYs of the trial. The authors performed a Bayesian analysis that used 50,000 replications of a Markov Chain Monte Carlo analysis. The probability of cost-effectiveness was calculated at the willingness to pay (WTP) threshold of £20,000/QALY. The authors concluded that there were no major differences between the different strategies, both in costs and QALYs, but that the PCR-based strategy was the most likely to be cost-effective.

Two studies assessed the cost-effectiveness of diagnosing community-acquired pneumonia (CAP). Böhmer et al. assessed a computer algorithm that aided the prescription of antibiotics in hospital settings compared to usual care¹⁵³. Two groups of 15 patients were followed in a single hospital in Germany and the clinical outcomes considered were: days with symptoms, days with antibiotics and hospital length-of-stay. Differences between trial arms were calculated using t tests. The algorithm was considered to be cost-saving, resulting in fewer costs and better treatment¹⁵³. Dinh et al. assessed the cost-effectiveness of a rapid pneumococcal antigen test for CAP patients in the Emergency Department (ED) setting¹⁵¹. 1,224 patients were included over three years; however, no control arm was used. In total, there were 51 positive test results, which led to a change in prescription for seven patients. The authors concluded that the costs of implementing the antigen test

(€8,748 annually) were too high compared to the benefits¹⁵¹.

Six trial-based analyses considered specific TB strategies: different culture-based methods in Kenya¹⁵⁸, Xpert testing in South Africa in laboratories¹⁵⁷ or at POC^{152,154}; automated microscopy in the South African laboratory setting¹⁵⁶; and a second Xpert test in China¹⁵⁵. Patient-level clinical and cost data were collected. Cost-effectiveness outcomes were mostly influenced by the number of patients correctly diagnosed, screened or treated^{152,154–158}, one study included TB morbidity measured with a numerical TB score¹⁵⁴. Differences between the various groups were compared using standard frequentist methods^{152,155}, logistic regression¹⁵², univariate analyses^{154,156,158} and Monte Carlo analyses^{154,156}. Two studies presented a cost-effectiveness frontier to compare the different strategies included in the analysis^{155,156}. The two studies assessing POC Xpert testing in South Africa had different conclusions compared to current care: cost-saving¹⁵² or cost-effective (albeit more expensive)¹⁵⁴, while the study in the South African laboratory setting concluded that the higher costs were not matched by the improvement in TB diagnostic efficacy¹⁵⁷. Wang et al. concluded that the price increase related to performing a second Xpert test is relatively high¹⁵⁵. Four studies questioned the affordability of the assessed TB diagnostic strategies in low-income countries^{155–158}, even if the result of the analysis was that the assessed strategy was cost-effective.

There were some common gaps in the reporting quality of the trial-based and regression analyses. Mostly, this was a result of the relatively short time horizons: the percentage of trial-based studies that reported the time horizon was 20% and 30% reported the discount rate. 40% of the articles reported the measurement of effectiveness and the choice of model was reported in 20% of the articles. An example of a paper with a high reporting quality is written by Oppong et al.¹⁴⁸ Resource use, clinical outcomes and statistical methods were clearly described, and the performed regression analysis provided detailed insight in the parameters relevant for the model.

Decision trees

Decision tree models are used to calculate costs and effectiveness outcomes of different clinical interventions, usually over a limited time period as time cannot be modelled explicitly¹⁶⁰. A combination of decisions and probability rates of occurrence are used to calculate the outcomes for various cohorts in the model.

A total of 46 articles compared diagnostic techniques using a decision tree model. 32 articles focused on the use of diagnostic tests that identify bacterial infections (11 TB-specific tests, seven CRP, four PCT, six group A beta-haemolytic *Streptococcus pyogenes* (GABHS) infection and four used other diagnostic techniques). 12 articles focused on the use of diagnostic tests to detect influenza (FLU OIA, QuickVue and ZstatFlu). Finally, two articles compared tests for both bacterial and viral infection.

The main diagnostic test to detect TB was the Xpert test^{161–168}, with other articles assessing the lateral flow urine lipoarabinomannan assay Alere Determine™ test¹⁶⁹, the IGRA (Interferon-Gamma Release Assay) test¹⁷⁰ and the T cells detection test¹⁷¹. The target population consisted of patients presenting with symptoms of active pulmonary TB disease^{161–166,170}, in some cases Human Immunodeficiency Virus (HIV) patients specifically^{167–169,171}. The comparators were sputum smear microscopy^{161–164,168}, culture^{165–167} and chest radiography^{164,166,168}. In the case of testing positive, the treatment was a routine TB regime. Time horizons considered were six months¹⁶⁸, two months¹⁷¹ or lifetime^{169,170}. The clinical outcomes used were QALYs^{163,165,170,171}, DALYs^{164,169}, TB cases detected^{161,162,169,170}, days free

from disease¹⁶⁷ and deaths averted¹⁶⁸. One analysis included multi-drug resistance into the model as they switched to a second-line treatment if rifampicin resistance was identified¹⁶⁴. One study concluded that the delay in diagnosing active TB caused the test strategy not to be cost-effective¹⁷¹. Other studies showed that the combination of Xpert with LF-LAM was cost-effective compared to the usual care^{163,165,169} and testing was the most cost-effective strategy while varying the incidence of TB (even when as low as 0.2%)¹⁷⁰. Uncertainty was included using deterministic^{161–168,170} and probabilistic sensitivity analyses^{162–166,168–171}.

Seven articles assessed a CRP test with a decision tree^{172–178}. Patients were adults in hospital care^{172,173} or children in the ED¹⁷⁴, both with suspected influenza symptoms, adults with symptoms of acute respiratory tract infection attending primary care^{175,176,178} and children visiting the paediatric ED of a hospital with meningeal signs¹⁷⁷. The most common treatment included in the models was amoxicillin, in case of a positive CRP result^{172–177}. In case of a negative result, antiviral therapy was prescribed^{172–176}. Other strategies compared were treatment without testing^{173,176}, no treatment¹⁷³ and intensified communication after targeted training for general practitioners (GPs)¹⁷⁵. Different time horizons were used: 28 days^{175,176}, 15 years¹⁷⁷ and lifetime^{173,174}. Nelson et al. followed patients from ED through the rest of their lives, with a life expectancy of 78.7 years¹⁷⁴. Most analyses used QALYs as the clinical outcome^{172–174,176,177} and one analysis used the number of antibiotic prescriptions safely saved¹⁷⁵. One analysis¹⁷⁶ included the cost of antibiotic resistance, by increasing the price of each prescription with the estimated cost of AMR, based on the annual cost of resistance in the United States. Most articles concluded CRP testing was cost-effective except for one¹⁷². Notably, this specific study estimated that performing the test was only profitable with an influenza prevalence of under 2.5%, whereas it was higher during the study period¹⁷². Uncertainty was included using deterministic sensitivity analysis^{172–174,176,177}, probabilistic sensitivity analyses^{172–174,176} and cost-effectiveness acceptability curves (CEACs)^{172–174,176}.

PCT testing was compared to usual care in four studies^{179–182}. Patients were adults and children with suspected acute respiratory infections presented in primary care¹⁷⁹, the intensive care unit¹⁸⁰ or the hospital in general^{181,182}. Antibiotic treatment was prescribed to all who tested positive. In the usual care arm, empirical antibiotics were prescribed, as judged by the physician. The time horizon was short in all cases: 30 days^{181,182} or one episode of acute respiratory infection^{179,180}. Antibiotics avoided was used in three articles as the clinical outcome, expressed as the number of prescriptions saved¹⁷⁹ or as a reduction of days of treatment^{180,181}. Also, QALYs¹⁷⁹ and number of infections averted were used¹⁸⁰. All articles included AMR: three studies assumed that the value of a safely avoided antibiotic prescription equalled the health system cost of resistant infections attributable to that prescription^{179,181,182}. In another article, the reduction in resistant infections was calculated, multiplying the correlation of reduction in days of antibiotics and rate of resistance (estimated in previous publications¹⁸³) by the difference in days of antibiotics between PCT and the usual care group¹⁸⁰. Three articles concluded that PCT was cost-effective^{179,181,182}. Uncertainty was included using a sensitivity analysis graph^{181,182}, CEAC¹⁷⁹ and tornado diagram¹⁸⁰.

Six decision-tree studies included a marker to detect GABHS infection^{184–189}. Children and adults with symptoms of pharyngitis presenting to primary care^{184–186} or hospitals¹⁸⁷, and in other cases with a sore throat^{188,189}, formed the population. The strategy of performing a rapid test was compared with treating all^{184–188}, treating none^{184,187}, using a clinical scoring measure to determine the treatment (triage the diagnosis and treat those with a high score

with antibiotics)^{184–186} or culture¹⁸⁷. If the diagnostic test was positive, penicillin was prescribed^{187–189} or two types of antibiotics depending on the severity of the infection. Clinical outcomes were expressed as quality-adjusted life-days (QALD)^{184,187}, proportion of patients cured without complications^{185,186} and rate of appropriate use of an antibiotic per patient treated¹⁸⁹. The use of the rapid diagnostic test to detect GABHS was cost-effective^{184–187,189} and cost-saving¹⁸⁸. Uncertainty was included using deterministic analyses^{186,188,189}, a tornado diagram^{184,186,187} or a two-way sensitivity analysis graph¹⁸⁵.

Three articles^{190–192} used other diagnostic techniques to detect pneumonia: plain chest x-ray and blood count¹⁹⁰, different cultures (BinaxNOW-SP and urinary antigen test) as an add-on to standard cultures¹⁹², bronchoalveolar lavage (BAL), mini-BAL, or endotracheal tube or bronchoscopy¹⁹¹. The included populations varied: Bertrán et al. considered a population of patients with community-acquired pneumonia, under age 65, without hospital admission criteria, and patients with acute exacerbation of chronic bronchitis due to respiratory infection¹⁹⁰. Ost et al., modelled a hypothetical cohort of immunocompetent patients in the ICU, intubated for 7 days, with evidence of ventilator-associated pneumonia¹⁹¹. The target population in Xie et al. was hospitalised patients with community-acquired pneumonia¹⁹². The three articles used a healthcare centre's perspective, included uncertainty using a deterministic sensitivity analysis and concluded that testing for pneumonia was cost-effective^{190–192}.

In another article, acute sinusitis was identified by ultrasound or radiographic evaluation¹⁹³. The target population consisted of patients presenting with acute sinusitis in primary care. The analysis took a healthcare centre's perspective, with a time horizon of seven days. The clinical outcome was the probability of being cured. As a result, authors suggested that the most rational clinical response to a suspected case of sinusitis was first “to wait and see for one week”, with a “selective strategy by means of structured clinical assessment” as the next step. Uncertainty was included with a deterministic sensitivity analysis and a two-way sensitivity analysis graph.

In 12 articles, the strategy of a diagnostic test that detects the presence of viruses was studied in a decision tree. The population of the studies were adults^{194–200}, children^{201–203} and the elderly^{204,205} with influenza-like illness during the influenza season^{196–198,200,203,205}, and, in two papers, only patients without prior influenza vaccination were included^{200,201}. The diagnostic test to detect influenza was included in all decision trees and was compared to clinical judgment^{194,204}, empirical treatment^{195,198–200,203}, treating none^{195–197,201,202}, targeted or universal rapid influenza testing¹⁹⁸, culture¹⁹⁹ as well as other rapid diagnostic tests such as FLU OIA, QuickVue, ZstatFlu^{200,203,205} or other tests¹⁹⁶. In the case of a positive influenza test, the treatment was oseltamivir^{196–198,200,201,203–205}. Amoxicillin^{195,198–200,203} and/or oseltamivir^{194–198,201–203,203–205} were included in the empirical treatment strategies. The time horizon was one year^{199,202} or a single episode of influenza-like illness^{195,196,198,200}. The clinical outcome most used was QALYs^{196,197,199–205}, quality-adjusted life expectancy (QALE)^{200,203,205}, days free from disease^{194,196} and antibiotic prescriptions saved¹⁹⁸. Two decision trees considered resistance: oseltamivir resistance was included as a percentage of H1N1 strains²⁰¹ and, as assumed by Michaelidis et al.¹⁷⁹, authors supposed that the relationship between antibiotic use and antibiotic resistance was one-to-one linear, in order to determine the impact of antibiotics used in treating influenza-like illness on overall societal antibiotic resistance¹⁹⁸. Four analyses showed that rapid testing for influenza was not cost-effective during the influenza season^{202,203}, testing was only a cost-effective approach early in a pandemic¹⁹⁷ and, in unvaccinated patients, antiviral therapy without testing was economical-

ly more reasonable¹⁹⁶. Other authors concluded that the optimal strategy depended on the patient's vaccination status and the risk of hospitalisation²⁰⁵. The findings showed that testing saved QALYs by reducing the rates of subsequent hospitalisation for influenza and mortality²⁰⁴. Uncertainty was included using deterministic^{196–205} and probabilistic sensitivity analyses^{196,198,200,203,205}.

Two articles included diagnostic strategies for both viral and bacterial infections^{206,207}. The populations were adults with suspected infections²⁰⁶ and children with symptoms of acute bronchiolitis²⁰⁷, both in a hospital setting. In one article, three testing strategies were compared: a comprehensive strategy in which all available diagnostic tests were requested simultaneously; a stepwise strategy in which a limited number of diagnostic tests could be requested, prioritising those for the most prevalent diseases; and a minimalist strategy in which a limited number of diagnostic tests, prioritising those with the highest sensitivity and specificity could be requested²⁰⁶. In the case of a positive result, the treatment was five days of ceftriaxone²⁰⁶. The stepwise strategy was the most cost-effective in terms of cost per correct diagnosis. Uncertainty was included using deterministic analysis. In the other article, several diagnostic techniques were available (blood count, CRP, PCT, chest X-ray and respiratory virus detection tests) and a clinician could order any of these based on clinical suspicion and adhering to clinical practice guideline²⁰⁷. This forms a branch of the tree (named good practice) and it was compared with another branch in which any test was performed or, if it is done, these tests were not the appropriate ones based on the symptoms that the patient (named lack of good practice). In the case of a positive result from the test, the treatment was antibiotics. The utilisation of good practice in the diagnosis and management of patients with bronchiolitis was associated with both fewer patients readmitted within 10 days post discharge and lower costs. Uncertainty was included using deterministic analysis and a tornado diagram.

Frequent gaps in the reporting of decision tree models are also related to the relatively short time horizons, as is the case with trial-based analyses. The time horizon was reported by 65% of papers and the discount rate was reported by 24%. 68% of the articles reported the measurement and valuation of preference-based outcomes, and 43% the currency, price date and conversion. Michaelidis et al. provide a high-ranking decision tree model, based on the CHEERS score¹⁷⁹. The authors described an easy-to-understand decision tree to model PCT-guided antibiotic therapy for outpatient respiratory-tract infections over a short time horizon (one episode). Extensive sensitivity analyses showed the uncertainty associated with several model assumptions.

Static Markov models

A static Markov model presents a set of mutually exclusive and exhaustive states that describe the progression of a disease for a cohort of patients. In contrast to decision trees, Markov models can be used to incorporate time in the health-economic model²⁰⁸.

Two studies used a static Markov model in combination with a decision tree to model the diagnosis and treatment of respiratory tract infection in the community setting^{209,210}. Balk et al. considered acute bacterial sinusitis in the United States and compared four strategies: not prescribing antibiotics, empirical amoxicillin treatment, amoxicillin treatment based on a set of clinical criteria and amoxicillin treatment based on an x-ray²⁰⁹. A combination of a decision tree and a Markov model was used to model a 14-day period using daily cycles: the decision tree was used to model the index consultation, including any tests performed and treatment decision, while the Markov model was used for the disease development using daily cycles. The Markov model incorporated disease complications,

antibiotic side effects and symptom improvements. AMR was considered, by reducing the efficacy of the antibiotic compared to placebo over the 14-day period. The prevalence of sinusitis was varied using deterministic sensitivity analyses. Balk et al. concluded that prescribing antibiotics based on clinical criteria was cost-effective for settings where most patients experience mild or moderate symptoms, however, they also concluded that empirical antibiotics were cost-effective if a sufficient proportion of the population experienced severe symptoms²⁰⁹. Hunter considered the implementation of POC CRP tests in the UK, comparing three strategies to the current standard of care, in which a GP decides to prescribe antibiotics based on the GP's views and the patient's expectations²¹⁰. The strategies considered are: a CRP test performed by the GP; a CRP test performed by a practice nurse and a CRP test performed by the GP in combination with communication training for the GP²¹⁰. A combination of a decision tree and Markov model was used, with a time horizon of 3 years using 28-day cycles after the index consultation²¹⁰. The decision tree was used to model the consultation and direct follow-up (up to 28 days), while the recurrence of respiratory tract infections following the initial disease episode was modelled using the Markov model with two states: healthy and respiratory tract infection. The prevalence was not varied in the model. The model was probabilistic and a CE plane and CEACs were reported. Hunter concluded that CRP implementation is cost-saving, with the strategy with communication training not being cost-effective²¹⁰. The reporting quality of the study by Hunter was high.

5

Dynamic models

Dynamic models are characterised by a changing rate of infection within the population, usually based on the number of infected individuals²¹¹. Dynamic models can be individual-based or cohort-based.

One paper considered influenza: Nshimyumukiza et al. compared an influenza rapid diagnostic test followed by antiviral treatment to empiric antiviral treatment in Quebec, Canada, by using an individual-based dynamic model²¹². The model consisted of two parts: a “susceptible, infected, recovered” (SIR) model and an economic model, considering a time horizon of 1 year. The compartmental SIR model consisted of three differential equations to model three states using single-day cycles. The economic analytical model was used to simulate infected persons who could decide to seek care if they were symptomatic. Patients who sought care within 48 hours received oseltamivir, reducing the probability of complications such as pneumonia and death. Two outcomes were reported, the saved costs and life-years per 100,000 person years, and uncertainty was included using deterministic and probabilistic sensitivity analyses. The authors concluded that the testing strategy was dominant (fewer deaths and fewer costs) compared to empirical antiviral treatment²¹².

Six studies assessed TB diagnostic strategies using a dynamic model²¹³⁻²¹⁸, of which five assessed one or more Xpert-based strategies compared to other interventions (e.g. standard care)²¹⁴⁻²¹⁸, one assessed a public-private mixed programme for TB diagnosis²¹⁵ and one a national TB strain service. Countries included were various African countries^{214,216,218}, India^{215,217} and the UK²¹³. The transmission models incorporated stages such as uninfected/susceptible, latent infection and active infection, in four cases including TB resistance^{214,215,217,218} or HIV status^{214,216,218}. Included were individual-level models^{215,217} (agent-based modelling) and compartmental models^{213,214,216,218}. Langley et al. also incorporated a discrete-event simulation to model the patient (presumptive TB cases, visiting a diagnostic centre) and sputum pathways (samples flowing from the diagnostic centre to the lab-

oratory and undergoing various diagnostic tests)²¹⁸. Clinical outcomes considered were DALYs^{214,216–218}, QALYs^{213,215} and life years²¹⁴, with all models considering a time horizon of 10 years or more. Five models incorporated a PSA^{214–218}, four included a CEAC^{214,215,217,218}, all incorporated a deterministic sensitivity analysis^{213–218}, and two a cost-effectiveness frontier^{215,218}. The conclusions of the papers vary and are dependent on various factors, such as the affordability^{214,215}, uncertainty of the input parameters²¹⁶ or procedural factors (e.g. number of referrals and cost-sharing)²¹⁷. Langley et al. identified three cost-effective strategies, including Xpert testing and two microscopy-based strategies for Tanzania²¹⁸. Mears et al., who described universal strain typing in the UK, concluded that this was unlikely to be a cost-effective strategy²¹³.

Due to the complexity of dynamic models, these often are accompanied by extensive supplementary material containing the details of the performed analysis. Areas for improvement regarding the reporting quality are currency conversion methods and details regarding the valuation of QALYs or DALYs. Other than that, there were no major differences between the reporting quality of the various papers.

Other models

Lee et al. assessed the cost-effectiveness of POC testing for TB, including rifampicin resistance, with a new PCR test for India's public sector (Truenat)²¹⁹. The compared strategies were smear microscopy, Xpert and the Truenat test in designated microscopy centres and Truenat at POC. A microsimulation model was used to model a cohort of patients seeking care with TB symptoms, over a lifetime horizon. TB prevalence was based on a previous implementation study. The cost-effectiveness measure was costs per life-year saved; a budget impact analysis was also performed, using time horizons of two and five years. Uncertainty was included using one-way and two-way deterministic sensitivity analyses, varying Truenat sensitivity and linkage to care, and a Tornado diagram, varying various key model parameters. The authors concluded that implementing Truenat at POC was cost-effective²¹⁹.

Two CMAs used accounting data to study optimal healthcare resource use. Bogdanova et al. compared two diagnostic algorithms for TB in Russia: a culture-based diagnostic algorithm and line probe assay to detect resistant TB, using costs collected from the government's accounting systems²²⁰. The reduction in the number of hospital days to the correct diagnosis and treatment initiation were considered clinical outcomes. Oostenbrink et al. used hospital data to assess cost-savings related to the implementation of a decision rule to diagnose and treat children with meningeal signs visiting a Dutch ED²²¹. The considered outcomes were safely avoided lumbar punctures and empirical antibiotic treatment. Both studies estimated and compared the resulting costs of each algorithm. One-way sensitivity analyses were included by changing the cost parameters of the model, and both studies concluded that the investigated strategy was cost-saving compared to current care^{220,221}.

Discussion

In this study, we reviewed 70 economic analyses of applied diagnostic techniques for infectious diseases of the respiratory tract, covering a broad range of illnesses for which individuals seek care including influenza, pneumonia, TB and GABHS. The diagnostic techniques assessed range from POC to laboratory testing in numerous different country settings.

Advantages and disadvantages of different modelling methods

12 studies assessed the cost-effectiveness of a new diagnostic strategy within the context of a single trial. Seven studies were performed in HICs^{147–151,153,155} and five in LMICs^{152,154,156–158}. The scope of trials of diagnostics is sometimes rather limited. Of those trials included in this review, trials have only a few patients¹⁵³, only one trial arm¹⁵¹ or a limited scope (e.g. the cost-effectiveness was only assessed from the perspective of the laboratory)^{156,157}. Most trial-based analyses resorted to outcomes related to the direct performance of the diagnostics^{151,154–158}. The generalisability of the studies was affected by all these factors, and the results may not be applicable outside the direct setting where the analysis was performed^{151–153,157}. These and other aspects make it difficult to assess the effects of the diagnostic method beyond the trial; no trial-based analysis reported a time horizon longer than a couple of weeks. In addition, only a few studies used generic clinical outcomes that can be compared between various studies and disease areas, such as QALYs^{147–149}.

The type of model most frequently found in the review was a decision tree (46 of 70 articles). One of the reported advantages of using a decision tree analysis is that the technique enables comparison of a large number of strategies and even the possibility of combining them sequentially, mostly a clinical scoring system to identify patients to be tested^{184–186,189}. A decision tree can easily be adapted to different health systems and settings. 29 studies were performed in HICs^{162,165,170,171,173–177,179,180,182,184–186,188–193,195–197,199–201,203,205} and 17 in LMICs^{161,163,164,166–169,172,178,181,187,194,198,202,204,206,207}. Although authors usually focus on one age group, one decision tree can also be applied to more than one group, as evidenced by some articles, which included both paediatric and adult populations in their analysis^{181,186,188,194}. Decision trees are straightforward to model and interpret for researchers and clinicians who may not be familiar with pharmacoeconomic methods. The (computational) simplicity of decision trees also enhances feasibility to include several sensitivity analyses, such as calculating the cost-effectiveness under various disease incidence values^{172–178}. A disadvantage of using decision trees can be that long-term outcomes are difficult to include, as time as a factor is not modelled explicitly. Therefore, many of these studies incorporate only a short time horizon or do not detail a time horizon at all. Yet, some overcame this disadvantage by estimating the life expectancy and applying that as time horizon^{173,174} or extended a decision tree with a Markov model to be able to model time explicitly^{209,210}. The main disadvantage found when using a decision tree was that several simplifying assumptions are needed^{164,176,199}, which makes it difficult to generalize the results. The testing strategy was cost-effective in 32 articles and cost-saving in six. Factors that most affected the results were the prevalence of infection and the patient's vaccination status. First, below and above certain prevalence percentages, the testing strategy is no longer cost-effective, either because there is not a sufficient number of cases or because empiric treatment dominates the other strategies^{162,167,172–174,185,187,192,194,199,201,206}. Also, the patient's vaccination status is a key aspect that affected the results, as the vaccination status influences the probability of a patient having the disease of interest: the cost-effectiveness of testing can be reduced in vaccinated populations^{177,195,196,201–203,205}. The test parameters affected the results of the analysis, but also the physician's judgment was found to be influential.

Seven studies used a dynamic model to assess the use of a novel diagnostic strategy^{212–218}. These models included transmission of influenza²¹² or TB^{213–218}, providing more flexibility compared to most other model types included in this review. For example, the TB models included time horizons ranging from ten years to a lifetime^{213–218}, and included either QALYs or DALYs^{213–218}. Two studies were performed in HICs^{212,213} and five in LMICs^{214–218}.

Dynamic models require more data than more straightforward models and this was mentioned as a disadvantage by some studies included^{212,214,216,217}. The authors of two papers mentioned that the time to treatment was an important aspect that was not modelled in their analysis^{213,216}. Langley et al. found a solution to this problem, as the authors not only modelled TB transmission, but also the operational process of transporting test samples to external diagnostic laboratories for different types of microscopy and Xpert in Tanzania²¹⁸. Using a discrete event simulation (DES), the authors modelled the time to start the correct treatment and loss-to-follow-up²¹⁸. Lee et al. did not include transmission in their TB microsimulation, instead, they used incidence data from a previous study. In this model, continuity of care after a visit to a health centre was improved when diagnosing at POC compared to external laboratories, resulting in better patient outcomes²¹⁹.

Three models were CMAs^{188,220,221} with a main focus on financial outcomes and not on clinical outcomes, which we believe to be a feasible approach when the new diagnostic strategy is at least as effective as current care. As the data requirements of the CMAs included in this review (unit-level accounting data or micro-costing) are larger than most other reviewed studies, this type of study may be less reproducible and more difficult to interpret for clinicians.

Inclusion of AMR

Twenty articles included resistance in some way^{149,155–157,164,176,179–182,191,198,201,209,214,215,217–220}. We identified three main methods for including AMR, which were used by more than one paper. Seven models incorporated AMR by adding a ‘societal cost’ to any antibiotics prescription^{149,176,179,181,181,191,198}, which was based on a paper by Oppong et al²²². Six models used a fixed percentage of resistant infections, in some cases varied in sensitivity analyses^{155–157,164,201,218}. Five studies modelled resistance dynamically, by changing the resistance rate based on the consumption of antibiotics^{180,214,215}, by modelling both a sensitive and resistant strain²¹⁷, or by decreasing the efficacy of antibiotics in the future²⁰⁹. Clearly, the consequences of increasing AMR can be incorporated in the numerator or denominator of the ICER (i.e., included as a cost or a clinical effect). Still, most studies did not include AMR in the analysis at all, even though this is highly relevant for patients, care providers and policy makers¹³⁵.

Limitations

This review focused on diagnostic strategies, as defined in the methods. The distinction between a diagnostic test and tests used for other purposes, such as screening, disease monitoring or (pharmaco-)genetic tests, can be difficult to make in certain cases. In many cases, the authors do not clearly specify the population to which the test is applied. We therefore tried to clearly define what we consider to be a diagnostic and made the distinction in the full-text screening round, so that we could decide from the methods, often the model specification, whether the paper should be included. We included five languages in this review, which limited the papers we included (seven papers were excluded based on language). Additionally, we only included papers from the year 2000 onwards, which allowed us to focus on current health-economic methods and diagnostic strategies.

Due to the many different diagnostic strategies that are included in this review, as well as the large number of healthcare systems (over 30 countries), we have not included any comparison of cost-effectiveness results. The quality of reporting was included using the CHEERS checklist as described above.

Opportunities for further research

Considering the number of articles included in this review, there is great interest in the cost-effectiveness of diagnostics for respiratory infections. However, there are some gaps where further research could be warranted. For example, in POC diagnostics in general practice: for many HICs we found no study on the cost-effectiveness of any test. Considering the significant reductions of antibiotic consumption linked to these tests¹⁴⁹, this may be an important opportunity to contain increasing AMR. Even more reductions in inappropriate antibiotic prescribing may be possible in LMICs²²³, but few studies considered the cost-effectiveness of diagnostics for other respiratory infections than TB^{181,187,194,198,202,206,207}.

In the hospital setting, multiplex PCR systems may increasingly play a role in quickly testing for a range of viruses and bacteria, which can provide valuable insight into the local transmission of respiratory pathogens²²⁴. Only two papers included an analysis of multiplex PCR; both papers considered patient-specific outcomes, but not the broader value of knowing the epidemiology of respiratory tract infections in the community^{147,174}. Although multiplex PCR systems may be major investments for hospitals, the collected data on the aetiology of ca-arti and AMR could be used to inform prescribing decisions by GPs in the community setting as well.

This review shows that there are many different methodological approaches used in literature to assess the cost-effectiveness of diagnostics for respiratory tract infections. While 33 studies used generalisable outcomes such as QALYs^{147–149,163,165,170,171,173,174,176,179,184,187,197,199–205,209,210,213,215,221} or DALYs^{164,169,214,216–218}, 10 studies used outcomes related to the accuracy of the diagnostic test^{154–158,161,162,166,192,206} (such as the percentage of correct diagnoses) and eight used an outcome related to the prescribed treatment (such as the number of antibiotics saved)^{151,175,180,181,185,189,190,198}. Therefore, many studies did not incorporate a generally comparable clinical outcome in their cost-effectiveness analysis. This also translated into the time horizon used, with varying durations, various studies not reporting a time horizon at all^{150–152,154–158,161–167,171,184–189,197,202,206,220,221} or using only a limited time horizon of less than one year^{147–149,153,168,175,176,179(p201),180–182,190–193,195,196,198,209}. Generalizable outcomes and sufficiently long time horizons are regarded as important principles when performing health-economic analyses^{50,225} and identified as important areas for improvement for economic analyses of diagnostics of respiratory tract infections.

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Policy implications

None of the included articles assessed the diagnosis of a coronavirus. Due to the major economic impact of COVID-19, we expect any testing strategy here already to be worthwhile if this means that economies can function normally again. The recent public attention on rapid COVID-19 tests and the knowledge that respiratory-tract infections can be diagnosed rather precisely may result in a permanent change in treatment practice. There may be a shift for doctors, who have experienced the value of point-of-care testing during the COVID-19 pandemic, but also a shift for patients, who may demand to be informed regarding the cause of their respiratory complaints.

As the IVDR will come into effect soon, diagnostic companies will need to prove the clinical effectiveness of new products entering the European market¹⁴². Diagnostic test accuracy alone will not be sufficient to obtain market authorization and diagnostic companies will need to monitor patient outcomes associated with their tests over a longer term. We recommend these companies include quality-of-life measurements in their trials, enabling the calculation of QALYs or DALYs at a later stage if they want to draw any conclusions with regards to cost-effectiveness. Additionally, provided that sufficient clinical outcomes

are recorded, standard pharmaco-economic methods can be used to extrapolate the trial results so that longer time horizons can be included. The increased availability of clinical data on the performance of diagnostics after the introduction of the IVDR will present decision makers with a more evidence-based method of assessing diagnostics¹⁴². We expect HTA will play an increasingly important role here, as it has with pharmaceuticals¹⁴⁰. Many European countries have developed guidelines for economic analyses, which are most often tailored to and used for pharmaceuticals¹⁴⁰. Health-economic guidelines for diagnostics are not as well developed, an issue which has previously been raised by Garfield et al., who looked at the assessment of molecular diagnostics from the perspective of various HTA agencies²²⁶. We would recommend decision makers to consider the application of the pharmaco-economic guidelines to diagnostics and adapt these guidelines if needed.

Conclusion

This review shows that methods used to assess the cost-effectiveness of respiratory-tract infection diagnostics vary greatly. Main points for improvement in this field are the application of generalizable outcomes and the extrapolation of results beyond the time horizon of the trial.

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CHAPTER

6

Health-economic Analyses of Diagnostics

Guidance on Design and Reporting

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Abstract

Cost-effectiveness analyses (CEAs) can be used to assess the value of diagnostics in clinical practice. Due to the introduction of the European in vitro diagnostic and medical devices regulations, more clinical data on new diagnostics may become available, which may improve the interest and feasibility of performing CEAs. We present eight recommendations on the reporting and design of CEAs of diagnostics. The symptoms patients experience, the clinical setting, locations of test sampling and analysis, and diagnostic algorithms should be clearly reported. The used time horizon should reflect the time horizon used to model the treatment after the diagnostic pathway. Quality-Adjusted Life Years (QALYs) or Disability-Adjusted Life Years (DALYs) should be used as the clinical outcomes, but may be combined with other relevant outcomes, such as real options value. If the number of tests using the same equipment can vary, the economy of scale should be considered. An understandable graphical representation of the various diagnostic algorithms should be provided to understand the results, such as an efficiency frontier. Finally, the budget impact and affordability should be considered. These recommendations can be used in addition to other, more general, recommendations, such as the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) or the reference case for economic evaluation by the international decision support initiative.

Introduction

Over the past decades, policy makers in the healthcare sector have tried to control the rising costs of pharmaceuticals in different ways^{227,228}. As one approach, value-based pricing of new drugs aims to maximize the health-related and economic outcomes given a pre-specified willingness to pay: this has become a widespread method in many countries to assess the pricing and reimbursement of new pharmaceuticals entering the market^{229,230}. In recent years, attention has expanded towards companion diagnostics for innovative treatments as well: highly specialized diagnostic tests paired to a specific drug in the context of what is labelled personalized medicine^{29,231}. Personalized medicine entails that drugs are targeted more to specific patient subgroups, with the aim of reducing the uncertainty of whether the drug will be effective before administration and correspondingly improve cost effectiveness of the drug considered.

Diagnostic tests are used more widely in modern medicine than just as companion diagnostics, and often in less well-defined populations. Examples include C-reactive protein (CRP) tests to check whether a patient with cough has a viral or bacterial infection, an International Normalized Ratio (INR) test to diagnose bleeding disorders or an HbA1c test for diabetes. Many national pharmacoeconomic guidelines nowadays also consider the assessment of non-pharmaceuticals, such as diagnostics, although in practice, these analyses are not as common²²⁶. There is limited evidence on pricing and reimbursement policies of diagnostics^{232,233}. A recent report on pricing and reimbursement policies in various European countries concluded that health technology assessment is rarely used for diagnostics²³². We believe the role of cost-effectiveness of diagnostic methods will increase in the coming years, but with that, certain challenges will arise.

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Compared to pharmaceuticals, for which the market entry regulations are well established for various jurisdictions²²⁸, the evidence for diagnostics, and medical devices in general, is very limited²³². In 2017, the new European Union (EU) regulation on in vitro diagnostic (IVD) medical devices was approved, which will come into full effect starting in 2022²³⁴. An estimated 85% of IVDs will be under the oversight of a notified body, compared to 20% previously²³⁵. IVD companies will need to collect more data on the technical and clinical performance of new devices before market entry and also increase post-market surveillance²³⁵. Consistent and high-quality data will provide healthcare professionals and policy makers with more tools to assess the safety and effectiveness of new IVDs in clinical practice. We expect this will also lead to an increase in cost-effectiveness analyses (CEA) of these devices. Diagnostics are not limited to IVDs; software or devices used for the diagnosis of a disease fall under the EU regulation on medical devices (MDR)²³⁶ and similar regulations related to oversight apply²³⁵. An example for this would be a smartphone app used by clinicians to determine the most likely disease and optimal treatment, based on a patient's symptoms.

Aim and approach

Recently, we systematically reviewed many CEAs of diagnostic strategies of infectious disease, focussing on the modelling techniques used^{27,237}. In the process, we identified several gaps in the reporting of diagnostic interventions, but also common structural problems related to the design of health-economic models. These gaps included incomplete descriptions of the assessed diagnostic and setting, short time horizons and limited use of generalizable outcomes. Additionally, we consider our experience in consulting on the health-economic aspects of clinical trials of diagnostics. Our aim is to provide specific recommendations to aid in the design and reporting of CEAs of diagnostics.

Already, excellent recommendations are available to aid in the design and reporting of economic evaluations. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement is a collection of 24 recommendations aiding in the reporting on methods and results of economic analyses for interventions in healthcare²³⁸. CHEERS is not tailored to any specific intervention and can be used for preventive measures, diagnostics and treatment²³⁸. The International Decision Support Initiative's reference case for economic evaluation provides eleven principles to guide the conduct and reporting of economic evaluations to improve their methodological quality and transferability⁵⁰. The methodological specifications relate to the health outcomes used, the estimation of costs and transparency, among others.

However, due to their broad scope, these recommendations do not provide specific guidance for diagnostic strategies. We link this diagnostic-specific guidance to the related items of the more general CHEERS statement and the reference case^{50,238}, to enable other researchers to use this guidance in addition to the already available recommendations.

Definition of diagnostics

While many different tests are performed in the healthcare sector, not all of them can be considered diagnostic tests. We consider three types of strategies, depending on the aim of the test²³⁹:

- Screening: finding diseases in a defined population, in people without, or unaware of, symptoms²⁴;
- Diagnosing: identifying the most likely cause of, and optionally optimal treatment for, a previously undetected disease in a clinically suspect patient who is seeking care^{26,27}. A diagnostic specifically aimed at determining the optimal treatment option for a patient with a previously-diagnosed disease, is considered a companion diagnostic²⁹;
- Monitoring: periodic or continuous tests to observe a biological condition or function, including the effectiveness of treatment²⁴⁰.

Although similar or identical tests may be used for each of the strategies, the decision problem related to the various strategies are quite different, hence each strategy presents unique challenges when designing a CEA. In this paper, we specifically focus on diagnostic strategies.

Recommendations

An overview of our recommendations is displayed in table 6.1, including related CHEERS recommendations²³⁸ and specifications from the reference case for economic evaluations⁵⁰. The recommendations are explained in more detail below.

Target population

A common way to specify a certain population in the medical field is to identify patients having a specific disease: for example, heart failure patients or patients with neuroendocrine tumours. Especially in clinical trials, these specifications often are extended with patient characteristics such as age and comorbidities or with ranges of disease-specific biomarkers. When diagnosing a patient, a specific disease often is not yet known, however, the symptoms are. These specific symptoms will influence the clinician's decision to request additional diagnostic tests or use point-of-care (POC) diagnostics. Other determinants a clinician may use in deciding to use certain diagnostics include age, comorbidities

and, if available, vaccination status.

Therefore, when specifying the target population of a diagnostic intervention, it is highly important to specify the symptoms patients have and other relevant determinants which may influence the clinician's decision to continue diagnosing a patient. Additionally, it should be clear whether the patient population is screened, diagnosed, or monitored. However, this may be more difficult in the case of genomic tests, with potential spill over effects to relatives, where the population of interest is broader than just the patient tested²⁴¹: the diagnosis of one patient may lead to the screening of family members or inform reproductive planning.

Setting and location

Linked to the target population are the setting and location. Populations presenting in primary care are different from patients who are referred to hospital care, who are different from patients admitted to the intensive care unit. In a healthcare system where the general practitioner (GP) has a gate-keeping role, a decision based on clinical experience to refer a patient to a hospital, without performing any test, already should be regarded as a diagnostic intervention. The probability of having a disease will be higher in the hospital setting, considering the GP does not refer everyone and does not refer at random. Not all health systems rely on the gate-keeping role of the GP²⁴² and also factors for patients seeking care differ culturally²⁴³. These factors will have an influence on the prevalence and severity of diseases at different settings within the healthcare sector. Hence, this context is important to include when describing the setting in which diagnostic tests are performed.

Another consideration linked to the setting, is the location where the test sample will be collected and where it will be analysed, and how this affects the overall costs. Historically, samples were analysed in the laboratory, but increasingly, testing will be performed at POC³⁰. Clearly specifying the location of sample collection and analysis is important, especially when a CEA compares different tests at different locations. This may be especially relevant for low- and middle-income countries, where logistics can be more challenging. Although POC tests may be relatively expensive compared to tests analysed in large-scale laboratories³⁰, having a test result available during a consult can more directly influence a clinician's decision on prescribing treatment and enables the clinician to use the information when communicating with the patient⁴¹.

Comparators

The strategies being compared in the CEA should be clearly described²³⁸. While it may be convenient to think about comparing different, individual tests in the context of CEAs of diagnostics, it may be more fitting to compare different diagnostic algorithms. A diagnostic cannot be regarded in isolation. If we consider a single diagnostic test, the diagnostic algorithm already contains three steps. First the clinician decides to perform the test, which is influenced by guidelines and the clinician's experience; then there is the diagnostic itself, which may present a binary result, i.e. positive or negative, but also a quantitative result, an image or a recommendation; the final step is the interpretation of this result by the clinician and/or the patient, which may result in a decision to make lifestyle changes, to start treatment or continue with other diagnostics. Different diagnostics can be added, either simultaneously or sequentially, based on the results of prior tests. There may also be differences in the implementation of the algorithm in clinical practice, e.g., the implementation in clinical decision support software. Eventually, a diagnostic algorithm should lead to determining the most-likely cause of a patient's symptoms and aid in iden-

Table 6.1. recommendations for CEAAs of diagnostics, including direct quotations of relevant CHEERS recommendations²⁸ and reference case specifications⁵⁰

Topic	CHEERS recommendation ²⁸	Reference case specification ⁵⁰	Diagnostic-specific recommendation	Relates to
Target population	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	The decision problem must be fully and accurately described.	Specify the target population of the test, including the symptoms patients experience and other relevant determinants which may influence the clinician when diagnosing patients. Clearly state whether the aim of the intervention is to screen, diagnose or monitor patients.	Reporting
Setting and location	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	The decision problem must be fully and accurately described.	Specify the clinical setting in which the clinician operates, and where the diagnostic test is performed. Factors impacting the decision for patients to seek care and factors influencing the disease prevalence are important aspects that may influence the cost-effectiveness of a diagnostic. The location where the diagnostic is performed may impact the costs and time to obtain a test result and subsequently its value within the diagnostic pathway.	Reporting
Comparators	Describe the interventions or strategies being compared and state why they were chosen.	Current practice in context of decision problem to serve as comparator in the analysis. Best supportive, noninterventional care in context of decision problem should be explored as comparator as additional analysis.	Specify the diagnostic algorithm, including clinicians' decision processes (decision to perform the test), the diagnostic tests (including brand, type and frequency), and the relevant treatment options (the outcome of the diagnostic algorithm).	Reporting
Time horizon	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Lifetime time horizon should be used in first instance.	The assessed time horizon should be similar to the time horizon over which costs and consequences of treatment following the diagnostic process are typically evaluated.	Design
Choice of health outcomes	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	A shorter time horizon may be used when shown that all relevant costs and effects are captured.	Methodological choices include either DALYs averted or QALYs gained.	Design

<p>Estimating resources and costs</p> <p>Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.*</p>	<p>Estimates should reflect the resource use and unit costs/prices that may be expected if the intervention is rolled out to the population defined in the decision problem.</p> <p>Analysis should include estimation of changes in cost estimates due to economies (or diseconomies) of scale.</p>	<p>Consider the economy (or diseconomy) of scale related to collecting, transporting and performing more (or fewer) tests on the same equipment, as opposed to a fixed price per test.</p>	<p>Design</p>
<p>Incremental costs and outcomes</p> <p>For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.</p>	<p>No specification</p>	<p>Use an efficiency frontier to visualize the incremental costs and outcomes of the different strategies, if several diagnostic algorithms are assessed simultaneously.</p>	<p>Reporting</p>
<p>Affordability and reimbursement</p>	<p>No recommendation</p>	<p>Costs of all resource implications relevant to the decision problem, including donated inputs and out-of-pocket inputs from individuals.</p> <p>Budget impact analysis should estimate the implications of implementing the intervention on various budgets.</p>	<p>Define the perspective of the economic evaluation and identify which payers are included in the budget impact analysis.</p> <p>Calculate the budget impact of implementing the assessed diagnostic algorithm within the overall clinical care pathway and consider setting-specific reimbursement regulations</p> <p>Equity implications should be considered at all stages of the evaluation, including design, analysis, and reporting.</p>



tifying the most suitable treatment. These types of algorithms are already very common in economic analyses, where they translate into decision tree models^{27,237,244}. For diagnostic algorithms that include many different outcomes, i.e., a decision tree branching out to hundreds of outcomes, simplifications may be warranted or more flexible modelling approaches can be considered²⁴⁵.

We highly recommend specifying these algorithms very clearly in any economic analysis of a diagnostic strategy. Even when comparing a switch from one diagnostic test to another, the algorithm in which the test operates may have a major impact. The decisions made and information gathered before performing the test influences the prior probabilities of obtaining a positive or negative test result. For diagnostic algorithms that are more expensive than the comparator, the eventual cost-effectiveness is determined by to what extent the information gathered can improve patient outcomes, i.e., whether the information leads to more tailored treatment.

Time horizon

Many economic evaluations of diagnostics primarily use the algorithm or decision tree to model the health-economic outcomes, as specified above. However, this may lead to challenges in assessing the long-term clinical outcomes for patients as these cannot be modelled explicitly. Generally, a lifetime horizon should be used⁵⁰, however, there could be reasons to have a shorter time horizon, but they should cover all relevant costs and outcomes. Economic analyses only assessing a time horizon as long as the diagnostic process, as seen rather frequently in literature²⁷, will in most cases not cover all relevant costs and outcomes. The time horizon should be similar to the time horizon over which costs and consequences of treatment following the diagnostic process are typically evaluated.

An additional factor to consider for economic evaluations of diagnostics, is the time to correct diagnosis. A faster diagnostic algorithm may result in time reductions for patients, clinicians or laboratory technicians, leading to a more efficient decision-making process⁴¹. In case of infectious disease, faster diagnosis may reduce the transmission of a disease, a factor generally considered to be an important aspect of value in health care (fear and risk of contagion)¹⁰⁵.

Combining very short-term (time to correct diagnosis) and long-term modelling (a lifetime time horizon) may lead to rather complex models for economic assessments of diagnostics, such as a combination of a discrete-event simulation and a transmission model to model tuberculosis diagnostics in Tanzania²¹⁸. Depending on clinical perspectives, but also on data availability, it may be feasible to focus on only short- or long-term modelling. This decision process should be reported in a transparent manner.

Choice of health outcomes

Quality- or disability adjusted life years (QALYs and DALYs) generally are the preferred outcomes for economic analyses⁵⁰. Possibly due to the relatively many studies in the field of diagnostics with a short time horizon, authors commonly focus on rather short-term outcomes other than QALYs and DALYs^{27,246,247}. Examples are outcomes based on the technical performance of the test (e.g. proportion of correct diagnoses) or the treatment decision (e.g. antibiotics prescribed)²⁷. As stated in the introduction, IVD companies will be required to gather more information on the clinically relevant outcomes of novel diagnostics²³⁴, which presents an opportunity to include utility-based outcomes as well. This is not to say that other outcome measures are not relevant, we believe they are.

Other elements of value of particular interest to diagnostics are reduction of uncertainty due to a new diagnostic, adherence-improving factors, fear of contagion (already described above), insurance value and real options value¹⁰⁵. The reduction of uncertainty is relevant for both payers, as it reduces the uncertainty of the effectiveness of reimbursed care, and for patients and providers, as it may lead to more informed treatment decisions. This may also lead to increased adherence to treatment. There are several elements of value for diagnostics that may not only benefit the individual patient and have broader societal advantages. The fear of contagion is already described above, closely related to this is the insurance value, which may relate to the risk of an individual to become sick¹⁰⁵. For hereditary diseases, the results of diagnosing one patient may affect family members²⁴¹ and for infectious diseases the data gathered by diagnosing one group of patients may inform empiric treatment for another group of patients²⁴⁸. Finally, real options value is relevant for infectious disease where resistance may occur. Prescribing treatment provides a risk that the treatment will be less effective in the future; simultaneously, it is uncertain that novel treatment options will be developed in the future. A diagnostic, which increases the adequacy of prescriptions, can decrease the probability of untreatable, resistant infections in the future²⁴⁹. Discussions on how to include these other, still novel, elements of value are ongoing and will depend on factors such as the disease area covered and health system assessed^{105,241}. Continuing this discussion with all stakeholders, including policy makers, clinicians and patients, is important, as well as experimentation with novel methods in the field of CEAs. For some diseases with limited data on the effectiveness of treatment, such as genomic tests used for rare genetic disorders, it may be challenging to perform a CEA²⁴¹. In these cases multi-criteria decision analysis may be a feasible alternative²⁵⁰.

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Estimating resources and costs

For CEAs in general, the included costs depend on the perspective used and the decision problem analysed. Depending on the perspective used, diagnostic and subsequent treatment costs may be included differently or even not be considered at all. For diagnostics, the costs are of particular interest as there may be more flexibility as compared to most drugs. The whole chain from collecting the patient sample to the reporting of the result will impact the eventual cost of the diagnostic. While large volumes of tests performed in laboratories will be relatively inexpensive, a POC test performed by the GP may yield more diagnostic value, i.e., the test can immediately influence the clinical decision. The following costs will be relevant for a CEA assessing a novel diagnostic:

- Diagnostic sample collection costs (including personnel, reagent and material cost);
- Transport costs (if the test is not performed at POC);
- Costs of performing the test (including personnel, reagent, materials and depreciation costs);
- Costs associated with reporting the test result to the clinician and/or the patient and, if applicable, changing the clinical decision.

How precise test-related costs should be estimated depends on the perspective and decision problem, micro-costing will not always be useful or feasible²⁴⁴. However, using a fixed price per diagnostic test may underestimate the scale benefits associated with performing more tests using the same equipment¹⁰⁶. Sensitivity analyses to assess the impact of various assumptions to the economies (and diseconomies) of scale related to performing more (or fewer) tests should be considered and should be consistent with the evaluated setting and populations, including any health system factors that may limit scale-up. For

tests that can be used to diagnose various diseases (i.e., are part of several diagnostic algorithms, with patients experiencing different symptoms), these scale advantages should also be considered.

Incremental costs and outcomes

It is common to compare various diagnostic algorithms simultaneously within a CEA²⁷, as explained above. The different algorithms may contain different diagnostic techniques but may also be performed in different sequences or at different locations (e.g., at POC or in a laboratory). Clearly presenting the differences in incremental costs and outcomes is important. A common graphical method to present the incremental costs and outcomes of a various algorithms is an efficiency or cost-effectiveness frontier^{156,215,251}. This may be more easily interpretable than only providing a table of the results. An added benefit is that the efficiency frontier can be used to draw conclusions about the cost-effectiveness in the absence of a willingness-to-pay threshold, as described elsewhere²⁵².

Affordability and reimbursement

Factors outside of the direct scope of a CEA, but very relevant for its context, are the affordability and reimbursement of diagnostic interventions. The budget impact was seldom included in CEAs of diagnostics²⁷; however, we believe this may provide important information regarding the affordability²⁵³. Especially if the current standard-of-care is based on clinical expertise, a new diagnostic test may greatly increase the total costs and may have a major budget impact. This is particularly relevant for low- and middle-income countries (LMICs), where resource constraints are more prevalent than in high-income countries. An additional constraint in LMICs may be the availability of skilled personnel to perform and operate new diagnostic tests⁵⁰.

In general, the perspective of the budget impact analysis is important, also in relation to the reimbursement of the various diagnostics considered and the payers involved: can health-care providers claim the diagnostic costs, should they pay for it themselves or should a patient pay a fee? Additionally, it is relevant whether the diagnostic test is funded out of the same budget as subsequent treatment. This does not directly influence the cost-effectiveness, but it will probably affect the implementation and uptake of a novel diagnostic test: e.g., a very cost-effective test for which the patient has to pay, may have a lower uptake than a test which is provided free of charge (i.e., paid for by the health system). These factors can be explored in the discussion of an economic analysis of a novel diagnostic.

Summary and conclusions

In this paper, we formulated eight recommendations for CEAs of diagnostics. The symptoms patients experience, the clinical setting, locations of test sampling and analysis, and diagnostic algorithms should be clearly reported. The used time horizon should reflect the time horizon used to model the treatment after the diagnostic pathway. QALYs or DALYs should be used as the clinical outcomes, but may be combined with other relevant outcomes, such as real options value. If the number of tests using the same equipment can vary, the economy of scale should be considered. An understandable graphical representation of the various diagnostic algorithms should be provided to understand the results, such as an efficiency frontier. Finally, the budget impact and affordability should be considered.

These are not meant to supplant the CHEERS recommendations or reference case for

economic evaluations but may provide useful additions when designing and reporting CEAs of diagnostics. Although we based the recommendations in this paper on extensive reviews of the literature^{27,237} and the views of the authors, they were not developed or validated through a formal process, such as a Delphi process. Although we expect the issues raised in the paper to be generalizable to diagnostics or all disease areas, some issues relevant for specific disease areas may not have been included. However, this research could be used as a starting point for a follow-up project to further develop diagnostic-specific guidelines or a reference case for diagnostic CEAs.

Compared to pharmaceutical interventions, assessing the cost effectiveness of diagnostic strategies can be more challenging, as various diseases or treatment options may be important to consider. At the same time, the EU IVDR and MDR^{234,236} may drive manufacturers to collect more clinical evidence, which aids in the assessment of the value of diagnostics; providing opportunities for investments in better diagnosis and improved clinical care. The recommendations provided in this paper can be used to improve the design and reporting CEAs in the field of diagnostics, resulting in well-informed reimbursement decisions by policy makers.

CHAPTER

7

The Opportunity of Point-of-care Diagnostics in General Practice

Modelling the Effects on Antimicrobial Resistance

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Abstract

Objectives: Antimicrobial resistance (AMR) is a public health threat associated with antibiotic consumption. Community-acquired acute respiratory tract infections (CA-ARTI) are a major driver of antibiotic consumption in primary care. We aimed to quantify the investments required for a large-scale rollout of POC diagnostic testing in Dutch primary care, and the impact on AMR due to reduced use of antibiotics.

Methods: We developed an individual-based model that simulates consultations for CA-ARTI at GP practices in the Netherlands and compare a scenario where GPs test all CA-ARTI patients with a hypothetical diagnostic strategy to continuing the current standard of care for the years 2020-2030. We estimated differences in costs and future AMR rates caused by testing all patients consulting for CA-ARTI with a hypothetical diagnostic strategy, compared to the current standard-of-care in GP practices.

Results: Compared to the current standard of care, the diagnostic algorithm increases the total costs of GP consultations for CA-ARTI with 9% and 19%, when priced at €5 and €10, respectively. The forecast increase in *S. pneumoniae* resistance against penicillins, can be partly restrained by the hypothetical diagnostic strategy from 3.8% to 3.5% in 2030, albeit with considerable uncertainty.

Conclusions: Our results show that implementing a hypothetical diagnostic strategy for CA-ARTI patients in primary care raises the costs of consultations, while lowering antibiotic consumption and AMR. Novel health-economic methods to assess and communicate the potential benefits related to AMR may be required for interventions with limited gains for individual patients, but considerable potential related to antibiotic consumption and AMR.

Introduction

Antimicrobial resistance (AMR) is a major threat to public health; resistant organisms are estimated to account for over 650.000 infections and over 30.000 attributable deaths in Europe each year¹¹ or 1.27 million deaths globally²⁵⁴. The economic case for fighting AMR is increasingly being made^{13,14,255}. In light of the evidence that AMR results in considerable societal costs, it has been argued that costs associated with AMR need to be included in health-economic assessments^{256–258}. This is not straightforward as mechanisms for the development of resistance and the spread of resistant bacteria are not clear²⁵⁹.

Economic analyses of innovations in healthcare serve as important tools for policy makers in many health systems to inform reimbursement decisions. In these analyses, the incremental cost-effectiveness ratio (ICER) is an often-used outcome and is generally based on estimates of the costs per quality-adjusted life year (QALY) gained for individuals that benefit from a novel health-related technology. However, as resistant pathogens can spread through the general population and over the longer term, more individuals may benefit from reducing AMR than only those who directly benefit from stewardship interventions. Additionally, the harm caused by AMR is difficult to capture in terms of an ICER: studies assessing the burden of resistant versus susceptible infections rarely report short and long term illness duration, AMR effects on hospital length-of-stay (LOS) or productivity losses²⁶⁰. Moreover, if AMR levels reach uncontrollable levels and few new effective antibiotics are discovered, we could enter a post-antibiotic era, where simple surgical procedures, such as total hip replacements or caesarean sections can no longer be safely performed, due to the risk of infections¹³. Despite that this worst-case scenario is highly uncertain, and its costs are difficult to predict, working towards preventing this scenario should be a priority for clinicians and policy makers alike.

AMR has been associated with antibiotic consumption at the individual, regional and country level^{16,261}, and as such, appropriate prescribing of antibiotics is key in combating AMR²⁵⁵. Even though bacteria are estimated to cause a minority of community-acquired acute respiratory tract infections (CA-ARTI) cases in Europe¹⁷, CA-ARTI account for around 40% of antibiotic prescriptions by general practitioners (GPs) in the Netherlands²⁶². The most commonly prescribed class of antibiotics are broad-spectrum penicillins (BSPs)^{263–266} and the most common bacterial cause of CA-ARTI is *Streptococcus pneumoniae*¹⁷, with resistance of this bug-drug combination varying between 4% and 33% in Europe, depending on the country⁸⁵. Point-of-care (POC) diagnostics could ensure more people who are likely to benefit from antibiotic treatment are prescribed antibiotics, while those unlikely to benefit are not, and thus enhance the appropriateness of antibiotic prescribing^{136,137}. A commonly-used POC is the C-reactive protein (CRP) POC test, which can help identify patients presenting with a lower respiratory tract infection who are more likely to benefit from antibiotic treatment²⁶⁷. A recent meta-analysis concluded that CRP testing significantly reduced antibiotic use with a risk ratio of 0.79 (95% confidence interval [CI]: 0.70 – 0.90), without negatively impacting on recovery, hospital admissions and mortality²⁶⁷. Rapid Streptococcal A antigen detection testing may also help better target antibiotic treatment for another CA-ARTI, namely Streptococcal A pharyngitis²⁶⁸. In a recent meta-analysis, rapid testing to guide antibiotic treatment for patients consulting with sore throat was estimated to reduce antibiotic prescribing with 25% (95% CI 18% – 31%)²⁶⁸. POC tests for viral infections, such as influenza, for patients consulting for CA-ARTI can possibly contribute to decreasing antibiotic prescribing²⁶⁹ and targeting antiviral medication²⁷⁰.

We aim to quantify the investments required for a large-scale rollout of POC testing in primary care and the effects on AMR, using resistance of *S. pneumoniae* to BSPs in the Netherlands as an example. We developed a model that simulates consultations for CA-ARTI at GP practices, and compare a scenario in which GPs test all CA-ARTI patients to a hypothetical diagnostic strategy in which they continue to deliver current standard of care unchanged for the years 2020-2030.

Methods

Population and comparators

We estimated costs of testing all patients consulting for CA-ARTI with a hypothetical diagnostic strategy which is effective at reducing antibiotic prescribing, compared to the current standard-of-care in GP practices. To simulate the current standard of care in the Netherlands, we used data from a point-prevalence audit survey (PPAS) in primary care for patients of all ages consulting for CA-ARTI²⁶⁶, including data on tests performed and antibiotics prescribed. The CRP POC test is currently used in about a third of all patients in the Netherlands. A BSP is prescribed in two thirds of the 35% of patients who are prescribed an antibiotic for this condition²⁶⁶. More information is available in the appendix.

The efficacy of reducing antibiotic prescriptions of the hypothetical diagnostic strategy is assumed to be as effective as CRP testing, resulting in a 21% decrease in prescriptions (95% CI 10% – 30%), according to a recent meta-analysis²⁶⁷. The sensitivity and specificity of the diagnostic strategy were not considered, as we were interested in comparing the potentially optimal clinical outcomes for patients, and not in the technical performance of the diagnostic strategy. We used two price points in the calculation: €5 and €10 per patient consulting for CA-ARTI and the model was run separately for both price points. This is assumed to include not only the costs of the machine itself and materials used for the test, but also costs related to the depreciation and quality assurance related to the use of the hypothetical diagnostic strategy. For the price points, we used Dutch reference prices for laboratory diagnostics, which are considered a reasonable approximation for the real costs, which range from €1.89 to €8.44, excluding €1.89 for sample collection⁹¹. For our purpose, we analysed round figures of €5 and €10 as conservative estimates. We assumed clinical non-inferiority, meaning that the reduction of antibiotic prescriptions did not affect patient outcomes, in line with published literature^{267,271}, showing patient outcomes are neither improved nor worsened. As it is unrealistic that the diagnostic testing would be implemented overnight, we gradually implement the diagnostic strategy in three years (33%, 67% and 100% of consultations).

Model structure

The simulation was run in the Modelling the Economics of Respiratory tract Infections and AMR (MERIAM) model, an individual-based simulation model for CA-ARTI. The model consists of three modules, all programmed in R²⁷², which are combined to produce the results presented in this paper. Figure 7.1 provides a graphical representation of the analysis performed within MERIAM. The model was developed by SvdP, the model structure was validated externally by an expert advisory panel and the technical details internally by MJP and ADIvA. The R code is available online on GitHub.

The demographic and AMR modules use annual cycles, while the consultation module uses weekly incidence rates. To assess the long-term impact of large-scale testing using the hypothetical strategy, we assessed the intervention for a time horizon of 10 years: starting in 2020 and ending in 2030. An elaborate explanation of the various modules of MERIAM

can be found in the appendix.

Demographic module

In the simulation, 100,000 individuals were modelled, based on demographic data for the Dutch population²⁷³. The demographic module of the model was used to create the modelled population and simulate population changes based on Eurostat demographic data and population forecasts²⁷³, including ageing, births, mortality and migration.

Consultation module

The consultations for CA-ARTI were simulated using a separate module. This used the incidence of respiratory infections (acute respiratory infections and influenza-like illness) based on consultation data from the European Centre for Disease Prevention and Control (ECDC)²⁷⁴. Considering four age categories (0-4 years, 5-15 years, 15-64 years, and 65 and over) and the individuals from the demographic module, the incidence rates were used to simulate GP consultations. Within these consultations, the number of tests performed and the number of antibiotics were modelled using data from the PPAS, also considering age²⁶⁶.

AMR forecasting module

An ensemble of three machine-learning models was used to forecast AMR levels in the future for the care as usual scenario. Then, using the reduction in antibiotic consumption of implementing the POC test strategy, the reduction in AMR levels in the population was estimated for the diagnostic scenarios compared to the standard of care scenario²⁷⁵. Specifically, a bacterium-antibiotic-specific elasticity was applied, defining the subsequent percentage reduction in AMR following a one percentage reduction in antibiotic consumption.

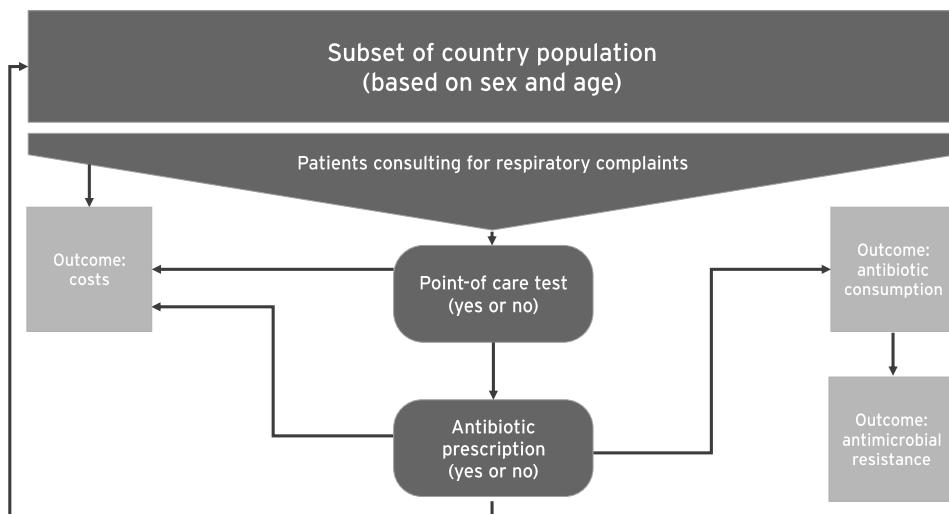


Figure 7.1. Overview of Modelling the Economics of Respiratory tract Infections and Amr (MERIAM)

Input parameters

Consultations

We used historic GP consultation data in the Netherlands²⁷⁴ for acute respiratory infection (seasons 2016-2017, 2017-2018 and 2018-2019) and influenza-like illness (seasons 2016-2017 and 2018-2019) to simulate the number of consultations for the modelled population. Using the incidence package for R²⁷⁶, two exponential models were fit to the incidence data for each season. Subsequently, these two models were combined to simulate a peak in the middle of the influenza season. For each modelled year, we randomly picked an incidence model from the historical data and predicted a representative number of consultations. This resulted in varying annual incidences over the time horizon, an overview of which is reported in supplementary figure 7.2. Performed tests and antibiotics prescribed during the initial consultation were modelled using data from the PPAS.

Antibiotic consumption and AMR

A risk ratio of 0.79 (95% confidence interval: 0.70 – 0.90), as reported by Martínez-González et al. for POC CRP testing was applied to estimate the reduction of antibiotic consumption in the hypothetical diagnostic strategy²⁶⁷. Total antibiotic consumption and AMR data for the period 2005-2018 were provided by the ECDC TESSy database²⁷⁴, but are also publicly available on the surveillance atlas for infectious disease⁸⁵ and the antimicrobial consumption database²⁶⁴. Building on methods developed by Hashigushi et al.¹², exponential smoothing was used to forecast consumption of BSPs⁹⁴ and an ensemble model was used to forecast future resistance of *S. pneumoniae* to BSPs, which were assumed to reflect the current standard-of-care. The ensemble model was constructed as a combination of three different statistical forecasting approaches: exponential smoothing⁹⁴, random forests²⁷⁷ and XGBoost models²⁷⁸. To estimate the impact of widespread diagnostic testing, the elasticity between reducing antibiotic consumption and reduced AMR was estimated. From this estimation, a 1 percentage point (ppt) decrease in antibiotic consumption, would lead to around 0.7 ppt decrease in AMR for *S. pneumoniae* against BSPs within one year. More information can be found in the appendix.

Costs

Dutch reference prices were used in the analysis⁹¹. List prices for medication were collected from the Dutch National Health Care Institute¹⁰⁰ and diagnostic test costs were collected from a major Dutch laboratory²⁷⁹. All costs were converted to Euros at the price level of the year 2019, using the harmonized index of consumer prices²⁸⁰. Training GPs is considered highly important to effectively reduce antibiotic prescribing for CA-ARTI, not only in the use of POC tests, but also in patient communication related to antibiotics. Annual training costs were incorporated into the model for the hypothetical testing strategy by quantifying the time spent by the GP based on a previous trial which included training on the use of CRP tests and patient communication^{91,149}. Results were rounded to the nearest hundred euros. A complete overview of all the included costs can be found in the appendix.

Costs were discounted with 4%, in accordance with Dutch health-economic guidelines²⁸¹, no long-term effects, such as quality-adjusted life years (QALYs), were included in the analysis, so no discounting rate was applied to effects.

Sensitivity analyses

To consider the uncertainty of all parameters simultaneously, a Monte Carlo analysis was run using 2,000 model replications. Uncertainty was incorporated in the antibiotic pre-

scribing reductions related to the hypothetical diagnostic strategy, incidence (consultation rates), PPAS data, antibiotic consumption projections, and AMR projections. For costs the median and 95% Bayesian credible intervals (CrI) are presented, calculated using the 2.5th and 97.5th percentile of the model replications.

Analogous to the widely applied cost-effectiveness acceptability curve, we used the probabilistic analysis to calculate the probability that the additional investments in a POC testing strategy is cost-effective based on the reduction in AMR, presented against various willingness-to-pay (WTP) thresholds for a 1 ppt reduction in resistance.

Results

Costs

In table 7.1, the costs are summarized, aggregated over the years 2020 up to 2030 for the care-as-usual scenario, as well as the hypothetical diagnostic strategy at both price points; figure 7.2 shows an overview of the discounted costs for the 10-year period. On average, the diagnostic strategy increases the total costs with 7.7% at the €5 price point and with 18% at the €10 price point over 10 years for a population of 100,000 individuals. In the hypothetical diagnostic scenario fewer antibiotics are prescribed (as can be seen in figure 7.3), but the cost savings are not sufficient to offset all costs of the additional POC tests. The hypothetical diagnostic strategy did not produce overall cost savings in any of the model replications. The total annual costs and details on the antibiotics prescribed are included in supplementary tables 7.2 and 7.3.

Table 7.1. 10-year costs of the base-case and hypothetical diagnostic strategy scenarios at two price points (median, including 95% credible interval in brackets)

	Current standard-of-care	Incremental costs hypothetical diagnostic strategy	
		€10	€5
Antibiotics	€868,100 (€718,100 - €1,036,000)	-€162,200 (-€324,400 - €8,300)	-€162,800 (-€321,800 - €11,800)
Consultations	€5,119,500 (€4,599,600 - €5,721,900)	€0 (-€200 - €200)	€0 (-€200 - €200)
Diagnostics	€199,300 (€165,000 - €240,500)	€1,282,300 (€1,146,900 - €1,437,500)	€640,900 (€565,400 - €728,400)
Training	€0 (€0 - €0)	€82,200 (€82,100 - €82,200)	€82,200 (€82,100 - €82,200)
Total	€6,189,000 (€5,554,900 - €6,907,700)	€1,202,000 (€999,100 - €1,425,400)	€559,100 (391,600 - 757,800)

All costs are discounted and displayed in local currency

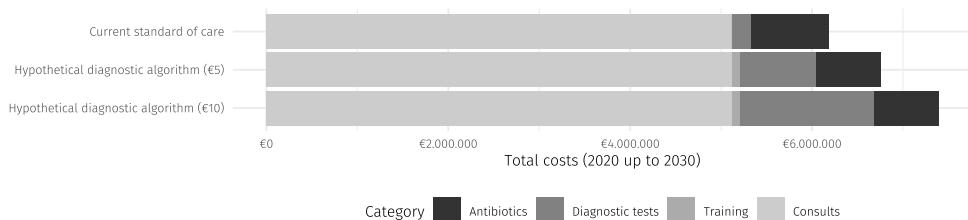


Figure 7.2. Total costs related to consultations for community-acquired respiratory tract infections in the period 2020-2030, per 100,000 individuals

Antibiotic consumption and antimicrobial resistance

The reduction in antibiotic consumption after implementing the hypothetical diagnostic strategy is shown in figure 7.3. Figure 7.4 shows the estimated development of resistance of *S. pneumoniae* against BSPs. Using the AMR forecasting module of MERIAM, we forecast resistance will increase in the coming years, which can be partly restrained by the hypothetical diagnostic strategy, albeit with considerable uncertainty. Figure 7.5 relates the WTP to reduce AMR to the modelled probability that this is achieved. It shows that at a WTP of €3 per citizen/year for a 1 ppt reduction of *S. pneumoniae* resistance against BSPs, the probability of the POC testing strategy to be cost-effective is around 80% at a price point of €5, and 40% at a price point of €10.

Discussion

Our results show that implementing a hypothetical diagnostic strategy in all patients with respiratory tract infections visiting a GP in the Netherlands would be a costly exercise, raising the total costs of these consultations by about 9% at the price point of €5. However, this strategy would reduce antibiotic prescribing by more than 7,500 DDDs annually for BSPs per 100,000 modelled individuals. This reduction in antibiotic consumption can be related to an estimated median reduction of resistance of *S. pneumoniae* to BSPs of 0.26 ppt in 2030 (3.8% compared in the usual-care group to 3.5% for the hypothetical diagnostic strategy). This is the first study to our knowledge that reports an AMR reduction acceptability curve. No country has a specified WTP threshold for reductions in resistance, but it may aid decision makers in prioritizing interventions aimed at reducing AMR. If the Dutch government would be willing to invest €3 per citizen in reducing the resistance of *S. pneumoniae* against BSPs, widespread POC testing has an 80% and 40% probability of being a cost-effective option at an increased price per consultation of €5 and €10, respectively.

For this analysis, we combined many publicly-available data sources^{85,91,264,273} and data prospectively collected in clinical practice²⁶⁶ to assess the opportunity of increased diagnostic testing in primary care to reduce AMR in the Netherlands. As presented results are based on a model that uses Dutch demographic data, we expect these results are generalisable to the whole of the Netherlands. Compared to other European countries, the Netherlands has relatively low antibiotic consumption and AMR rates^{85,264}, which means that the potential reduction in antibiotic prescribing and AMR is expected to be higher in other countries. In some countries resistance of *S. pneumoniae* to BSPs is ten times higher, for example 32% in France and 39% in Romania⁸⁵, so we expect the impact of a POC diagnostic strategy to be greater there.

Previously, few economic analyses in the field of diagnostics for infectious diseases incorporated considerations of AMR^{237,282,283}. The relative reduction of AMR in the analysis

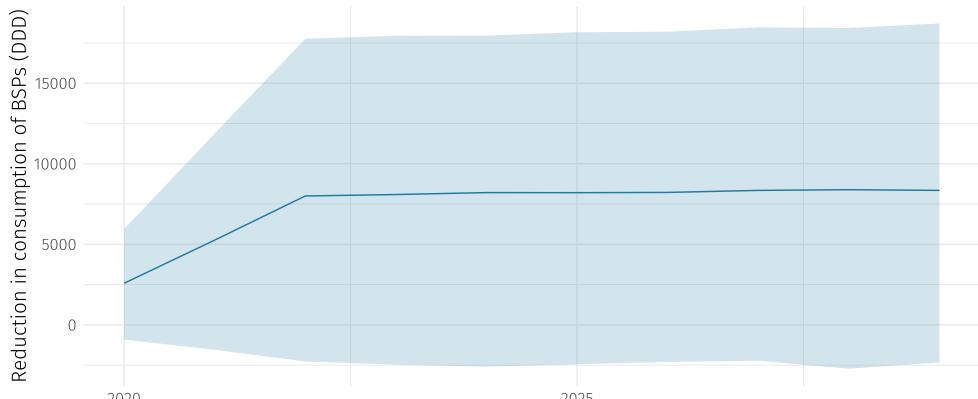


Figure 7.3. Development of antimicrobial resistance for both scenarios, including credible interval

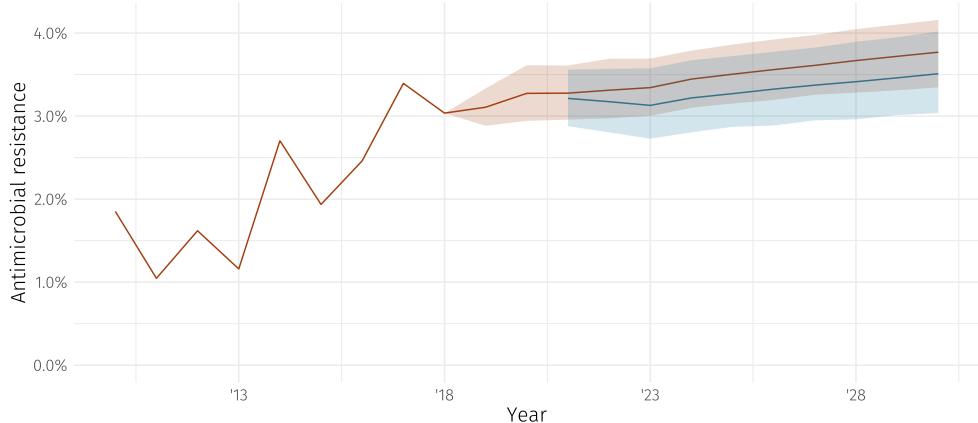


Figure 7.4. Costs-AMR-reduction acceptability curve
ppt: percentage point; AMR: antimicrobial resistance

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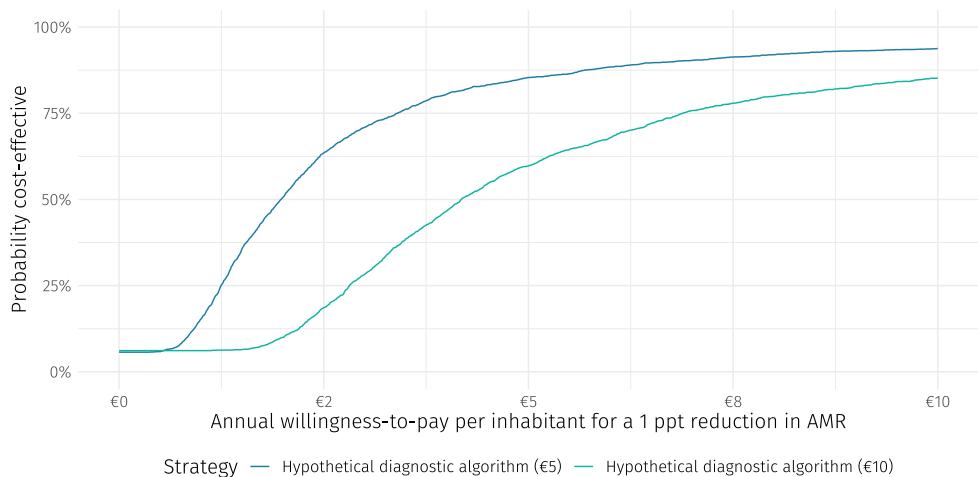


Figure 7.5. AMR-reduction acceptability curve (ppt: percentage point; AMR: antimicrobial resistance)

shows considerable uncertainty and there are some important assumptions to consider when interpreting these results. We assumed that the hypothetical diagnostic strategy was non-inferior, in that prescribing fewer antibiotics would not lead to worse patient outcomes. We also do not incorporate any follow-up in the model. This is supported by the results in a meta-analysis for CRP testing, which found no differences in clinical recovery, hospital admissions and mortality²⁶⁷. There might be a difference in re-consultations (within the same disease episode) and future consultations (for similar disease episodes in the future), but further research on patient consultation behaviour following novel POC diagnostics is required to quantify this. Combined, these limitations may result in an underestimation of the total costs of the hypothetical diagnostic strategy. Conservatively, we did not consider any long-term clinical effects or costs arising from AMR, as was done in other studies^{11,284}.

Two papers have been previously published on the cost-effectiveness of POC diagnostics in primary care in the Netherlands, both assessing the use of the CRP test²⁸². In 2009, Cals et al. reported an increase of €1.62 per consultation for the CRP group, which they relate to an investment of €5.79 to reduce antibiotic prescribing with 1%¹³⁶. A more recent cost-effectiveness analysis by Oppong et al. reported an incremental cost-effectiveness ratio of €27,186 per QALY for CRP versus usual care¹⁴⁹. This analysis incorporated AMR by adding a cost to all prescribed antibiotics, however, they did not take future AMR into consideration.

Our analysis has several limitations. We use country-wide data for influenza-like-illness and acute respiratory infections (including common cold, pharyngitis, rhinosinusitis, laryngitis and pneumonia^{285,286}) to estimate the number of consultations for different age groups²⁷⁴ and a PPAS to estimate testing and prescribing behaviour at this consultation²⁶⁶. It is uncertain whether the PPAS is representative for GPs' prescribing behaviour and of all patients seeking care for respiratory complaints, especially given the limited number of GP practices included. In the model, we assumed all consulting patients to receive a hypothetical POC diagnostic strategy, but there may be very limited clinical benefit to performing a test when the clinician has a high degree of certainty that prescribing an antibiotic would be unnecessary on clinical grounds alone.

Finally, we provide future AMR estimates in this paper, based on previously discussed methods¹². Although some uncertainty was included (e.g. uncertainty in some input parameters and imputation methods), development of AMR is a complex process influenced by many factors¹⁴. Although the used historical AMR rates are representative for the whole of the Netherlands due to a high coverage of participating laboratories^{85,287}, they are based on hospital data and may be different for the community setting. Even though the relation of antibiotic consumption and AMR has been described previously^{14,275,288}, the exact relation (or elasticity) is not known. Hence, we expect the uncertainty around our AMR estimates to be wider than the quantified uncertainty as displayed in figures 7.4 and 7.5. Still, we believe that figures like these could inform decision makers when making decisions on AMR policies, provided they are well-informed regarding the caveats.

In this study, the reduction in antibiotic prescriptions was based on previous research of CRP POC testing²⁶⁷. Additionally, the effectiveness of POC testing may wane after implementation. However, these reductions, as seen in clinical trials^{267,268} may not translate to the reductions achieved in clinical practice²⁸⁹. The currently running PRUDENCE trial will assess the implementation of a diagnostic algorithm in primary care and includes diagnostics for various types of CA-ARTI: both higher (Strep A) and lower (CRP) respiratory

tract infections, influenza and SARS-CoV-2. The results from this trial can be used to add further detail to the analyses described in this paper, model the reduction of antibiotic prescriptions specifically for various countries and subgroups, and investigate potential waning effects over a longer period.

This modelling study investigates the potential AMR reductions if a POC test strategy would be implemented for CA-ARTI in primary care in the Netherlands. Yet, we believe just having these POC tests available would not be sufficient to reach the full potential of this intervention. The right conditions need to be in place, including educating GPs and supportive staff, reimbursement of the additional costs and updated treatment and diagnostic guidelines. Direct costs of some tests are reimbursed in Dutch primary care, including CRP, but this does not include the additional time spent by the GP or supportive staff.

Novel health-economic methods to assess and communicate the potential benefits of AMR reductions may be required for interventions with limited gains in terms of QALYs, but with a lot of potential related to antibiotic consumption and AMR. The potential to contain, or even reduce AMR is relevant when deciding to reimburse interventions focusing on reducing antibiotic use, as AMR is a priority for policy makers worldwide^{18,290-292}. The general public also seems to be willing to invest in the containment of AMR, with a recent study estimating the WTP for the United Kingdom at £8.35 billion for five years²⁹³. Future clinical trials will further investigate the assumption of non-inferiority and provide data to estimate macro-economic effects related to POC diagnostic strategies for CA-ARTI and improve our AMR projections. We expect this will aid decision makers in prioritizing strategies to combat AMR.

In the current analysis, we considered the situation before the COVID-19 pandemic. It is difficult to predict how the management of CA-ARTI will evolve as the pandemic transforms into an endemic situation. We do not know how it will affect consultation rates for CA-ARTI, tests performed, and antibiotics prescribed. During the first COVID-19 wave in the Netherlands, antibiotic use for CA-ARTI reduced compared to the previous year²⁹⁴, but we do not know whether this effect will last after the pandemic. However, diagnostic tests for COVID-19 have received a lot of attention by clinicians, policy makers and the public, which we expect will change expectations and attitudes regarding diagnostics in the future.

7

Conclusion

Introducing a hypothetical diagnostic strategy for all patients seeking care for CA-ARTI in the Netherlands would increase the costs related to these consultations by 9% and 19% at the €5 and €10 price points, respectively. We estimate resistance will have an upwards trend in the coming years, which can be ameliorated by such increased use of diagnostics, albeit with considerable uncertainty. Considering the potential detrimental effects of AMR on health, we expect investments in affordable POC diagnostics and other interventions that can reduce antibiotic prescribing in primary care to be valuable and justifiable from a health-economic point of view.

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This paper reflects only the authors' view, not that of the funder or supporting organizations. The views and opinions of the authors expressed herein do not necessarily state or

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Appendix: detailed methods

MERIAM (Modelling the Economics of Respiratory tract Infections and AMR) is a model built to assess the long-term health-economic effects of improved diagnostics for community-acquired acute respiratory tract infections at the first point of care. The model is developed within the VALUE-Dx project.

MERIAM has three modules: the demographic module, used to model the population over a long time horizon; the consultation module, used to model patients going to care with an acute respiratory tract infection and the antimicrobial resistance (AMR) forecasting module, used to forecast AMR levels.

The demographic module contains a representative sample of the modelled country. The consultation model uses incidence data to simulate the care-seeking behaviour for community-acquired respiratory tract infections of a subset of individuals from the demographic model and their outcomes, including diagnostics, costs and antibiotic consumption. The AMR module uses antibiotic consumption data to forecast AMR levels.

The time framework of this model is as follows:

- Individuals may seek care for respiratory complaints, with associated costs and health outcomes (in this case mainly prescriptions of antibiotics). The incidence depends on the time of the year (e.g. there will be an annual peak in the Winter).
- Annually, assess the impact of AMR, based on the consumption of antibiotics.
- Annually, demographic changes (mortality, births, migration) is applied.
- Repeat for 10 years.

Demographic module

Within the model, nodes are created to represent individuals. Populations are based on demographic data from Eurostat mainly incorporating age and sex, and can be made as large as needed. The ID number is a unique identifier of each node; active indicated whether an individual is alive, sex is 0 for male and 1 for female, age is age (0-99).

The population changes over time are made visible using population pyramids. See an example with 10 individuals below in table 7.2.

Table 7.2. Example of ten individuals in the model

id	active	sex	age
43036423497	1	0	43
85104809341	1	1	85
14026435658	1	0	14
86199747714	1	1	86
84031463928	1	0	84
67186889220	1	1	67
66092057582	1	0	66
9131192424	1	1	9
36054804299	1	0	36
78071680821	1	0	78

Annual demographic changes

Every year the population is updated to reflect the Eurostat projections, here we use model cycles of one year. The following is included:

- Mortality
- Ageing
- Fertility
- Migration

This effectively means we assume everyone is born and dies on January 1.

Mortality

Mortality is based on the Eurostat mortality probability projections. The mortality probability is sampled for the active nodes of all age

groups. A major assumption in the model is that all nodes over 99 are excluded: we do not include centennials in the model. This is mainly due to data availability for this group.

Ageing

Ageing is straightforward in that it increases the age with 1 annually.

Fertility

Data on births are used from the Eurostat population projections. The number of babies born is related to the population aged 15-45. The `births()` function takes the `node_list` as an input and returns the `node_list` with newly-created nodes (`babies`).

Migration

The model accounts for migration by using the Eurostat projections. The Eurostat projections provide total numbers of immigration (positive number) and emigration (negative number) for 2019-2100. In MERIAM this is related to the total population and converted to a rate. This rate is then used to calculate the total number of immigrants and emigrants. This basically assumes that both immigration and emigration increase when the population size increases.

Overview data sources

For countries within the European Union, the Eurostat²⁷³ data sources used are displayed in table 7.3.

Consultation module

Each week, a subset of nodes will seek care. These nodes are selected based on real-world incidence data.

Incidence

Incidence is modelled using the Incidence package. Data is from ECDC. Both Acute Respiratory Infection (ARI) and Influenza-Like Illness (ILI) are modelled (if data is available). Incidence data is stratified by the following age groups:

- 0-4 years
- 5-14 years
- 15-64 years
- 65 years and over

Incidence data is read into R and then converted into an incidence object from the Incidence package. Two exponential models will be created for each year, one where the number of cases increases over time and one where the number cases decrease. This way, an annual peak is created in the influenza season. The function `fit_optim_split()` from the incidence package is used to automatically determine the peak of the influenza season.

Table 7.3. Overview data sources

Data	Used for	ID
Population projections	Population, sex, age, fertility	proj_19np
Migration rates	Migration	proj_19nanmig
Mortality rates	Mortality	proj_19naasmr

At the start of each model run, the exact incidence is calculated using the model for all weeks. See an example in table 7.4 for 4 weeks in a model run with 10,000 nodes for the Netherlands.

Table 7.4. Example of incidence in model (per 10,000 inhabitants), for Influenza-like illness (ILI) and Acute respiratory-tract infection (ARI), per week

Index consultation

During the index consultation, a clinician will perform tests, prescribe antibiotics etc. on the individuals seeking care. For all nodes seeking care (as described above), tests and antibiotic prescriptions are sampled.

As far as the tests are not part of the intervention (in the CRP testing scenario, everyone received a CRP test), they are sampled using the PPAS data²⁶⁶.

Week	ILI	ARI
2020-01	65	278
2020-02	66	275
2020-03	69	272
2020-04	63	270

Antibiotics are also sampled using the PPAS data: the proportion of antibiotic prescriptions is stratified by age (two categories: younger than 60 and 60 and older).

Overview data sources

Probabilities

In table 7.5, the probabilities related to diagnostics and antibiotics are displayed. These data are from the PPAS²⁶⁶.

Costs

For general practitioner (GP) consults, the Dutch costing manual was used⁹¹, while for pharmaceuticals, including the delivery costs, Dutch list prices are used¹⁰⁰. An overview can be found in table 7.6.

7

Training costs

Training GPs is considered highly important to effectively reduce antibiotic prescribing for CA-ARTI, not only in the use of POC tests, but also in patient communication related to antibiotics. Annual training costs were incorporated into the model for the hypothesis testing strategy by quantifying the time spent by the GP based on a previous trial which included training on the use of CRP tests and patient communication, which was 39.76 minutes^{91,149}. The GP's time was valued using the unit prices as displayed in table 5, considering a consult duration of 10 minutes, i.e. €3.537 per minute. The number of GPs was estimated using the average number of patients per GP using data from Statistics Netherlands from 20198, which was 1470 patients per GP. This was then related to the number of individuals in the simulation (population size divided by 1470) for every modelled year. The GPs in the model were assumed to take the training every year.

AMR module

The AMR model uses a two-step approach. First, the baseline AMR projections are generated, using an ensemble model. This is a data-driven approach where current trends are used to forecast future AMR rates. These baseline projections are then used as for the current-care scenario, where we assume current patterns in AMR will continue in the future. The second step is to incorporate the impact on antibiotic consumption from the diagnostic strategies, in the baseline AMR projections. This uses a more mechanistically driven approach. The steps are described in more details below.

Within the VALUE-Dx project, we aim to assess the long-term effects of rapid diagnostics

Table 7.5. Probabilities related to diagnostics and antibiotics for the Netherlands

Probability	Value [alpha - beta]	Distribution
Antibiotic prescription (age: 60 and older)	0.47 [58 - 66]	Beta
Antibiotic prescription (age: younger than 60)	0.28 [54 - 141]	Beta
Prescription of amoxicillin	0.68 [76 - 36]	Beta
Prescription of flucloxacillin	0.05 [6 - 106]	Beta
Prescription of amoxiclav	0.06 [7 - 105]	Beta
Prescription of doxycycline	0.21 [23 - 89]	Beta
Prescription of azithromycin	0.04 [4 - 108]	Beta
Prescription of levofloxacin	0.01 [1 - 111]	Beta
Diagnostic: CRP	0.32 [99 - 213]	Beta

Table 7.6. Consult costs used in the model

Item	Costs	Reference
Consults (costs per consult)		
GP consult	€35.37	Costing manual
pharmacy fee	€13	List prices pharmaceuticals
Antibiotics (costs per course)		
amoxicillin	€5.56	List prices pharmaceuticals
flucloxacillin	€4.76	List prices pharmaceuticals
amoxiclav	€7.72	List prices pharmaceuticals
doxycycline	€3.15	List prices pharmaceuticals
azithromycin	€1.95	List prices pharmaceuticals
levofloxacin	€6.80	List prices pharmaceuticals
Diagnostics		
crp	€4.36	Costing manual

on antimicrobial resistance (AMR). The first step in this process is to forecast AMR rates when the status quo is preserved, i.e. current AMR policies remain, but no additional measures are taken. Predicting antimicrobial resistance (AMR) is a challenging task, as the development and subsequent spread of resistance genes is highly uncertain. Two methods of modelling AMR in the population over time have been identified²⁹⁵:

- Mechanistic dynamic transmission models, which models the transmission of resistant pathogens through populations, requiring information on the mechanisms of spread of resistant pathogens.
- Statistical forecasting methods, which is a data-driven approach where the underlying mechanisms of resistance is not considered: past trends are used to forecast future AMR rates.

Additionally, expert elicitation is a viable method to forecast AMR, which can be combined with these modelling approaches²⁹⁶. The mechanisms to attain and retain resistance may differ between various pathogens. As we aim to assess the impact of diagnostics for all community-acquired respiratory-tract infections in the population, which can be caused by various pathogens¹⁷, we considered a mechanistic dynamic transmission model not to be a viable strategy. A statistical forecasting method, comparable to the methods used by Hashiguchi et al. was used for this study¹².

Several methods are available for time series forecasting^{94,297}, but selecting a single ‘best’ model is challenging. Ensemble methods are an often-used technique to improve forecasts: instead of picking one model, several models are used simultaneously and then combined to provide an average. We developed an ensemble model, averaging three models:

- An exponential smoothing (ETS) model, which forecasts future data using weighted averages of past observations⁹⁴.
- A random forest, which aggregates many regression trees to estimate the outcome of interest (AMR rates in our case)²⁹⁸. Bagging (bootstrapping and aggregating) is used, where each decision tree is informed by a random sample, with only a subset of the available regressors, of the original data set. The different trees are grown in parallel, i.e. new trees are not informed by previous trees.
- An XGBoost model, which also combines many regression trees to estimate the outcome of interest, however, as opposed to random forests, a sequential tree growing algorithm (boosting) is used, where each new tree informs the creation of the next tree²⁷⁸.

7

Missing data

The European consumption and AMR data had some missing data. These were imputed using the Amelia algorithm²⁹⁹ which allows for time-series-cross-sectional data to be imputed. To incorporate uncertainty in the various forecasts, the imputation algorithm was run 2000 times to incorporate uncertainty.

Forecasts of antibiotic consumption

Antibiotic consumption of broad-spectrum penicillins was forecast using an ETS model.

There are different ETS methods. As we considered annual data, we did not consider seasonal components. The trend can be either none, additive, additive damped or multiplicative. Multiplicative trends tend to produce poor forecasts and additive trends can over-

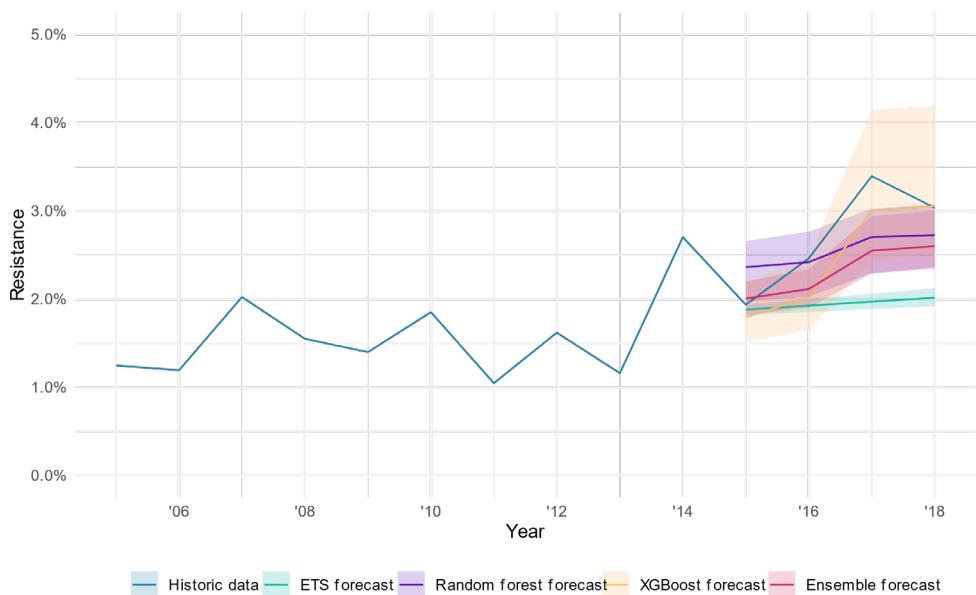
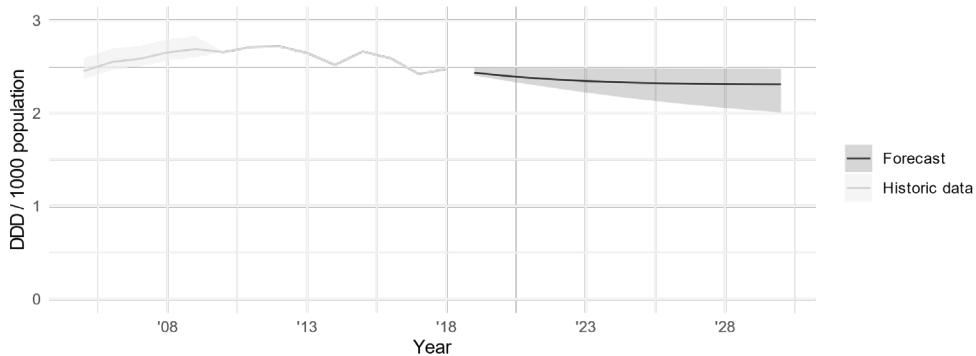


Table 7.7. Overview accuracy metrics AMR predictions

Model	mae	mape	mase	rmse	rsq	smape
RANGER	0.07 [0.04 - 0.11]	2.8 [1.67 - 4.3]	0.68 [0.41 - 1.03]	0.08 [0.05 - 0.12]	0.6 [0.01 - 0.97]	2.77 [1.66 - 4.23]
XGBOOST	0.06 [0.03 - 0.11]	2.34 [1.06 - 4.41]	0.58 [0.26 - 1.08]	0.07 [0.03 - 0.12]	0.88 [0.66 - 0.98]	2.32 [1.06 - 4.41]
ETS	0.14 [0.12 - 0.17]	5.57 [4.91 - 6.51]	1.34 [1.17 - 1.52]	0.16 [0.15 - 0.19]	0.76 [0.76 - 0.78]	5.36 [4.74 - 6.23]

mae: mean absolute error; mape: mean absolute percentage error; mase: mean absolute scaled error; rmse: root mean square error; rsq: r-squared; smape: symmetric mean absolute percentage error

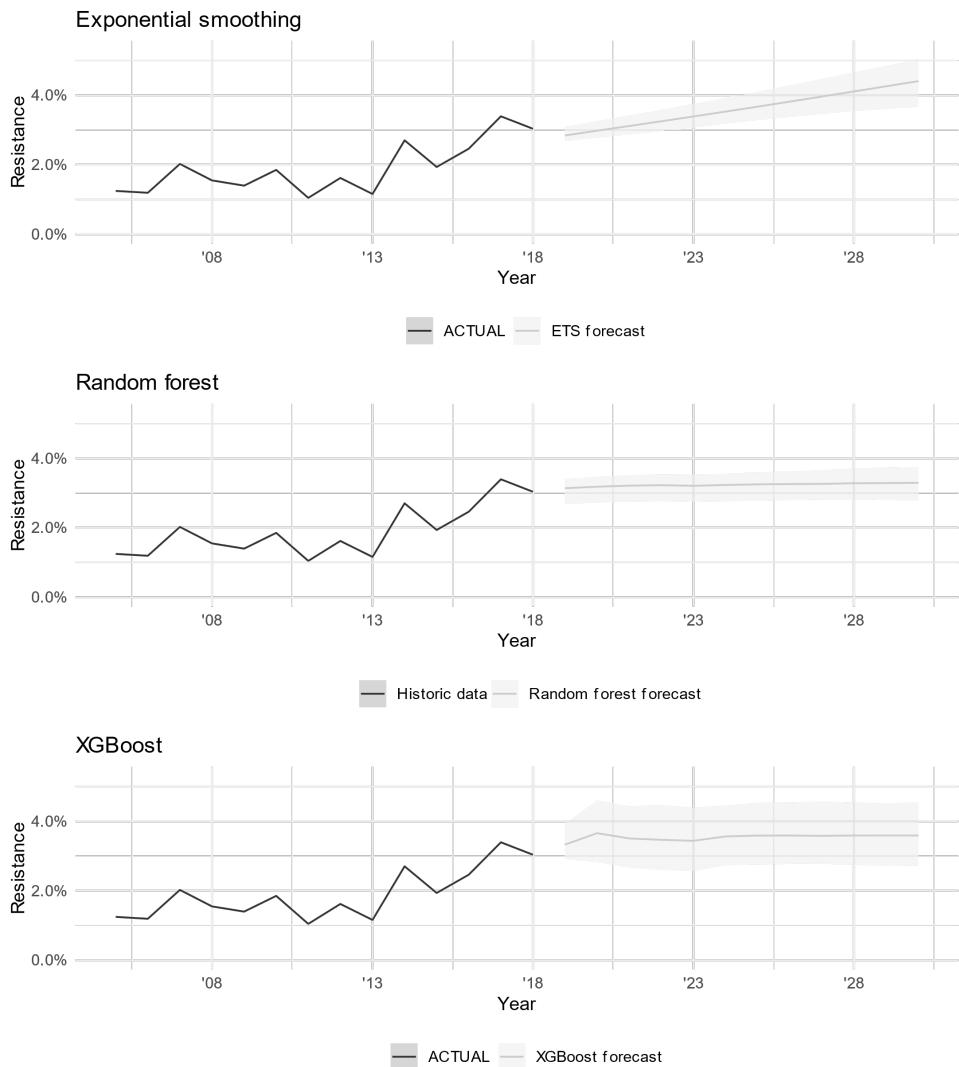


Figure 7.8. Antimicrobial resistance forecasts

7

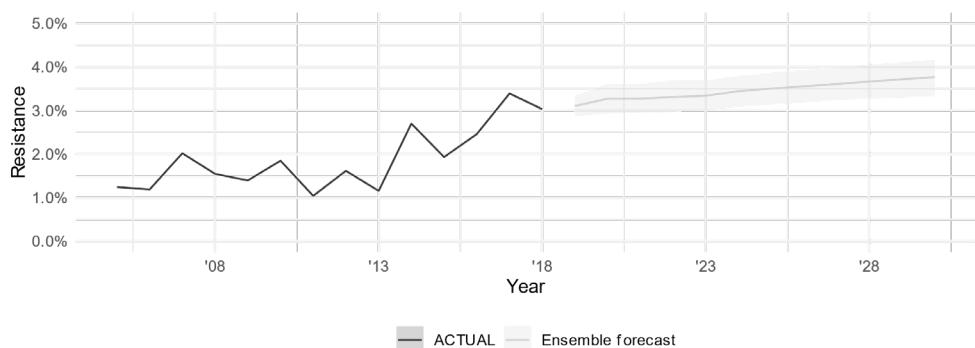


Figure 7.9. Ensemble model forecasts

estimate the trend on the long term⁹⁴, hence we considered an additive damped trend. The consumption data were box-cox transformed so that the data resembled a normal distribution. An example is displayed in figure 7.6.

AMR forecasts

For the antimicrobial resistance forecasts the dataset was split into a training and a testing set (training: 2005-2014, testing: 2015-2018), to be able to measure the performance of the forecasts. After fitting the different models to the training set, the prediction of the testing set was assessed. Then the models were refit to the full dataset to forecast the AMR rates up to 2050. Although we only assessed resistance of *Streptococcus pneumoniae* to broad-spectrum penicillins in the Netherlands in this paper, we incorporated data from other bug-drug combinations and European countries as regressors in the random forest and XGBoost models.

Exponential smoothing model

The exponential smoothing model uses a similar approach as described for the consumption forecasts, hence an additive, damped, trend.

Random forest model

The random forest model uses the following regressors to predict the AMR rate:

- Antibiotic consumption
- GDP forecasts (corrected for purchasing power parities)
- Forecasts proportion population aged < 15 years
- Forecasts proportion population aged > 64 years
- Forecasts healthcare expenditure (% of GDP)
- Forecasts out-of-pocket spending on health (% of total spending on health)

The ranger R package was used to build the model²⁷⁷. The model was tuned to minimize the root mean square error (RMSE), which resulted in a mtry (number of variables included in each bootstrapped sample of 25 and a min.node.size (minimum number of observations in terminal nodes) of 3³⁰⁰.

XGBoost model

The XGBoost²⁷⁸ model uses the same dependent variables as the random forest model. After tuning the following hyperparameters were chosen:

- min_child_weight: 3 (minimum number of instances in child node)
- max_depth: 11 (maximum depth of each tree)
- eta 0.00920 (learning rate)
- gamma: 0.00158 (minimum loss reduction to make a further partition on a lead node of the tree)

Accuracy of predictions

The accuracy of the different models is calculated on the testing set, using the models trained only on the training set. Figure 7.7 shows an example of the calibration of one model iteration. The performance of time-series forecasts are often represented using the root mean squared error (RMSE), which is calculated using the following formula⁹⁴:

$$RMSE = \sqrt{mean(e_t^2)}$$

Where e_t is the forecast error of values from the testing set. The values differ within the probabilistic analysis, table 7.7 gives an overview.

Forecasts of individual models

Figure 7.8 gives the AMR forecasts of the individual models.

Ensemble

The ensemble model is created by averaging (with equal weights) the predicted values across the models. An example is provided in figure 7.9.

Incorporating uncertainty

The previously described forecasting methods generate point forecasts, that is, a mean is forecast, but no statistical distribution. To incorporate uncertainty in the AMR forecasting model, the following input parameters are varied and the models are fitted for 2000 iterations:

- A different imputed data set is used for both the historical AMR data and antibiotic consumption
- Forecasts healthcare expenditure (% of GDP) are varied for the model replications
- Forecasts out-of-pocket spending on health (% of total spending on health) are varied for the model replications

Consequently, all model replications use slightly different AMR projections. However, we have not quantified all uncertainty associated with the projections, i.e. not all possible future AMR rates are included in the modelling.

Incremental effects of diagnostic strategies

As has been described elsewhere, there is a clear relationship between antibiotic consumption and national AMR rates^{275,288}. We use this relationship to relate the change in antibiotic consumption, as estimated in MERIAM, to future AMR levels (projected as described above). The following formula is used:

$$p_{Test,t}^{Ab,B} = p_{Base,t}^{Ab,B} \left(1 + \frac{C_{Test,t-1}^{Ab} - C_{Base,t-1}^{Ab}}{C_{Base,t-1}^{Ab}} \times \epsilon^{Ab,B} \right)$$

Where $p_{Test,t}^{Ab,B}$ is the proportion of resistance of bacterium B to antibiotic Ab under the testing scenario in the year t; the proportion of resistance of bacterium B to antibiotic Ab under the base case scenario in the year t; the antibiotic consumption of antibiotic Ab in the year t-1 in the testing scenario; the antibiotic consumption of antibiotic Ab in the year t-1 in the base case scenario and ϵ the elasticity between antibiotic consumption of antibiotic Ab and the development of resistance in bacterium B.

Estimating elasticity

The elasticity ϵ is given by the following formula:

$$\epsilon = \frac{\% \text{ change in resistance}}{\% \text{ change in consumption}}$$

We calculate the elasticity from the historical antibiotic consumption and resistance data

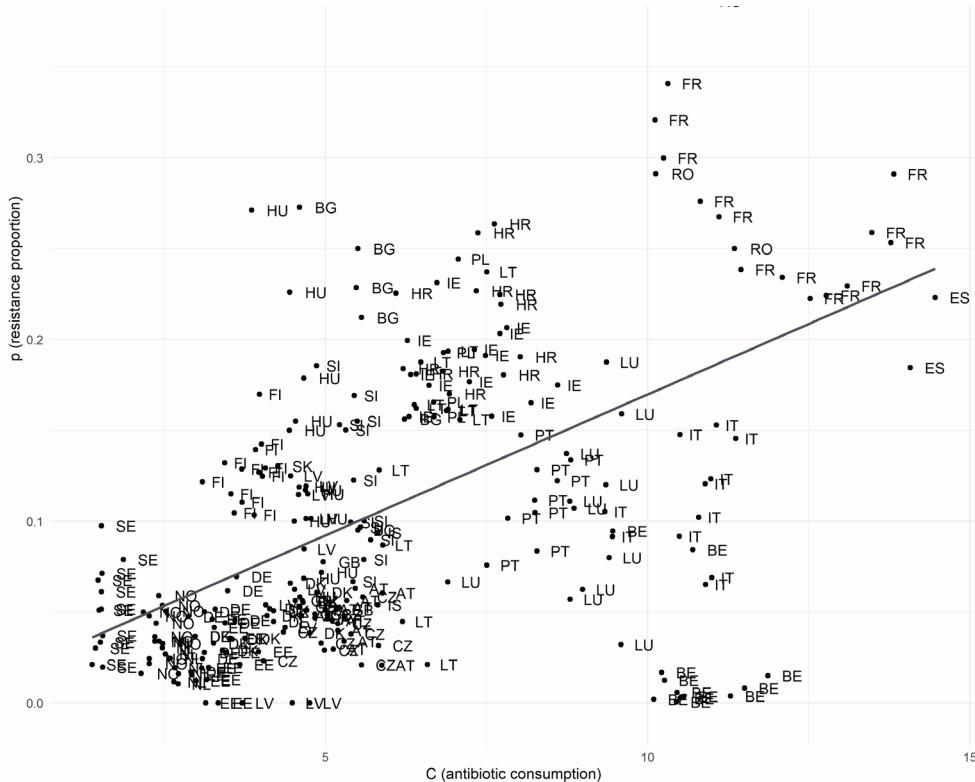


Figure 7.10. Historical consumption of broad spectrum penicillins and resistance of pneumococci

from the ECDC across all countries included in the dataset⁸⁵. Using ordinary least squares regression on the historical (non-missing) data, a linear function is estimated. See figure 7.10 for the example of the proportion of resistant pneumococci and the consumption of broad-spectrum penicillins. This function is then used to estimate the elasticity using the midpoint method, which uses the average percent change of both resistance proportions (p) and antibiotic consumption (C) between two points on the linear function:

$$\epsilon = \frac{p_2 - p_1}{(p_2 + p_1)/2} / \frac{C_2 - C_1}{(C_2 + C_1)/2}$$

The elasticity is not constant, it varies based on the location on the line. To give two examples, a drop from 3 ddd to 2 ddd (daily per 1000 population), a 33% drop, corresponds to an elasticity of 0.72, resulting in a decline of AMR levels by 24%. However, a drop from 9 ddd to 6 ddd (also a 33% drop), corresponds to an elasticity of 0.89, causing an AMR rate decline of 29%. This also matches prior beliefs, as we would expect a larger influence of antibiotic consumption reductions in countries with a high consumption, compared to countries with a lower consumption. Although antibiotic consumption is the only parameter used here to estimate AMR levels, in reality this is not the only parameter. This is also clear from the figure 7.10, the R^2 is 0.28, so the correlation is by no means perfect.

Overview data sources

The input data were used based on literature¹² and export opinion, see table 7.8 for an overview.

R environment and packages

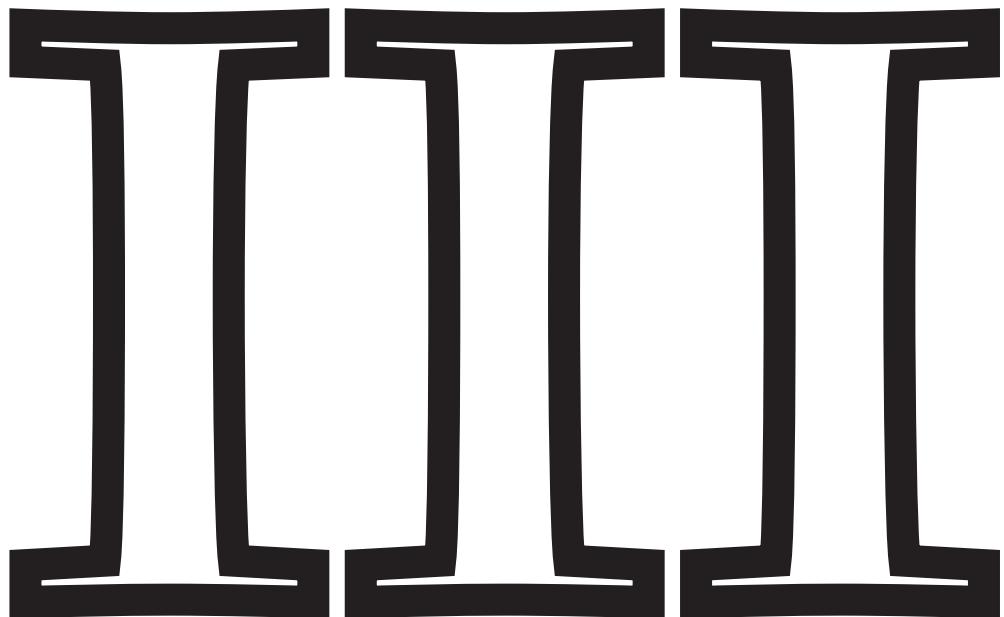
The current R version in use for MERIAM is R version 4.1.0 (2021-05-18). The Checkpoint package is used to be able to use packages in a reproducible manner, this forces all packages to use the version as published on CRAN on 20 July, 2021. The following packages are used:

Amelia 1.8.0, AMR 1.7.1, checkpoint 1.0.0, compiler 4.1.0, countrycode 1.3.0, dials 0.0.9, doFuture 0.12.0, doRNG 1.8.2, dplyr 1.0.7,forcats 0.5.1, furrr 0.2.3, ggplot2 3.3.5, incidence 1.7.3, lubridate 1.7.10, magrittr 2.0.1, modeltime 0.7.0, purrr 0.3.4, readr 1.4.0, readxl 1.3.1, stringr 1.4.0, tibble 3.1.2, tidymodels 0.1.3, tidyverse 1.1.3, timetk 2.6.1, truncnorm 1.0.8, yaml 2.2.1, gt 0.3.0, kableExtra 1.3.4, knitr 1.33, patchwork 1.1.1, reactable 0.2.3, rmarkdown 2.10, scales 1.1.1

Table 7.8. Overview data sources AMR model

Data	Database	Notes	Reference
Antimicrobial resistance	Surveillance Atlas for Infectious Disease		85
Antibiotic consumption	ECAC-Net		264
Population projections	Eurostat		301
Historical demographic data	Eurostat		302
GDP projections	OECD	Used for OECD countries	303
GDP per capita	World Bank	Used for non-OECD countries	304
Health expenditure projections	Literature		35
Out-of-pocket healthcare payments projections	Literature		35

PART



**Improving Development,
Assessment, and Financing**

CHAPTER

8

Using Real Option Values to Prepare for Infectious Disease Outbreaks

This chapter is based on a memorandum of initiative (*initiatiefnota*) submitted in the Dutch House of Representatives by Hayke Veldman, a member of parliament.

This memorandum was the result of an internship of Simon van der Pol in Dutch parliament as part of his PhD trajectory. First, a brief overview of the main points made in the memorandum are provided in English, while the appendix contains the full original text in Dutch.

Tweede Kamer der Staten-Generaal. Initiatiefnota van het lid Veldman over anticiperen op toekomstscenario's: beschikbaarheid van vaccins en antibiotica met behulp van reële optiewaarden. 2020.

Introduction

The impact of COVID-19 is enormous, with many cases of illness and death, pressure on the hospital capacity and expected substantial negative health effects as a result of delayed care and care-avoiding behaviour. In addition, there is social damage and our economy declines. Ultimately, vaccines are the best way out of the pandemic, as they provide a safe method to gain herd immunity and offer protection to our population. At the same time, the question arises: what would have happened in recent months if there had been a vaccine already? How many deaths could have been avoided? How many entrepreneurs would not have been on the verge of bankruptcy? Could we not have seen this health crisis coming, or at least have been better prepared for it?

The outbreak of the current coronavirus was meticulously predicted in 2007; a bat from an exotic meat market in southern China was to transmit the virus to humans³⁰⁵. The question arises, why did no one act on this warning? In addition, there is an increasing number of bacteria that already are or will become resistant to antibiotics³⁰⁶, a problem that could also cause substantial damage in the future, related to both health and the economy.

In a survey including 11,000 medical professionals on the most important medical innovations since the industrial revolution, good hygiene, antibiotics and vaccines were in the top four³⁰⁷. These relatively inexpensive interventions have played an important role in enhancing the health of individuals and populations and are still crucial for public health today³⁰⁸. Over the past decades, the danger of infectious diseases has increasingly faded into the background; possibly also due to the success of the prevention programmes that are in place. This has reduced the willingness to invest in these programmes: only 3% of the healthcare budget is spent on prevention in the Netherlands³⁰⁹. This seems low compared to medicines at 8%, curative care at 19% or long-term care at 27%³⁰⁹. Obviously, the spread and development of infectious diseases is difficult to predict. Mutations in viruses can occur spontaneously, with the greatest risk lying in viruses that can be transferred from animals to humans (zoonoses)³⁰⁵. Although bacterial infections can usually be treated well, antimicrobial resistance (AMR) is already estimated to cause over 33,000 deaths in Europe annually and is a growing problem worldwide¹¹. New antibiotics are hardly developed at all, because the earnings model is unattractive due to reluctance on the use of novel antibiotics, as frequent use can lead to resistance. In addition, the production of existing antibiotics is also becoming less interesting for companies due to increasing price pressure. If we do not act on AMR, there may be several bacteria for which there is no adequate treatment available in the near future. Viruses and bacteria are constantly evolving and outbreaks of new or existing (resistant) pathogens are lurking. This poses a dilemma whether to invest in solutions with uncertain benefits and challenging profit models.

If there is one thing the COVID-19 crisis shows us, it is that we should be prepared. The impact of an epidemic without adequate treatment is enormous. The government must therefore make rational choices to anticipate outbreaks of infectious diseases. This can be done, for example, by investing in the development or taking an option on the availability of vaccines, or by creating favourable economic conditions for the development of new antibiotics. Too often, policy makers assume that the situation regarding infectious disease will remain stable, while they forget to anticipate future crises. Going forward, the government should explicitly include uncertainty in decisions related to outbreak prevention.

How do we deal with infection prevention and investments in vaccine development and

vaccine availability in particular? How can we stimulate breakthroughs in life sciences and health, and facilitate innovation in companies in the medical-pharmaceutical sector? In the memorandum of initiative, included in Dutch in the appendix, several recommendations are made to explicitly include risks, options and associated uncertainty in policy making related to infectious diseases. In this English overview, I provide an example on how real options can be applied to decisions related to vaccines specifically.

Vaccines: assessment, availability and cost-effectiveness

Governments worldwide invest in the development of vaccines, particularly through research funds. An example of this is the European Joint Action on Vaccination (EU-JAV), whose goals include better forecasting of vaccine supplies and prioritising vaccine research. As far as research priorities are concerned, governments are mainly reactive: they wait for vaccine manufacturers to develop new vaccines and then initiate market authorization and a health technology assessment (HTA). Proactive action, such as investing and stimulating research for public health purposes seems less prioritized but may be more relevant. Research proposals for funds related to new vaccines are primarily assessed on scientific quality; priorities from the public health perspective are given less weight³¹⁰. Government bodies are not the appropriate parties to assess the biological mechanisms of vaccines or to develop vaccines themselves, but governments can act more proactively. One way in which governments can contribute to a proactive agenda setting is by investing in vaccine research and development for priority areas. This includes fundamental research, where new technologies are developed to deliver faster, better-performing vaccines and antibiotics against specific infectious diseases. For research into specific vaccines, there is the possibility for the government to guarantee demand for the vaccine once it has been developed. This creates a sales market even before a vaccine is developed, reducing the uncertainty of the return on investment for innovative start-ups, but also for established pharmaceutical companies. Of note, whatever the circumstances and agreements, it always remains important to only vaccinate people when it is safe and effective, and certainly not too expensive.

The Health Council of the Netherlands has an important role in the evaluation of vaccines, particularly in the context of the Dutch vaccination programmes (*Rijksvaccinatieprogramma* and *Nationaal Programma Grieppreventie*). New vaccines can be authorised by the Minister of Health after advice from the Vaccination Committee of the Health Council. The committee has drawn up a number of criteria for this, including the burden of disease, effectiveness and safety, acceptability and cost-effectiveness³¹¹. Over the past five years, five advisory reports have been published by the Health Council of the Netherlands on the approval of new vaccines or existing vaccines for new target groups. These show that the cost-effectiveness of vaccines is a highly important consideration in authorisation. For example, in 2017, the rotavirus vaccine, which has been approved for children since 2006 in Europe, was only reimbursed for a limited group on the basis of cost-effectiveness³¹². In 2018, it was decided not to vaccinate against Meningococcal B (MenB) due to “very unfavourable cost-effectiveness”³¹³ and last year it was decided that a shingles vaccine for the elderly was not cost-effective³¹⁴. In such recommendations, only the present burden of disease and cost-effectiveness are considered, and not potential future scenarios.

Cost-effectiveness calculations for vaccines use methods similar to those used for medicines⁴⁰. Depending on the burden of disease, the Health Care Institute uses limits of €20,000, €50,000 and €80,000 per QALY for medicines; the Health Council usually uses a limit of €20,000 per QALY for vaccines³¹³. This means that more importance is attached

to prolonging the life of someone who is already ill than to preventing disease. One can wonder whether that is the right approach. Several aspects complicate these calculations. First of all, the spread of infection through the country is important: if an infection occurs more frequently, the cost-effectiveness of a vaccine will improve. In addition, if a vaccine has already been implemented, it is very difficult to estimate how the spread would have been if the vaccine had not been administered. Finally, the calculation usually assumes averages based on the current situation, disregarding the risk of an outbreak and the importance of herd immunity. Solidarity is crucial to the realisation of herd immunity; taking a vaccine not only protects you from becoming ill yourself, but it also protects other people, potentially with an increased risk or weaker health. In addition to other parameters for which assumptions must be made, there is still much uncertainty as to how herd immunity should be taken into account in health-economic models. Broader benefits of vaccines that often are not considered, are macro-economic effects linked to the labour market and healthcare capacity. Vaccines could be regarded more as investments in future health, as opposed to a mere expense.

Four different levels of availability can be distinguished for vaccines that have been authorised for the Dutch market:

1. Vaccines are available to individuals. These are individuals from specific target groups such as travellers (travel vaccinations) or the frail elderly (e.g. the influenza shot). The primary purpose of the vaccination is to protect the individual. Reimbursement for these vaccines can come from a national programme, but can also be the responsibility of employers (e.g. in healthcare) or the individual (travellers).
2. Vaccines are made available at the population level. The most important example of this is the Dutch *Rijksvaccinatieprogramma*, to which every child is invited. The primary goal of vaccination is to prevent the spread of a disease through the population, striving for herd immunity, next to individual protection.
3. Vaccines are available in case of outbreaks. An example of this is the contracting of two manufacturers for 7.5 million influenza vaccines for a potential pandemic, on which the government informed Parliament in 2019³¹⁵, or more recently, the purchase of 300 million promising COVID-19 vaccines together with Germany, France and Italy³¹⁶. These are both examples of options under uncertainty: by taking options on vaccines, the state ensures that, in case of outbreaks, the population can be vaccinated.
4. Vaccines are not reimbursed and are therefore available to a much lesser extent. If the added value of a vaccine is insufficient, or the cost-effectiveness is unfavourable, a vaccine will not be included in an immunisation programme or reimbursed for individuals. Although a vaccine has theoretically been admitted to the Dutch market, in practice it is either not available or very difficult to obtain.

Real option value applied to vaccines

Despite having four different levels of availability, there are really only two outcomes in terms of cost-effectiveness: a vaccine is either cost-effective or it is not. This may be too limited, however. The decision to invest in the availability of a vaccine is more nuanced; the choice is not “yes” or “no”, but “now” or “maybe later”. A decision to invest can change over time, for example, due to an increase in disease, development of newer vaccines or a more favourable price. Additionally, in terms of availability, currently only two options are available in the Netherlands: individual or population level vaccination schemes (see

above). The third option, where a vaccine is made available in the event of outbreaks (option 3 above), is not proactively considered. This has only happened once, in 2019 with the European purchase of a pandemic influenza vaccine³¹⁵. We are currently dealing with the COVID-19 crisis, and major investments are made in the development of such vaccines. However, we could have been further ahead already, potentially preventing the enormous impact on health, society and the economy if we had taken the threat of novel viruses more seriously and had made investments in pandemic preparedness. So, the development of new vaccines seems very important in order to be prepared for future pandemics, but how do we decide what to invest in? Is it enough, for example, to focus on just one vaccine? As with influenza, shouldn't we consider a changing virus that could affect the effectiveness of the vaccine?

The real option value is a method of explicitly including the above considerations in investment decisions³¹⁷. However, it is not often applied in decision-making. Nevertheless, there are some examples in other policy areas to learn from, for example, decisions taken in wet infrastructure³¹⁸. Of course, it is possible to predict water levels and maritime traffic for the next 50 years, but these predictions will be highly uncertain. By quantifying this uncertainty and formulating different approaches, it is possible to introduce more agile policies. Components that can be explicitly included are for example: timing (postponement, phasing), developments in the future (traffic flows, climate change), innovation (cheaper techniques in the future) and new information (research results)³¹⁸. Similarly, we invest in raising the dikes on the basis of scenarios for rising sea levels. In short, future scenarios play an important role when making investment decisions.

For vaccines too, it is essential to anticipate on possible futures within uncertain predictions. Vaccine research is a long process, the vaccines have to be produced somewhere, the vaccines have to be in stock and our healthcare system has to have the capacity to administer them. This is essential healthcare infrastructure which also takes some time to build. Take the meningococcal B vaccine, for example, which currently has a 'very unfavourable cost-effectiveness'³¹³, but what if there is an outbreak? In that case, very unfavourable could quickly turn into very favourable. And to be on the safe side, it would be reassuring to know that we are prepared. But what is it worth to society to be prepared? By constantly monitoring the costs of vaccinating and the spread of the virus, one could make an informed decision to administer the vaccine to all children. Vaccine availability in case of outbreaks is uncertain, especially during a pandemic, when we should expect countries to compete for vaccine supplies. Sufficient production capacity and availability in Europe is essential for the health of us all and to avoid negative economic consequences. In this respect, COVID-19 is an example that illustrates the potential impact, but every infectious disease outbreak has a price for the health of people, society and the economy. The uncertainty surrounding the risk versus the certainty of expenses concerning the investment means that we now often choose a "wait and see" option.

The real option value makes it possible to include all conceivable considerations and scenarios in the advice of the Health Council, the Minister's decision and the tendering procedure. Vaccine policy can be adapted much more flexibly to advancing knowledge and changing circumstances. The availability of vaccines during health crises can be safeguarded using vaccine supplies or flexible manufacturing capacity.

We know that vaccines are among the greatest successes in modern medicine and that millions of people are protected from infectious diseases caused by viruses and bacteria every year. To continue this success, investment in new research and the development of

new vaccines remains necessary. Applying the real option value method aids in making a timely commitment to the development and availability of new vaccines.

Appendix: Initiatiefnota van het lid Veldman over anticiperen op toekomstscenario's: beschikbaarheid van vaccins en antibiotica met behulp van reële optiewaarden

Inleiding

COVID-19 heeft ons land lange tijd stilgelegd en nog steeds in de greep. De jarenlange impact die deze crisissituatie zal hebben is op dit moment nog moeilijk voor te stellen. De impact is breed met vele ziektegevallen en overlijdens, enorme druk op de zorgcapaciteit en naar verwachting substantiële negatieve gezondheidseffecten als gevolg van uitgestelde zorg en/of zorg mijdend gedrag. Daarnaast is er de maatschappelijke schade en heeft onze economie het zwaar te verduren. Uiteindelijk is de hoop gevestigd op vaccins, alleen hiermee kunnen we groepsimmunitéit opbouwen en échte bescherming bieden aan onze bevolking. Tegelijkertijd rijst de vraag: wat was er de afgelopen maanden gebeurd als er al een vaccin was geweest? Hoeveel impact op gezondheid en overlijdens hadden dan voorkomen kunnen worden? Hoeveel ondernemers hadden dan niet op de rand van een faillissement gestaan? Hadden we deze gezondheidscrisis niet kunnen zien aankomen en hadden we daarop voorbereid kunnen zijn? De uitbraak van het huidige coronavirus is minutieus voorspeld in 2007, een vleermuis van een exotische vleesmarkt uit Zuid-China zou het virus overdragen op mensen³⁰⁵. Allicht is het achteraf makkelijk voorspellen, maar er zijn nog vele vergelijkbare virussen bekend die een dergelijke uitbraak zouden kunnen veroorzaken. Daarnaast zijn er in toenemende mate bacteriën die resistent zijn of worden voor antibiotica³⁰⁶, een probleem wat in de toekomst ook veel (economische) schade zou kunnen veroorzaken. Alhoewel er diverse impactscenario's circuleren, is zeker dat de maatschappelijke én financieel-economische impact in geen verhouding staat tot de benodigde investering in de ontwikkeling en beschikbaar maken van vaccins en antibiotica. In een interview bij 11.000 medici naar de belangrijkste medische innovaties sinds de industriële revolutie, stonden goede hygiëne, antibiotica en vaccins in de top 4³⁰⁷. Deze relatief goedkope interventies, hebben een belangrijke rol gespeeld bij de gezondheid van individuen en populaties en zijn nog steeds van cruciaal belang voor de volksgezondheid³⁰⁸. De afgelopen decennia is het gevaar van infectieziekten steeds meer naar de achtergrond verdwenen; mogelijk ook door het succes van de (preventie)programma's die er zijn. Hierdoor is de bereidheid om te investeren in deze programma's verminderd: in Nederland wordt van het gezondheidsbudget slechts 3% in preventie gestoken³⁰⁹. Vergelijk dit met geneesmiddelen (8%), curatieve zorg (19%) of langdurige zorg (27%)³⁰⁹. Echter, de huidige pandemische crisis heeft aangetoond hoe kwetsbaar we zijn; een land als Nederland kan vrijwel van de ene op de andere dag platgelegd worden door een virus. De verspreiding en ontwikkeling van infectieziekten is erg moeilijk te voorspellen. Mutaties in virussen kunnen spontaan ontstaan; het grootste risico lijkt te liggen bij virussen die van dier op mens overgedragen kunnen worden (zoönose)³⁰⁵. Bacteriële infecties kunnen op dit moment meestal goed behandeld worden, maar antibioticaresistentie veroorzaakt naar schatting op dit moment al ruim 33.000 doden in Europa en is wereldwijd een groeiend probleem¹¹. Nieuwe antibiotica worden nauwelijks ontwikkeld, omdat het verdienmodel onaantrekkelijk is door (begrijpelijkerwijze) terughoudend beleid voor wat betreft het gebruik van nieuwe antibiotica (veelvuldig gebruik kan eerder leiden tot resistentie). Daarnaast wordt de productie van bestaande antibiotica ook in toenemende mate minder interessant voor bedrijven door een toenemende prijsdruk. Als we niets doen aan antibioticaresistentie, zijn er op de lange termijn mogelijkerwijs meerdere bacteriën waarvoor er geen beschikbaarheid is over adequate behandelingen. Virussen en bacteriën ontwikkelen zich constant en uitbraken van nieuwe of bestaande (resistente) ziekteverwekkers liggen op de loer. Dit vormt een dilemma om al dan niet te

investeren in iets waarvan niet zeker is of het ook echt tot een uitbraak of epidemie gaat leiden en daarmee een probleem gaan worden. Dit zou dan achteraf door de publieke en politieke opinie kunnen worden gezien als weggegooid geld, zoals dat bijvoorbeeld het geval was bij de Mexicaanse griep, die destijds niet doorzette tot een pandemische situatie. Als er iets is wat de COVID-19-crisis ons laat zien, is het wel dat we maar beter voorbereid kunnen zijn. De impact van een epidemie zonder adequate behandeling is enorm. De overheid moet daartoe op rationele wijze keuzes maken om te kunnen anticiperen op een volgende uitbraak van infectieziekten. Dit kan bijvoorbeeld door een investering in de ontwikkeling of een optie te nemen op de beschikbaarheid van vaccins, of door gunstige economische condities te creëren voor de ontwikkeling van nieuwe antibiotica. Op dit moment wordt er nog te veel uitgegaan van hoe de situatie nu is en te weinig geanticipeerd op hoe de situatie in de toekomst kan veranderen. De overheid zou bij een risicoafweging de bijbehorende onzekerheid explicet moeten meenemen in een besluit om al dan niet te willen anticiperen op een mogelijke uitbraaksituatie door daar op welke wijze dan ook in te investeren. Hoe gaan we om met infectiepreventie en investeringen in ontwikkeling en beschikbaarheid van vaccins in het bijzonder? Hoe maken we doorbraken in de *life-sciences & health* en voor bedrijven in de medisch-farmaceutische sector aantrekkelijker? De initiatiefnemer doet een aantal aanbevelingen in deze initiatiefnota om onzekerheden bij infectiepreventie explicet mee te nemen bij het maken van beleid.

Ontwikkeling van vaccins

Vaccins bevatten van oudsher vaak verzwakte ziekteverwekkers die worden ingespoten, zodat er een immuunrespons op gang komt. Innovaties, zoals DNA-technieken, hebben bestaande vaccins verbeterd en de ontwikkeling van nieuwe vaccins mogelijk gemaakt³¹⁹. De (door)ontwikkeling van vaccins is een kostenintensief proces, waarbij een aantal vragen van belang zijn, te weten: is er vraag naar een vaccin tegen een bepaalde ziekte? Hoe maakt de bacterie of het virus iemand ziek? Hoe reageert het immuunsysteem hierop en is het aannemelijk dat dat met een vaccin te beïnvloeden is? Is het veilig om het vaccin te ontwikkelen en toe te dienen? Gedurende fasen van klinisch onderzoek worden vaccins in onderzoekssetting – net als geneesmiddelen – uitvoerig getest op kwaliteit, werkzaamheid en veiligheid³¹⁹. Het College ter Beoordeling van Geneesmiddelen (CBG) of de *European Medicines Agency* (EMA), besluit op basis van de klinische data over markttoelating. Wereldwijd investeren overheden in de ontwikkeling van vaccins, met name via onderzoek fondsen. Een voorbeeld hiervan is de *European Joint Action on Vaccination* (EU-JAV), met onder andere de doelen om betere voorspellingen te kunnen doen over de vaccinvoorraad en om vaccinonderzoek te kunnen prioriteren. Overheden zijn wat betreft de onderzoeksrioriteiten vooral reactief; ze komen pas echt in beeld bij de beoordeling. Onderzoeksvoorstellingen voor fondsen, gerelateerd aan nieuwe vaccins worden met name beoordeeld op de wetenschappelijke kwaliteit; de prioriteiten vanuit de publieke gezondheid worden minder zwaar gewogen³¹⁰. Overheidsorganen zijn niet de geëigende partijen om de biologische mechanismen van vaccins te beoordelen of om zelf vaccins te ontwikkelen, maar er is wel iets waar de overheid meer aan zou kunnen doen. De overheid kan onder meer bijdragen aan een proactieve agenda met investeringen in onderzoek en ontwikkeling van vaccins voor prioriteitsgebieden. Dit omvat fundamenteel onderzoek, waarbij nieuwe technologie ontwikkeld wordt om sneller, beter werkende vaccins en antibiotica tegen specifieke infectieziekten. Voor onderzoek naar specifieke vaccins bestaat de mogelijkheid voor de overheid om een garantie af te geven voor de aankoop, zodra het vaccin is ontwikkeld. Hierdoor wordt er al een afzetmarkt gecreëerd vóórdat een vaccin is ontwikkeld, waardoor de onzekerheid op de terugverdienvmogelijkheden voor innovatieve startups, maar ook gevestigde farmaceutische bedrijven wordt beperkt. Hierbij blijft

het natuurlijk wel van belang mensen alleen te vaccineren, als dit veilig en effectief is, maar zeker ook niet te duur.

Beschikbaarheid en kosteneffectiviteit van vaccins

Dat een vaccin op de markt is toegelaten, betekent nog niet dat het voor iedereen ook beschikbaar is of zelfs vergoed wordt. De Gezondheidsraad heeft een belangrijke rol in de beoordeling van vaccins, met name in de context van het Rijksvaccinatieprogramma (RVP) en het Nationaal programma grieppreventie (NPG). Nieuwe vaccins kunnen worden toegelaten door de Minister van VWS na advies door de Commissie Vaccinaties van de Gezondheidsraad. Hiervoor heeft de commissie een aantal criteria opgesteld, waaronder de ziektelest, effectiviteit en veiligheid, aanvaardbaarheid en kosteneffectiviteit³¹¹. De afgelopen vijf jaar zijn er vijf adviezen gepubliceerd van de Gezondheidsraad over de toelating van nieuwe vaccins of bestaande vaccins voor nieuwe doelgroepen. Hieruit blijkt dat de kosteneffectiviteit van vaccins een erg belangrijke overweging is bij toelating: In 2017 is het rotavirusvaccin (dat sinds 2006 op de Europese markt is) voor kinderen op basis van de kosteneffectiviteit alleen voor een beperkte groep toegelaten. In 2018 is besloten niet te vaccineren tegen Meningokokken B (MenB) o.a. vanwege een “zeer ongunstige kosteneffectiviteit” en vorig jaar is besloten dat een gordelroosvaccin voor ouderen niet kosteneffectief was. Bij dergelijke afwegingen om tot een advies te komen worden veelal niet de mogelijke toekomstige scenario’s gewogen, maar wordt met name gekeken naar de relatieve ziektelest en de kosteneffectiviteit op dit moment. Besluitvorming wordt ook niet zelden beïnvloed door minder rationele publieke en politieke overwegingen. Voor de berekeningen van kosteneffectiviteit van vaccins worden vergelijkbare methodes gebruikt als voor geneesmiddelen⁴⁰. De gezondheidswinst van de invoering van een nieuw vaccin wordt gerelateerd aan de kosten voor de invoering. Dit wordt vervolgens vergeleken met een situatie zonder vaccinatie. Dit resulteert in een incrementale kosteneffectiviteitsratio (IKER): de extra kosten die gemaakt moeten worden om het vaccin toe te dienen per voor kwaliteit-gecorrigeerd gewonnen levensjaar (QALY). Afhankelijk van de ziektelest, hanteert het zorginstituut voor geneesmiddelen grenzen van €20.000, €50.000 en €80.000 per QALY; voor vaccins wordt door de gezondheidsraad veelal een grens van €20.000 per QALY gehanteerd³¹³. Er is een aantal aspecten die het interpreteren van deze berekening wat ingewikkeld maakt. Allereerst is bij deze berekening de verspreiding van de infectie door het land belangrijk: hoe vaker een infectie voorkomt, des te gunstiger de kosteneffectiviteit van een vaccin. Daarnaast is het, indien er al een vaccin is geïmplementeerd, erg moeilijk om in te schatten hoe de verspreiding zou zijn geweest mocht vaccinatie niet zou zijn toegepast. Ten slotte gaat de berekening veelal uit van gemiddelden in het hier en nu, waarbij het risico op een uitbraak en belang van kudde-immuniteit buiten beschouwing wordt gelaten. Voor het realiseren van groepsimmunitet is solidariteit cruciaal; niet alleen vaccinneer je jezelf om zelf niet ziek te worden, ook bescherm je hiermee mensen met een verhoogd risico of zwakkere gezondheid. Naast andere parameters waarvoor aannames gedaan moeten worden, is er nog veel onduidelijkheid over hoe je groepsimmunitet mee moet nemen in (kosten)effectiviteitsberekeningen. Zo weten wij op dit moment bijvoorbeeld nog niet wie we het beste kunnen vaccineren en wat dan de vaccinatiegraad zou moeten zijn mocht er een COVID-vaccin zijn. Voor deze initiatiefnota worden vier verschillende niveaus van beschikbaarheid onderscheiden voor vaccins die zijn toegelaten op de Nederlandse markt:

1. Vaccins zijn beschikbaar voor individuen. Dit zijn individuen uit specifieke doelgroepen zoals reizigers (reisvaccinaties) of kwetsbare ouderen (bijvoorbeeld de griepprijs). Het primaire doel de vaccinatie is ook de bescherming

- van het individu. De vergoeding van deze vaccins kan uit een nationaal programma, maar kan ook de verantwoordelijkheid zijn van werkgevers (bijvoorbeeld in de zorg) of het individu (reizigers).
2. Vaccins worden beschikbaar gesteld op populatieniveau. Het belangrijkste voorbeeld hiervan is het RVP, waar ieder kind voor wordt uitgenodigd. Het primaire doel van de vaccinatie is het tegengaan van de verspreiding van een ziekte door de populatie, waarbij naar groepsimmuniteit wordt gestreefd.
 3. Vaccins zijn beschikbaar in het geval van uitbraken. Een voorbeeld hiervan is het contracteren van twee fabrikanten voor 7,5 miljoen griepvaccins in het geval van een pandemie, waar de regering deze Kamer in 2019 over heeft geïnformeerd³¹⁵, of meer recent, de aankoop van 300 miljoen kansrijke COVID-19-vaccins samen met Duitsland, Frankrijk en Italië³¹⁶. Dit zijn beide voorbeelden van opties: onder bepaalde voorwaarden is een vaccin in de toekomst beschikbaar voor Nederland. Door opties te nemen op vaccins in het geval van uitbraken, zorgt de staat ervoor dat (een deel van) de populatie gevaccineerd kan worden.
 4. Vaccins worden niet vergoed en zijn dus in veel mindere mate beschikbaar. Indien de toegevoegde waarde van een vaccin onvoldoende is, of de kosteneffectiviteit ongunstig is, wordt een vaccin niet opgenomen in een immunisatieprogramma of vergoed voor individuen. Hoewel een vaccin theoretisch is toegelaten tot de Nederlandse markt, is het in de praktijk niet of zeer moeilijk beschikbaar.

Reële optiewaarde

Ondanks dat we vier verschillende niveaus van beschikbaarheid kennen, zijn er wat betreft kosteneffectiviteit eigenlijk maar twee uitkomsten: een vaccin is kosteneffectief of niet. De initiatiefnemer vindt dit echter te beperkt. De beslissing om in de beschikbaarheid van een vaccin te investeren ligt genuanceerder, de keuze is niet “ja” of “nee”, maar “nu” of “nu niet”. Een keuze om te investeren kan namelijk veranderen over tijd, bijvoorbeeld door een toename in ziektegevallen, ontwikkeling van nieuwe vaccins of een gunstigere prijs. En niet alleen kosteneffectiviteit kent maar twee uitkomsten, ook wat betreft beschikbaarheid kennen we in Nederland nu eigenlijk maar twee opties: individueel of populatieniveau (zie hierboven). De derde optie, waarbij een vaccin beschikbaar wordt gemaakt in het geval van uitbraken (optie 3 van hierboven), wordt niet proactief overwogen. Dat is pas eenmaal voorgekomen, in 2019 bij de Europese aankoop van een pandemisch griepvaccin³¹⁵. Op dit moment hebben we te maken met de COVID-19-crisis en ook nu wordt er in alle haast gezocht naar een werkend vaccin. Daarvoor wordt er nu veel geïnvesteerd in de ontwikkeling van dergelijke vaccins, maar eigenlijk zijn we hier te laat mee en hadden we al verder kunnen zijn. Dan hadden we eventueel de enorme impact op gezondheid, maatschappij en economie kunnen voorkomen. De ontwikkeling van nieuwe vaccins lijkt dus erg belangrijk om voorbereid te zijn op toekomstige pandemieën, maar hoe bepalen we waar we in moeten investeren? Is het bijvoorbeeld voldoende om op slechts één vaccin in te zetten? Zouden we niet net als bij griep rekening moeten houden met een veranderend virus wat van invloed kan zijn op de effectiviteit van het vaccin? De reële optiewaarde is een methode om de hierboven genoemde overwegingen explicet mee te nemen in analyses voor investeringsbeslissingen³¹⁷. Dit wordt op dit moment echter weinig toegepast in de besluitvorming. Toch zijn er op andere beleidsterreinen enkele voorbeelden waar de gezondheidszorg wellicht wat van kan leren, bijvoorbeeld in de natte infrastructuur³¹⁸. Natuurlijk is het mogelijk om nu een voorspelling te doen van het waterpeil en de scheepvaart voor de komende 50 jaar, maar deze voorspellingen zullen

zeer onzeker zijn. Door deze onzekerheid te kwantificeren en verschillende benaderingen te formuleren, is het mogelijk om meer wendbaar beleid te introduceren. Onderdelen die expliciet meegenomen kunnen worden, zijn bijvoorbeeld: timing (uitstel, fasering), ontwikkelingen in de toekomst (verkeersstromen, klimaatverandering), innovatie (goedkopere technieken in de toekomst) en nieuwe informatie (onderzoeksresultaten)³¹⁸. Zo investeren we ook in verhogen van de dijken op basis van scenario's voor het verhogen van de zeespiegel. Kortom, toekomstscenario's spelen op andere domeinen een belangrijke rol in overwegingen om tot een investeringsbesluit te komen en zo wachten we niet totdat de dijken doorbreken. Dit kan ook voor vaccins, want ook hier is het essentieel om een vooruitziende blik te hebben, ondanks onzekere voorspellingen. Vaccinonderzoek is een lang proces, de vaccins moeten ergens geproduceerd worden, de vaccins moeten voorradig zijn en ons zorgsysteem moet de capaciteit hebben om ze toe te dienen. Dit is essentiële infrastructuur in de gezondheidszorg. Neem als voorbeeld het MenB-vaccin, met op dit moment een "zeer ongunstige kosteneffectiviteit", maar wat als er een uitbraak plaatsvindt? In dat geval kan zeer ongunstig snel omslaan naar zeer gunstig. En voor alle zekerheid is het geruststellend te weten dat we hierop voorbereid zijn. Maar wat is het de maatschappij waard om hierop voorbereid te zijn? Door constant de kosten van vaccinatie van deze risicogroep en de verspreiding van het virus te monitoren, zou je ook goed geïnformeerd tot een besluit kunnen komen om het vaccin aan alle kinderen toe te dienen. De beschikbaarheid van vaccins in het geval van uitbraken is onzeker, vooral wanneer een uitbraak internationaal plaatsvindt en een pandemisch karakter heeft. Voldoende productiecapaciteit en beschikbaarheid in Europa is essentieel voor de gezondheid van ons allemaal en het voorkomen van negatieve economische gevolgen. COVID-19 is in dit opzicht een voorbeeld dat de (mogelijke) impact illustreert, maar zo heeft elke uitbraak van een infectieziekte een prijs voor de gezondheid van mensen, maatschappij en de economie. De onzekerheid rondom het risico versus de zekerheid als het gaat om de investering, maakt dat we nu veelal voor een "*wait and see*" optie kiezen. De reële optiewaarde maakt het mogelijk alle denkbare overwegingen en scenario's mee te nemen in het advies van de Gezondheidsraad, het oordeel van de Minister en de aanbestedingsprocedure. Het vaccinbeleid kan veel flexibeler worden aangepast aan voortschrijdende inzichten en veranderende omstandigheden.

Toegevoegde waarde in de praktijk

Het toepassen van de reële optiewaarde-methode om hiervoor genoemde overwegingen mee te nemen in analyses die kunnen leiden tot een besluit om te investeren doet de vraag opkomen wat dit concreet voor voordelen oplevert voor de individuele burger? We weten dat antibiotica en vaccins een van de grootste successen zijn in de moderne geneeskunde en dat miljoenen mensen jaarlijks tegen infectieziekten van virussen en bacteriën worden beschermd. Om dit succes voort te zetten blijft investeren in nieuw onderzoek en het ontwikkelen van nieuwe antibiotica en vaccins nodig. De werking van huidige antibiotica dreigt snel effectiviteit te verliezen door toenemende resistentie, en zoals in de inleiding gesteld, bevinden we ons op dit moment in een van de grootste gezondheidscrisis door een virus waarvan een uitbraak een aantal jaar geleden al aangetoond is en waar een vaccin de hoopvolle oplossing lijkt te bieden. We zien wat een gebrek aan een vaccin op dit moment met onze samenleving doet. We weten ook, dat wanneer het probleem rondom antibioticaresistentie niet wordt aangepakt, onschuldige infecties ernstig en zelfs fataal kunnen worden, met mogelijk vele doden als gevolg. Het toepassen van de reële optiewaarde-methode helpt om tijdig in te zetten op de ontwikkeling van vaccins en nieuwe antibiotica en zo de samenleving te behoeden voor een dergelijke nieuwe gezondheidscrisis die zo impactvol en omvangrijk is als de coronacrisis.

Beslispunten

Onderzoek en Ontwikkeling

Voor het verbeteren van onze gezondheidszorg en de introductie van innovaties, zoals vaccins, speelt onderzoek een essentiële rol. Een initiatief als de EU-JAV is een goede eerste opstap, maar het heeft als beperking dat de focus met name ligt op al bestaande vaccins. Het zou beter zijn om een stap vooruit te kunnen kijken: met bijvoorbeeld een horizonscan kan je in kaart brengen welke vaccins in ontwikkeling zijn en binnen welke termijn deze op de markt komen. Nog een stap vooruit is een risicoanalyse van de ziekteverwekkers met een groot risico op een uitbraak. Als we dit toepassen op de COVID-19-uitbraak kunnen we stellen dat er iets is misgegaan. De ontwikkelingen voor coronavirusvaccins stond niet hoog op de prioriteitenlijst, terwijl een uitbraak van een SARS-virus in 2007 al is voorspeld³⁰⁵ en de economische gevolgen enorm zijn. De principes van de reële optiewaarde kunnen hier goed worden toegepast: Wat zijn, op basis van data, de belangrijkste vaccins om te ontwikkelen en onder welke voorwaarden? Voor bedrijven is het weinig lucratief te investeren in onderzoek naar een vaccin tegen een verwekker waar mogelijk de komende decennia een uitbraak van is. Overheden kunnen opties nemen in deze vaccins en daarmee zowel investeren in de ontwikkeling, als de daaropvolgende beschikbaarheid. De overheid is dan beter voorbereid en voor de ontwikkelaar is er een prikkel om te investeren het nieuwe vaccin: een win-win. Hier ligt een taak van overheden; door internationaal samen te werken, onderzoek op onderbouwde wijze te prioriteren en opties te nemen in veelbelovende vaccins, kunnen wij ons beter voorbereiden op de volgende pandemie.

Beslispunten

1. De kamer wordt gevraagd in te stemmen de regering te verzoeken: zich op Europees niveau in te zetten een inventarisatie te doen van mogelijke ziekteverwekkers die een pandemie kunnen veroorzaken en te onderzoeken in welke mate vaccins beschikbaar zijn hiervoor.
2. De kamer wordt gevraagd in te stemmen de regering te verzoeken: op nationaal en Europees niveau de onderzoeksagenda meer af te stemmen op onderzoek naar nieuwe vaccins, gebruikmakend van de reële optiewaarde van investeringen.

De beoordeling van vaccins

Het gezondheidsbudget is beperkt; hoewel de totale uitgaven jaarlijks stijgen, proberen wij ze onder controle te houden door bijvoorbeeld te kijken naar de kosteneffectiviteit van nieuwe interventies. Het is een balans tussen beschikbaarheid en kosten. Bij vaccins wordt grotendeels op eenzelfde wijze de kosteneffectiviteit beoordeeld als bij reguliere geneesmiddelen. Zoals eerdergenoemd is de kosteneffectiviteit van vaccins vaak gecompliceerder dan voor reguliere geneesmiddelen, met name omdat infectieziekten lastig te voorspellen zijn, de gezondheidswinst in de toekomst ligt en de gezondheidswinst op populatieniveau gemeten wordt i.p.v. op individueel niveau. Ook wordt de meest strenge grens gehanteerd van € 20.000 per QALY en wordt deze strikter toegepast. Volgens de huidige kosteneffectiviteitsrichtlijnen wordt er daarmee meer maatschappelijk belang gehecht aan het verlengen van het leven van iemand die al ziek is, dan het voorkomen van ziektes. Je kan je afvragen of dit terecht is. Deze aspecten moeten meegenomen worden bij de beoordeling van nieuwe vaccins; er moet verder gekeken worden dan het individu dat wordt gevaccineerd. Macro-economische effecten op de werkgelegenheid en zorgcapaciteit moeten worden meegenomen. Het is een verschil tussen budgettering, waarbij kos-

ten worden gedeckt vanuit het zorgbudget en een investering, waar geld wordt vrijgemaakt dat je in de toekomst verwacht terug te verdienen. Reguliere gezondheidszorg is in veel gevallen een budgetteringsbeslissing; er is een beperkte hoeveelheid geld en dit moet zo efficiënt mogelijk worden ingezet zodat zoveel mogelijk zieke mensen weer gezond worden. Vaccins zijn een investering in de gezondheidszorg, maar zeker ook in de economie van de toekomst. Het is duidelijk dat vaccins een brede maatschappelijke meerwaarde hebben die verder rijkert dan de kudde-immunititeit. Gezondheidszorg is meer dan een kostenpost: gezond zijn is essentieel voor elk individu om tot volle ontplooiing te komen.

Beslispunten

3. De kamer wordt gevraagd in te stemmen de regering te verzoeken: de beoordeling van vaccins meer te beschouwen als een investerings- dan een budgetteringsvraagstuk.
4. De kamer wordt gevraagd in te stemmen de regering te verzoeken: bij de beoordeling van nieuwe vaccins, naast de gezondheidswinst van individuen, de brede maatschappelijke en macro-economische effecten mee te wegen.

De beschikbaarheid van vaccins

Hoe kunnen wij principes van de reële optiewaarde van vaccins toepassen in de besluitvorming om een vaccin al dan niet op te nemen in een nationaal immunisatieprogramma? De Gezondheidsraad brengt een beperkt aantal adviezen uit over vaccins en formuleert uitgebreide argumentaties bij deze adviezen. Ook plaatst zij bij een negatief advies vaak kanttekeningen over wanneer het advies positief geweest zou zijn, bijvoorbeeld bij een lagere vaccinprijs of groter aantal ziektegevallen in Nederland. Op dit moment is het echter niet vastgelegd onder welke precieze voorwaarden een vaccin opgenomen zou kunnen worden in het RVP of het NPG bij veranderende situaties. Laten we dit explicet maken: bij een negatief advies wordt de Gezondheidsraad gevraagd om meetbare criteria vast te stellen wanneer het advies positief zou worden. Als de vaccinprijs te hoog is, monitordan de prijsontwikkeling en vergoed het vaccin zodra de prijs tot onder een door de Gezondheidsraad gestelde grens daalt. Ook is het belangrijk de veranderende incidentie van de ziekte waarvoor het vaccin beschermt mee te nemen. Bij de beoordeling moet het risico op uitbraken explicet worden meegenomen in de modellen waarop de kosteneffectiviteit wordt bepaald. Hoe groot is dit risico en de bijbehorende onzekerheid; wat zou de schade zijn voor de volksgezondheid en de economie? Hoe snel kunnen we kwetsbare doelgroepen vaccineren als er toch een uitbraak plaatsvindt? Deze gevolgen kunnen gekwantificeerd worden, op basis waarvan een beslissing genomen kan worden om een vaccin bijvoorbeeld toch op te nemen in het RVP of de incidentie van een risicovolle ziekte strikter te monitoren. Dit betekent niet dat ineens veel meer vaccins zouden moeten worden opgenomen in een vaccinatieprogramma: er wordt meer flexibiliteit in het systeem gecreëerd, waarbij snel geanticipeerd kan worden op veranderende omstandigheden. Wel kunnen er naar aanleiding van de beoordeling al maatregelen genomen worden om te garanderen dat de overheid deze flexibiliteit heeft; en er dus niet bij een eventuele epidemie een vaccintekort is. De verschillende vormen van beschikbaarheid: individuele beschikbaarheid, populatiebeschikbaarheid en beschikbaarheid in specifieke situaties (m.n. uitbraken), moeten allen overwogen worden. Duidelijkheid over de beschikbaarheid en vergoeding zal ook een prikkel geven aan bedrijven om weer te gaan investeren in de vaccinontwikkeling.

Beslispunten

5. De kamer wordt gevraagd in te stemmen de regering te verzoeken: bij de

beoordeling van nieuwe vaccins rekening te houden met veranderende epidemiologische/economische bewijslast en behoeften voor de toekomst, door vaccins die niet worden vergoed jaarlijks te evalueren en de optiewaarde van bestaande afspraken al dan niet aan te scherpen in het belang van de publieke gezondheid. Dit allemaal gebruikmakend van door de Gezondheidsraad geformuleerde criteria.

6. De kamer wordt gevraagd in te stemmen de regering te verzoeken: bij de beoordeling van (nieuwe) vaccins het risico voor de toekomst – zoals uitbraaksituaties, beschikbaarheid vaccins – explicet mee te nemen in de overwegingen voor besluitvorming.
7. De kamer wordt gevraagd in te stemmen de regering te verzoeken: bij de beoordeling van nieuwe vaccins meerdere opties van beschikbaarheid mee te nemen, waaronder het nemen van opties op het vaccin in het geval van een uitbraaksituatie.

Implementatie

Het gebruik van de reële optiewaarde voor infectieziekten of specifiek voor vaccins is niet nieuw, maar om op nationaal niveau te implementeren, is dat wel. Vandaar dat nader onderzoek belangrijk is, waaronder een voortdurende evaluatie van de toepassing van deze aanpak. Onderzoeks vragen waaraan gedacht kan worden: zouden er met reële opties in het verleden andere keuzes zijn gemaakt voor vaccins die al dan niet zijn toegelaten in het RVP? Aan welke indicatoren kan worden gedacht om te monitoren voor de periodieke her-evaluatie van vaccins (zie ook beslispunt 5)? Hoe is de reële optiewaarde uit te leggen aan professionals (zoals de leden van de Gezondheidsraad) en beslissingen die hieruit volgen aan het algemeen publiek? Hoe kan de reële optiewaarde methodiek praktisch toegepast worden bij de beoordeling van vaccins ten behoeve van besluitvorming? Is het mogelijk om reële optiewaarde bij wijze van pilot mee te laten lopen bij een aantal adviserings-/besluitvormingstrajecten voor vaccinaties? De toepassing van reële optiewaarde wordt hier voorgesteld voor vaccins, maar er zijn op andere vlakken in de gezondheidszorg ook gerede kansen voor deze methode. Twee andere belangrijke uitdagingen in de gezondheidszorg op dit moment het probleem van antibioticaresistentie en kostbare geneesmiddelen. Ook hier zijn mogelijkheden om de beslissingen van de overheid beter te onderbouwen en beter te kunnen anticiperen op veranderende omstandigheden. De ontwikkeling van antibiotica verloopt moeizaam, omdat de ontwikkelaar vrijwel zeker weet dat elk nieuw antibioticum zo min mogelijk gebruikt zal worden. Namelijk alleen in het geval dat alle andere antibiotica niet werken. Hierdoor blijven de verkochte volumes laag, en wordt het lastig de investeringen in de ontwikkeling terug te verdienen. Door opties te nemen in nieuwe antibiotica, belonen we niet langer het gebruik van antibiotica, maar de beschikbaarheid. Zo stimuleren wij de antibioticaontwikkeling en zorgen wij ervoor dat artsen ook extreem resiente infecties kunnen behandelen. De reële optiewaarde kan ook helpen bij het prioriteren van investeringen in de beschikbaarheid van bestaande antibiotica, zodat tekorten voorkomen kunnen worden.

Beslispunten

8. De kamer wordt gevraagd in te stemmen de regering te verzoeken: een onderzoek te starten naar de exacte rol en implementatie van de reële optiewaarde bij de beoordeling van nieuwe vaccins.
9. De kamer wordt gevraagd in te stemmen de regering te verzoeken: een onderzoek te starten naar andere gebieden binnen de infectieziektepreventie waar de reële optiewaarde toegepast kan worden.

Financieel

Bestaande onderzoeksfondsen kunnen worden ingezet voor het onderzoek naar vaccins met behulp van de reële optiewaarde. Met een her-prioritering kan daarmee deze initiatiefnota grotendeels budgetneutraal uitgevoerd worden. Wat betreft de toelating van nieuwe vaccins of het nemen van opties in nieuwe vaccins zal de reële-optiewaarde-methode de genomen besluiten meer kwantitatief onderbouwen dan nu het geval is en daarmee bijdragen aan een rationele en planbare allocatie van het zorgbudget. Het kan zijn dat de conclusie van een dergelijke analyse is dat we meer moeten investeren in een specifiek vaccin of immunisatieprogramma, buiten de kaders van de huidige begroting, in dat geval zal dat onderdeel moeten zijn van de begrotingsbehandeling. Aan onderzoek naar de implementatie in de praktijk zijn wel kosten verbonden, maar dit moet uitgevoerd kunnen worden binnen de financiële kaders van de begroting van het Ministerie van VWS.

Slotwoord

De wereld van ontwikkeling en vergoeding van vaccins en antibiotica is ingewikkeld. Deze nota was er dan ook niet geweest met medewerking van vele anderen. Een bijzonder woord van dank ben ik verschuldigd aan Simon van der Pol (Promovendus Gezondheidseconomie), Cornelis Boersma (Hoogleraar Sustainable Health and Innovation) en Maarten Postma (Hoogleraar Global Health Economics).

CHAPTER

A large, bold black number '9' is centered within a thick black circle. The circle has a slight shadow or drop shadow effect, giving it a three-dimensional appearance.

Cost-effectiveness of Sacubitril/valsartan in Germany An Application of the Efficiency Frontier

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**Appendix: An Economic Evaluation of
Sacubitril/valsartan for Heart Failure
Patients in the Netherlands**
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Fabian Degener
Maarten J. Postma
Pepijn Vemer

Abstract

Objectives: To assess the cost-effectiveness of new treatments in Germany, the efficiency frontier (EF) method has been developed. We compared the cost-effectiveness analysis using international standards and the German methodology, using the heart failure drug, sacubitril/valsartan, as an example.

Methods: A previously-developed Markov model was adapted to include four treatment options: no treatment, enalapril, candesartan and sacubitril/valsartan. The internationally-used incremental cost-effectiveness ratio (ICER) was calculated, as well as cost-effectiveness acceptability curves (CEAC). Additionally, EFs, net monetary benefits (NMBs) and price-acceptability curves were created according to German guidelines. All analyses were performed from the perspective of the German Statutory Health Insurance.

Results: The base-case ICER for sacubitril/valsartan compared to enalapril, is €19,300/QALY. On the CEAC, sacubitril/valsartan is most likely to be cost-effective, out of all included comparators, from a hypothetical willingness-to-pay threshold of €18,250/QALY onwards. No EF could be constructed for the base case. Taking the uncertainty of the input parameters in account for the probabilistic sensitivity analysis, a NMB of around -€14.000 was calculated, depending on the outcome considered, with the NMB being zero at a daily price for sacubitril/valsartan ranging from €1.52 to €1.67.

Conclusions: We calculated an ICER for Germany, comparable to previously published cost-effectiveness analyses for Europe, which widely concluded sacubitril/valsartan to be cost-effective. Using the German EF approach, a considerable discount needs to be applied before sacubitril/valsartan can be considered cost-effective.

Introduction

In Germany, pharmaceutical companies do not need to perform a cost-effectiveness analysis for new drugs to gain market authorization. Instead prices are negotiated between the statutory health insurance funds and the pharmaceutical companies^{320,321}. An economic evaluation is merely one of the tools that can be used to negotiate a reimbursement price, but is seldom used^{320,322}. If an economic evaluation is commissioned in this process, the *Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (IQWIG) is responsible for its assessment; it has developed the concept of the efficiency frontier (EF) as a method to compare the cost-effectiveness of interventions^{320,321,323,324}. The benefits and pitfalls of this approach, compared to the more internationally-common cost-effectiveness/utility analysis, has been debated internationally^{325–328}.

Internationally, Incremental Cost-Effectiveness Ratios (ICERs) are commonly used as outcomes of cost-effectiveness analyses, which is the costs per Quality-Adjusted Life Year (QALY) gained. This outcome has the advantage that it enables transferability of cost-effectiveness analyses between different diseases^{329,330}. The methods to create an ICER also have some challenges, such as difficulties in assessing disease-specific outcomes with general instruments; differences in health-related quality of life assessment between informants such as patients and the public; and the choice of a willingness-to-pay threshold to decide on the cost-effectiveness of an intervention^{325,331}. Using the EF as an outcome to decide whether a new intervention is cost-effective, circumvents these challenges.^{324,332} As an alternative to QALYs, disease-specific, health-related outcomes can be used and the threshold, created from the various alternatives for a specific disease, can be used to assess the cost-effectiveness^{324,332}. This however, comes at a major disadvantage: different disease areas cannot be compared³²⁷. Additionally, the costs of the existing interventions in a certain disease field have a profound effect on the possible costs of an innovative intervention.³²⁶

Chronic Heart Failure (CHF) has a prevalence of around 1.7% and a one-year all-cause mortality of 23% among newly diagnosed CHF patients³³³. CHF has a large impact on the German healthcare budget: the costs per patient are estimated to be €2100–€9100, with 45–72% of the costs originating from hospitalizations³³⁴. In 2017, over 460,000 hospitalizations were caused by HF (over 2% of total hospitalizations) and the total costs of HF were over €5.2 billion in 2015 (over 1.5% of total healthcare expenditure)^{335,336}.

In 2015, sacubitril/valsartan (Entresto™, previously known as LCZ696), a new drug for the treatment of CHF with a reduced ejection fraction (HF-REF), was approved by the European Medicines Agency (EMA)³³⁷. In the PARADIGM-HF trial, reduced mortality and hospitalization rates in addition to an improved quality of life were found for sacubitril/valsartan as compared to enalapril³³⁸. Subsequent to the approval of sacubitril/valsartan by the EMA, pharmacoeconomic evaluations have been published for many other European countries.^{339–343} In a previous study from the Dutch perspective, we concluded that sacubitril/valsartan was cost-effective³³⁹. To date, one analysis for Germany has been published, reporting an ICER of €23,401 per life-year gained³⁴⁴. However, the article by Gandjour and Ostwald does not include a comparison to the EF³⁴⁴.

We aim to assess the use of the EF for sacubitril/valsartan, an intervention, which replaces the broadly available generic drug classes: angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB). This includes the assessment of the cost-effectiveness of sacubitril/valsartan in Germany, using a previously-developed model (see appendix), adapted to incorporate the EF, according to German guidelines^{323,324,339}. Additionally, we perform a cost-utility analysis using globally-used guidelines, including

the calculation of an ICER using QALYs, enabling the comparison with results from other countries. We then compare the conclusions decision makers could draw based on the German methodology, using the EF, and the international health technology assessment standards, using the ICER as an outcome^{40,244,323,324}.

Methods

Model design

A Markov model, previously published for the Netherlands and described in detail in the appendix, which primarily incorporated data from the PARADIGM-HF trial, was adapted to the German market^{338,339}. Monthly cycles were used for a time horizon of 30 years. The following four health states were incorporated (figure 9.1):

- Outpatient treated HF-REF;
- Hospital admissions to a general ward;
- Hospital admissions including a stay at the ICU; and
- Death.

All patients started in the outpatient HF-REF state and were admitted to hospital, using the time-dependent rates as reported in the PARADIGM-HF trial³³⁸. The duration of stay of the PARADIGM-HF trial was used as reported by Packer et al. and 10% of hospital admissions included ICU treatment^{345,346}. In the outpatient setting, the mortality rates were calculated using the rates reported in the PARADIGM-HF trial for the death from heart disease and the general German population parameters for other causes of mortality^{338,347}.

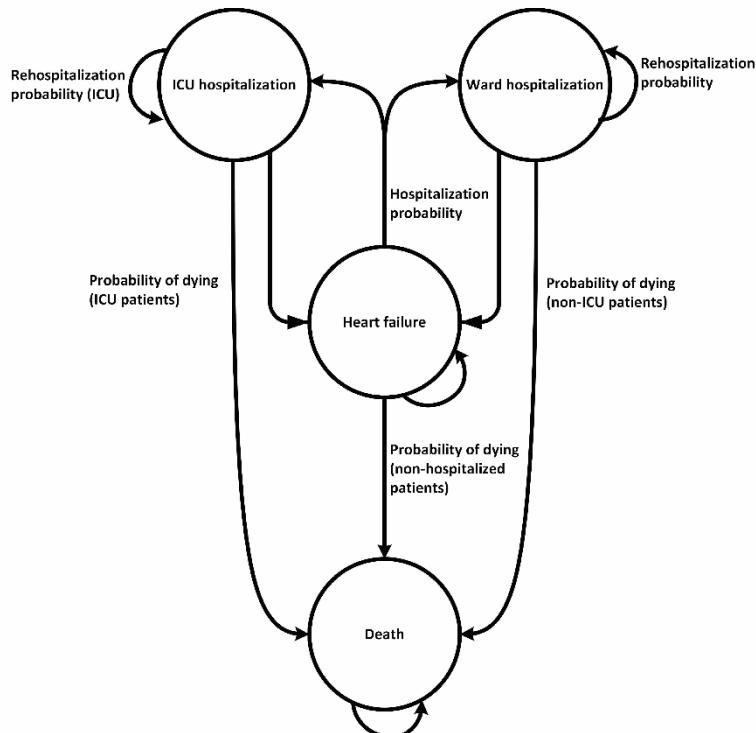


Figure 9.1. Schematic representation of the chronic heart failure Markov model.
ICU: intensive care unit

Mortality and hospitalization data from the PARADIGM-HF trial were used, as reported in our analysis for the Netherlands³³⁹. For the inpatient setting, data published for the CHF population by Corrao et al. were used for both mortality and hospitalizations, since the 30-day hospital deaths from PARADIGM-HF were not publicly available³⁴⁸. Rehospitalization rates as published by Desai et al. were used³⁴⁹. All transition probabilities are displayed in supplementary table 9.1 and all treatment effects are displayed in supplementary table 9.2. Scenario analyses for patients at a starting age of 55 and 75 years were also included.

The model was developed using Microsoft Excel® 2016 (Redmond, WA, USA, available from <https://www.office.com/> [accessed August 31, 2018]).

Target population

HF-REF patients, as described in PARADIGM-HF, were followed through the Markov model³³⁸. At the time of writing, sacubitril/valsartan is only registered for use within this group³³⁷. The starting age was the mean age of the trial: 64 years, with scenarios for patients with a starting age of 55 and 75 years³³⁸. If no data were available for the HF-REF group or a specific age category, data for the general CHF population were used.

Comparators

Primarily, sacubitril/valsartan was compared to enalapril, an ACEi, as in the PARADIGM-HF trial³³⁸. German guidelines recommend the prescription of an ACEi to all HF-REF patients. If an ACEi is not tolerated, an angiotensin receptor blocker (ARB) can be used, such as valsartan or candesartan³⁵⁰. The cost-effectiveness of sacubitril/valsartan was assessed using the German EF approach, which was constructed using three mutually-exclusive treatment options: placebo (no treatment); enalapril, representing the group of ACEis; and candesartan, representing the group of ARBs^{323,324,351–353}. For the base case, we included the differences in effects and costs of the four treatment options for the full time horizon. As no head-to-head trials were available for candesartan vs. sacubitril/valsartan placebo vs. sacubitril/valsartan and enalapril vs. candesartan, adjusted, indirect comparisons were performed^{354,355}. In supplementary figure 9.1 and supplementary table 9.3 further details are provided on the relative risks of all direct and indirect comparisons. Regarding ICU admissions, only comparative data on enalapril vs. sacubitril/valsartan was found; patients on placebo and candesartan were assumed to have the same risk of an ICU admission as placebo³⁴⁵.

9

Costs

The costs in the model were taken from the perspective of the Statutory Health Insurance (SHI)³²³. The exact input parameters can be found in supplementary table 9.4. The price of sacubitril/valsartan was used from the appraisal dossier for Germany: €6.66 per day³⁵⁶. Other drug costs were taken from the German institute of medical documentation and information (dimdi) or the site of the SHI³⁵⁷. Hospitalization costs were based on the German diagnosis related group (G-DRG) system and the method previously used by Schmidt et al.^{358,359} One-day, general and ICU hospitalization costs were determined by their respective DRG codes, considering the length-of-stay of PARADIGM-HF as reported by Packer et al., multiplied by the average German lumpsum (*Landesbasisfallwerte*)^{345,358,360}. Outpatient care costs were added monthly to all patients in the model and consisted of both general practitioner and cardiologist costs, visited on average 1.8 times annually, distributed equally^{361,362}. Sickness allowance (*Krankengeld*) was not included in the model, as the starting age in the model is higher than the effective age of labour market exit, and

were therefore assumed to be negligible^{323,363}. All costs were converted into 2018 euros³⁶⁴.

Health outcomes and utilities

The health outcomes considered in the model were: hospitalizations averted in the first 42 modelled months, 42-months survival, life-years gained and QALYs gained. The 42-month follow-up period for survival and hospitalizations was selected as this corresponds to the total follow-up of PARADIGM-HF³³⁸. For the QALY calculations, EQ-5D utility values from PARADIGM-HF were used, since no German-specific utilities were found in the literature^{365,366}. The baseline utility value was 0.78, a disutility value of 0.21 was used for hospitalized patients and for sacubitril/valsartan treatment a utility benefit of 0.011 was incorporated^{365,366}.

Time horizon and discounting

A 30-year time horizon was used to approach a lifetime horizon, with a starting age of 64. Both costs and effects were discounted at 3%, with 0% and 5% used in scenarios, in line with the German guidelines³²³.

Model outcomes

Incremental cost-effectiveness ratio, sensitivity analyses and scenario analyses

ICERs were constructed for placebo, enalapril and candesartan compared to sacubitril/valsartan, with the main outcome considered being enalapril compared to sacubitril/valsartan, enabling us to compare our outcomes to other cost-utility analyses. The increase in costs was divided by the increase in quality adjusted life years (QALYs). The ICERs reported are rounded to the nearest hundreds of euros. To study the uncertainty in the model, a probabilistic sensitivity analysis (PSA) was performed using 10,000 replications, leading to a conventional cost-effectiveness (CE) plane and a cost-effectiveness acceptability curve (CEAC), incorporating placebo, enalapril, candesartan and sacubitril/valsartan. For the univariate sensitivity analysis, a Tornado diagram was created to display the effects of the uncertainty of specific values, using the 80%-120% interval of the means, recording the corresponding effects on the ICER of sacubitril/valsartan compared to enalapril.

To account for potential changes in drug costs, various price points were included in the scenario analyses: for sacubitril/valsartan the daily costs of €3 and €10 were included. For enalapril and candesartan a price point of €1 per day was included. To see the effects of the extrapolation of costs and effects of sacubitril/valsartan, a scenario was included where the benefits and added costs of sacubitril/valsartan were only included for the follow-up of the PARADIGM-HF trial: 42 months. Additionally, the discount rates were varied to 0% and 5%. The starting ages of the cohort were also varied, by including 55 year-old and 75 year-old cohorts.

Efficiency frontier

As mentioned, the IQWIG guidelines recommend an alternative method to perform health technology assessment^{323,324}. The EF is drawn on an inverted CE plane between the non-dominated alternative current treatment options, the new intervention is then compared with respect to this (linearly extrapolated) frontier³²³. Although the use of QALYs is not ruled out, their use are not mandated in Germany, as opposed to many other countries^{322,323}. The EF method was developed with the use of direct, disease-specific and clinical outcomes in mind, without the need to use QALYs³²⁴. To create a usable EF, at least two non-dominated alternatives should be available next to the novel treatment that is considered for reimbursement. We designed an EF with placebo, enalapril, cande-

sartan and sacubitril/valsartan. The uncertainty of the EF was considered by constructing a price-acceptability curve and calculating the net monetary benefit (NMB)^{329,367}. The price-acceptability curve was plotted by calculating the daily price where sacubitril/valsartan would be situated precisely on the EF, and thus be cost-effective, for all replications of the Monte Carlo analysis. The median NMB and interquartile range for the introduction price of sacubitril/valsartan (€6.66 /day) was calculated, as well as the median daily price where the NMB was equal to zero, this being the highest price where sacubitril/valsartan could be considered cost-efficient (i.e. it is situated on the EF). Model replications where no EF could be constructed, were excluded from the NMB analysis.

Results

Base case results

The base case results are displayed in table 9.1. Sacubitril/valsartan costs more than enalapril, but both life years and QALYs are gained. In the sacubitril/valsartan group, over 2,000 hospitalizations are prevented in the 30-year time horizon compared to the enalapril group. The base case ICER is €19,300/QALY for sacubitril/valsartan versus enalapril; enalapril and candesartan are cost-saving compared to placebo, mainly due to the decrease in the number of hospitalizations.

No EF can be created for the base case, regardless of the considered outcome: enalapril dominates all other comparator treatment options, resulting in the inability to assess the efficiency of sacubitril/valsartan. Inverted base-case cost-effectiveness planes are displayed in supplementary figure 9.2.

Table 9.1. Base case results, per 10,000 patients

	Placebo	Enalapril	Candesartan	Sacubitril/ valsartan
Costs	€ 83,261,040	€ 73,298,835	€ 74,111,116	€ 231,145,386
Hospitalizations (30 years)	13,915	10,192	10,531	8,121
Hospitalizations (42 months)	6,367	4,141	4,350	2,930
Percentage of patients surviving after 42 months	59%	65%	64%	70%
Life years	54,527	63,037	61,825	72,450
QALYs	42,323	49,020	48,069	57,192
ICER (/QALY, compared to placebo)	-	Dominating	Dominating	€9,900
ICER (/QALY, compared to enalapril)	Dominated	-	Dominated	€19,300

Table 9.2. Probabilistic results of efficiency frontier approach

Outcome	Hospitalizations averted (compared to placebo, first 42 months)	42-month survival	Average total life years	Average total QALYs
Number of model replications where an EF could be constructed	31.4%	77.5%	77.5%	77.5%
Median NMB at introduction price of sacubitril/valsartan [IQR]	-€14,300 [-€11,600 – -€16,200]	-€14,100 [-€12,300 – -€15,400]	-€14,000 [-€12,200 – -€15,300]	-€13,800 [-€12,000 – -€15,200]
Median daily price sacubitril/valsartan with NMB=0 [IQR]	€1.52 [€0.67 – €2.57]	€1.57 [€0.95 – €2.31]	€1.61 [€0.99 – €2.37]	€1.67 [€1.03 – €2.43]

NMBs are rounded to the nearest hundreds of euros

QALY: quality-adjusted life-year; EF: efficiency frontier; NMB: net monetary benefit; IQR: interquartile range

CE plane and CEAC

Figure 9.2 displays CE planes, showing the results of the probabilistic sensitivity analysis. Compared to placebo, most iterations show additional costs for sacubitril/valsartan and savings for enalapril and candesartan. Enalapril and candesartan have similar costs and effects. The CEAC is displayed in figure 9.3. If the willingness to pay is equal to the base-case ICER (€19,300/QALY), sacubitril/valsartan is the most likely treatment to be considered cost-effective, with a probability of 41%.

Efficiency frontier

Although no EF could be constructed for the base case, this was possible in the probabilistic analysis. Table 9.2 shows that this was possible for 77.5% of model replications, when survival, life-years gained or QALYs were considered as outcomes of the analysis and for 31.4% of replications if reduced hospitalizations were considered. The median NMB for sacubitril/valsartan at its introduction price in Germany is similar for all included outcomes: around -€14,000. The median calculated daily price of sacubitril/valsartan where the NMB is equal to zero, ranges from €1.52 to €1.67, depending on the outcome considered. The price-acceptability curves (figure 9.4), display the probability of sacubitril/valsartan being cost-effective at different price points (costs are per day) for the included outcomes.

Univariate sensitivity analysis and scenario analyses

The univariate sensitivity analysis, displayed as a tornado diagram, with the ICER of sacubitril/valsartan compared to enalapril as the considered outcome, is displayed in supplementary figure 9.4. The ICER is mainly impacted by the effect of sacubitril/valsartan on the mortality, the costs of this drug and the utilities of HF patients in the home setting.

The results of the impact on the ICERs of the various included scenario analyses are shown in supplementary table 9.5. Sacubitril/valsartan, enalapril and candesartan drug costs have a major impact on the results. As long as the daily price of enalapril and candesartan are not increased, these drugs will dominate placebo.

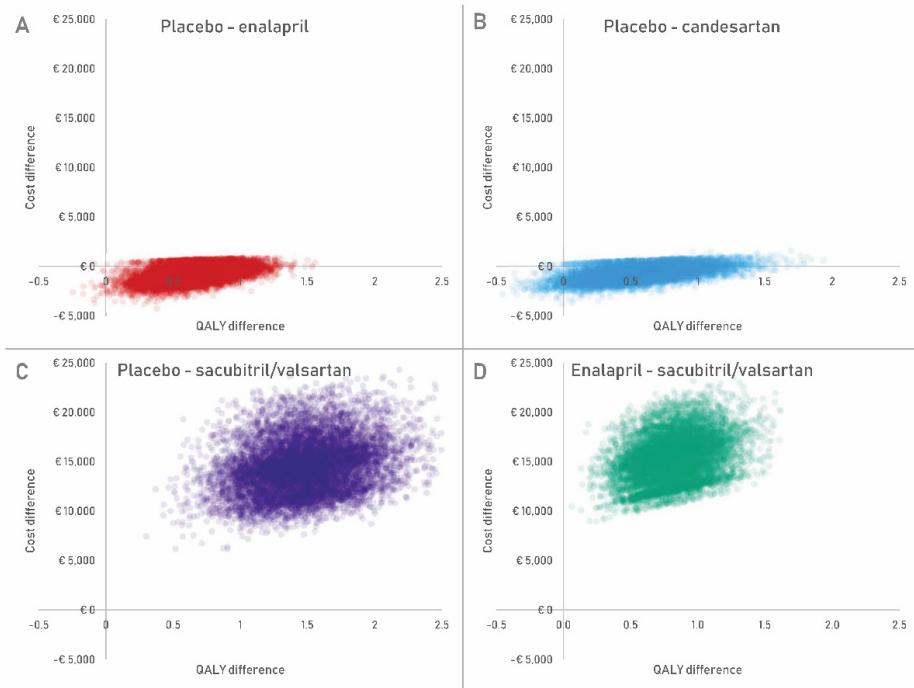


Figure 9.2. Cost-effectiveness planes of enalapril, candesartan and sacubitril/valsartan compared to placebo; and sacubitril/valsartan compared to enalapril

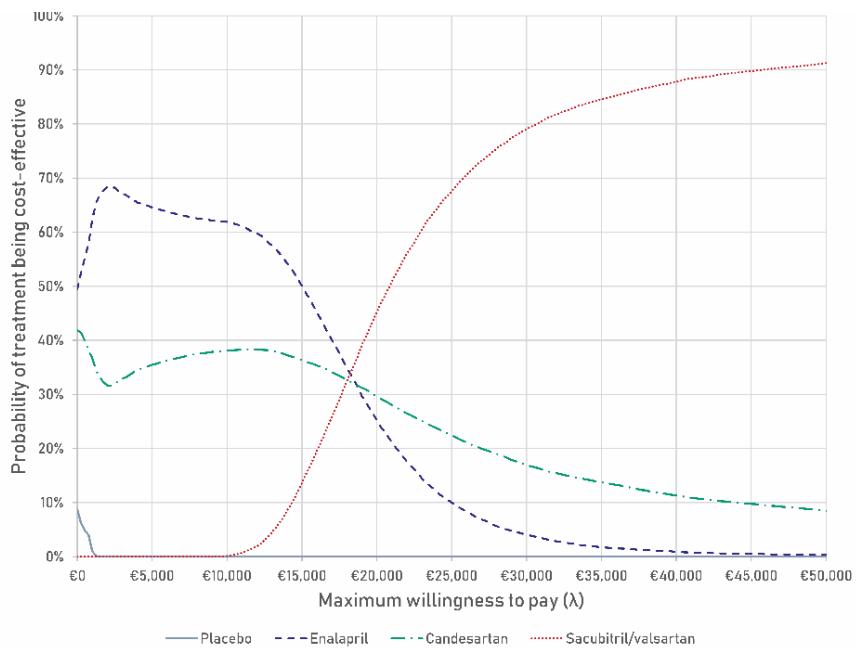


Figure 9.3. Cost-effectiveness acceptability curve

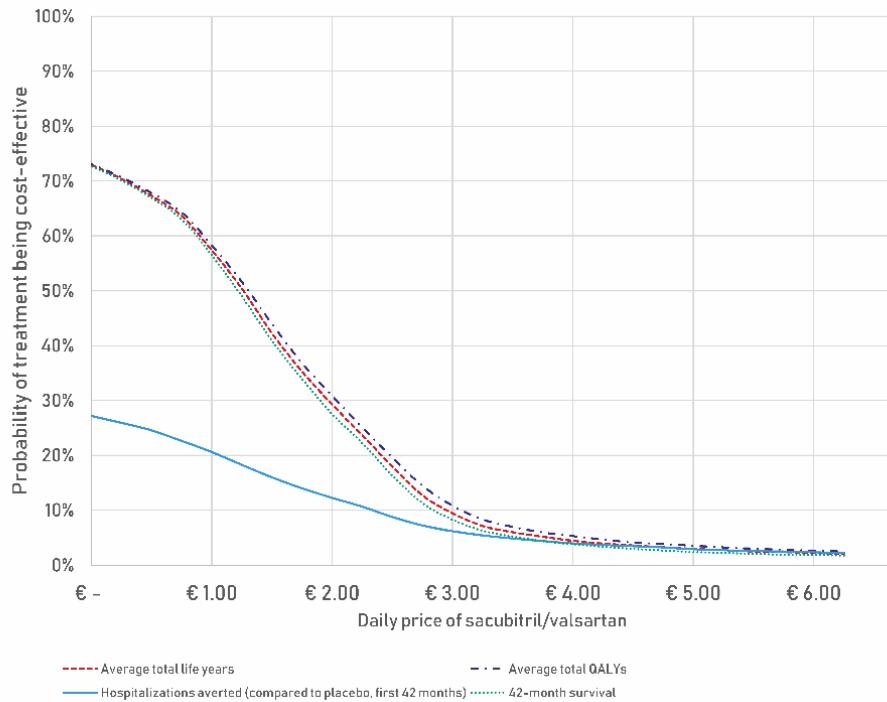


Figure 9.4. Price-acceptability curves of the cost-effectiveness of sacubitril/valsartan

Discussion

At €6.66 per day for sacubitril/valsartan, the ICER compared to the current treatment enalapril is €19.300/QALY. To reach a probability of 90% of being cost-effective, a willingness-to-pay threshold of €45,000/QALY would have to be considered (figure 9.3). Using the EF approach, the base case does not result in interpretable results; as enalapril, the cheapest alternative considered, is dominating placebo and candesartan, resulting in the inability to draw an EF using the available treatment options. The median daily price of sacubitril/valsartan where the NMB is equal to zero (i.e. it is situated on the EF), ranges from €1.52 to €1.67.

The CE plane (figure 9.2) displays the incremental costs and effects of enalapril, candesartan and sacubitril/valsartan as compared to placebo. Enalapril and candesartan are overlapping on the plane, due to their very similar costs and effects. However, the uncertainty surrounding candesartan is greater, mainly due to the method its effects are modelled: there was no direct comparison with enalapril available. Compared to the other interventions, sacubitril/valsartan is more effective and more expensive. The univariate sensitivity analysis shows that the impact on mortality of sacubitril/valsartan is the main driver of the cost-effectiveness, followed by its costs, the quality-of-life measurements in the outpatient setting and the reduction in hospitalizations caused by sacubitril/valsartan.

Using the EF approach, sacubitril/valsartan could not be considered cost-effective in more than 5% of model replications, at a daily price of €6.66, independent of the outcome considered. The different outcomes considered do not influence our results to a large degree. The outcomes used to construct the EF based on gained life years (42-month survival, total life years gained and QALYs gained) provided comparable results: the cost-effectiveness

planes are very similar, the price-acceptability curves are overlapping and an EF could be constructed in almost 80% of model replications. Using the decrease in hospitalizations to construct the EF gives a similar shaped price-acceptability curve, although a EF could only be constructed in about 30% of replications, moving the vertical intercept down. The interquartile range of the NMB is also considerably wider compared to the other outcomes considered. This difference can be explained by the larger benefit of enalapril on hospitalizations than on mortality, compared to candesartan (see also supplementary table 9.3)^{351,352}.

As compared to our previously-reported results for the Netherlands, the base-case ICER is approximately the same (both around €19,000/QALY). Compared to previously-published ICERs for European countries, which range from €17,600 to €23,401 with an average of €20,676, our ICER for Germany is within this range³³⁹⁻³⁴⁴. For Germany, Gandjour and Ostwald calculated an ICER of €23,401, a small difference when regarding their very different model design: the included discounts on sacubitril/valsartan, their inclusion of indirect medical costs and their adjustments to the PARADIGM-HF mortality rates, based on Germany-specific data³⁴⁴.

This analysis has a number of limitations, first of all, for the inclusion of candesartan and placebo, we focused on the model parameters with the largest impact on the results: mortality and hospitalizations, as data on the other inputs were not available in scientific literature. This also limited the number of clinical outcomes we could consider for the EF. The comparison between sacubitril/valsartan and placebo or candesartan is indirect, as no clinical trials have been performed with these comparators; the same holds true for candesartan vs. enalapril – of course, this has been considered for the PSA. The selection of comparators has a major impact on the construction of the EF: next to placebo, we included two comparable and mutually-exclusive drugs, representing two large classes of drugs (ACEis and ARBs)³²⁴. These will however not be used as monotherapy in most patients and be combined with several other drugs, such as diuretics and beta blockers, and possibly other treatments, such as a pacemaker or cardiac resynchronization therapy; these treatments cannot really be considered true alternatives in the context of the EF and were therefore not included as comparators to sacubitril/valsartan^{324,338,350,353,368}. In addition to the EF analysis, IQWIG guidelines detail the calculation of the budget impact, that can also be used in the decision-making process³²³. Notably, we considered the budget impact outside of the scope of this research, however, Gandjour and Ostwald previously reported a maximum annual increase of the German healthcare budget of €88 million, which corresponds to less than 0.04% of total SHI expenditure³⁴⁴.

The median daily price where sacubitril/valsartan is situated on the EF (NMB=0) ranges from €1.52 to €1.67. Using the price indicated by the EF, the introduction price of sacubitril/valsartan would warrant negotiations by German decision makers, to further approach this price point. If the ICER would instead be used to assess the cost-effectiveness of sacubitril/valsartan in the German context, it would most likely be deemed cost-effective at market entry, as reported for other European countries³³⁹⁻³⁴³.

This comparison marks a major difference in conclusions decision makers would draw using either the ICER or EF approach. If we consider a fixed budget for CHF alone, the EF may provide more relevant information for decision makers: the health gains per euro will not decrease as long as the treatment is on or above the frontier. However, if we accept that patented drugs are more expensive, due to the coverage of development costs, the EF approach is not very useful in this case, since currently there is no method

to determine an acceptable price point for innovative drugs replacing generic drugs. The latter issue was also raised by Sculpher and Claxton: a disease area with a concentration of generics, will have a low acceptable price point for innovative drugs³²⁶. Using both approaches (ICER and EF) simultaneously, which are not mutually exclusive, as this research shows, may have benefits in the decision making process. If a new product has an ICER that is regarded cost-effective, but the efficiency, as determined using the EF is low, the results could still be used to negotiate a discount. This might be especially relevant for innovations with a potentially large budget impact. Additionally, the EF's ability to consider various outcomes may be helpful if alternative outcomes, such as patient-reported outcomes, are generated by clinical trials³⁶⁹. We think it may be useful to perform similar comparisons in various other fields, where patented drugs reflect important treatment modalities, such as oncology.

Currently, sacubitril/valsartan is only registered for the use in HF-REF patients, although this model partly uses data for the general CHF population. German guidelines advice to only treat patients with the new drug if patients still are symptomatic under enalapril³⁶⁸. New data could improve knowledge regarding the long-term effects of the new drug and the certainty of its cost-effectiveness. Additionally, the results of the PARAGON-HF trial, which is expected to be completed in 2019, can indicate whether sacubitril/valsartan improves clinical outcomes for CHF patients with a preserved ejection fraction^{370,371}. A Post-hoc analysis from PARADIGM-HF indicates that sacubitril/valsartan might improve glycaemic control, which could improve the cost-effectiveness considering a diabetes is a common comorbidity in this patient population^{372,373}. As this outcome was not routinely assessed, this aspect could not be considered in our analysis and further research would be useful from a clinical point of view, as well as from an economic perspective³⁷⁴.

In conclusion, our model shows that sacubitril/valsartan can be considered cost-effective, at its introduction price in Germany, when using globally-used methods to perform the economic evaluation³²⁹. In contrast, using the EF approach, a discount of around 75% for sacubitril/valsartan should be targeted to make it cost-effective.

Appendix: An Economic Evaluation of Sacubitril/Valsartan for Heart Failure Patients in the Netherlands

Introduction

Around 1% of the Dutch adult population suffers from chronic heart failure (CHF)³⁷⁵ and about 20% of the total population will be diagnosed with CHF at some point in their lives³⁷⁶. The total costs of heart failure (HF) for the Netherlands in 2011 were €939.7 million, over 1% of all national healthcare expenses, using the definition of costs from Dutch Health and Social Care Accounts³⁷⁷. These costs include all expenditures related to health, welfare and social care in a broad sense. No truly curative interventions are currently available for HF patients and treatment focuses on improving the clinical status, functional capacity and quality of life, while preventing hospitalizations and reducing mortality³⁷⁸. The standard of care for clinically stable patients with objective evidence of cardiovascular disease (i.e., a New York Heart Association (NYHA) class II or higher³⁷⁸) is a combination of up to four drugs, a diuretic, an Angiotensin Converting Enzyme inhibitor (ACEi), a beta blocker and a mineralocorticoid receptor antagonist³⁷⁹.

In 2014, McMurray et al.³⁸⁸ published the results of the clinical trial PARADIGM-HF, which compared enalapril to a combination of the neprilysin inhibitor sacubitril and the angiotensin receptor blocker (ARB) valsartan (Entresto, Novartis). The clinical trial showed a significant reduction in deaths (16%) and hospital admissions for CHF (21%) in the patient group treated with sacubitril/valsartan compared to the enalapril group³⁸⁸. The European Medicines Agency (EMA) has granted an accelerated assessment procedure³⁸⁰ and approved the drug by the end of 2015³⁸¹.

While the list price of sacubitril/valsartan is known at this point (€5.25 per day)¹⁰⁰, hospitals, health insurance companies and the Dutch ministry of health may negotiate other price points to reduce the costs. Since no economic evaluation for The Netherlands has been published to date, this article aimed to determine the cost-effectiveness of sacubitril/valsartan compared to enalapril at different price points, using the clinical data from PARADIGM-HF.

Methods

Model design

A Markov model was developed to simulate a cohort of 10,000 CHF patients using cycles with the duration of one month (figure 9.5). There are four major health states in the model:

- Heart Failure: patients receiving home care only;
- Ward hospitalization: patients receiving treatment on the hospital ward within a month;
- Intensive Care Unit (ICU) hospitalization: patients receiving ICU treatment within a month;
- Death: Deceased patients.

All patients started in the Heart Failure state. When hospitalized, 10% will also receive ICU treatment for a portion of their stay³⁴⁶. After a month in which they were hospitalized, patients can either be rehospitalized, go back to the Heart Failure state or die. The length of stay of each patient varies within a month of hospitalization. The probabilities for hospitalization and death from PARADIGM-HF were used to calculate the monthly transition probabilities for sacubitril/valsartan and the comparator group. Each month,

both the total quality-adjusted life years (QALYs) and costs were calculated. A healthcare payer's perspective was applied. The model was built using Microsoft Excel® 2013 and is included in the supplementary data (supplementary file 9.1).

Time horizon

In the base case-analysis, the effects of sacubitril/valsartan versus enalapril were limited to the first 42-month period, equivalent to the available data from PARADIGM-HF³³⁸. After this, both treatment arms maintained the same probabilities of dying and hospitalization, and the costs were the same (i.e. no treatment advantage of one intervention over the other). We used a 30-year time horizon. Given the age of the cohort at the start, and status as an CHF patient, this can be considered a lifetime horizon as prescribed in the Dutch pharmacoeconomic guidelines⁴⁰. As a scenario analysis, we have assumed a persistent treatment effect of sacubitril/valsartan versus enalapril during the complete 30 years model run.

Input Parameters

Transition probabilities

Both the hospitalization probabilities and cardiovascular death rate were taken from PARADIGM-HF, the hospitalization probability being time dependent^{338,345}. Since the underlying data from the Kaplan-Meier curves were not presented in the publication,

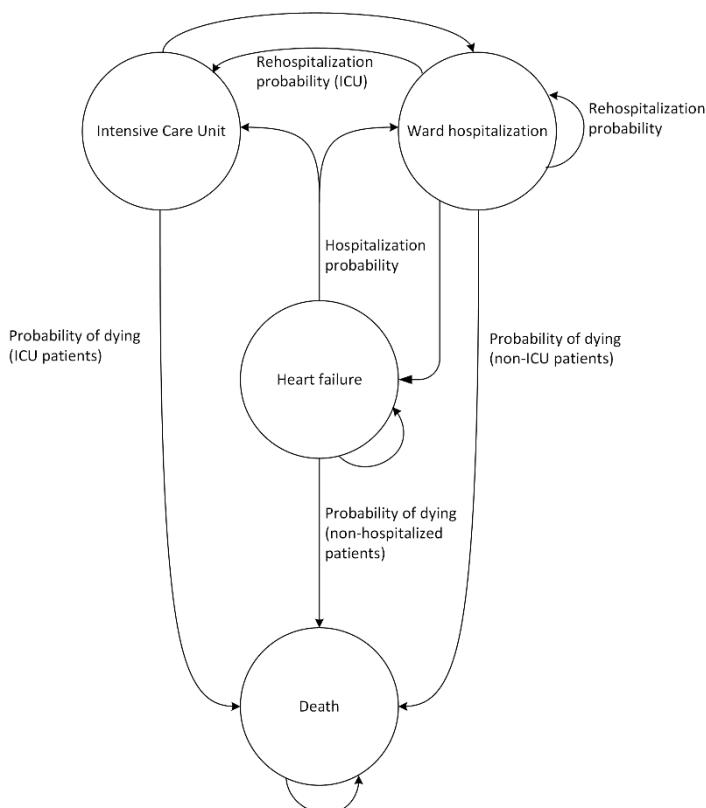


Figure 9.5. Schematic Representation of the Markov Model. The circles represent the four states of the model, while the arrows indicate all possible transitions between the states during each monthly cycle.

the necessary parameters were derived using the software tool DigitizeIt³⁸² and plotted using Microsoft Excel® 2013. A linear function was found for the cardiovascular death rate and a logarithmic function for the hospitalizations. The 30-day rehospitalization data were also taken from PARADIGM-HF, specifically concerning the data for western Europe (only reported combined with “other”)³⁴⁹. Unfortunately, the 30-Day hospital deaths from PARADIGM-HF are not publicly available. Instead, data was used from Corrao et al.³⁴⁸ Fortunately, these data are very recent and include age dependent differences to optimally align this information with our model. The transition probabilities associated with dying due to other causes than CHF were also age dependent and taken from the Dutch statistics³⁸³. The resulting individual monthly transition probabilities are shown in table 9.3. These data do not have a distribution associated in the model, since these were not available. However, all-causes death, in-hospital death and rehospitalization are based on large numbers and inherent uncertainty may be small. Yet, these variables vary by age, as well as the initial hospitalizations are varying by the progression of time in the model (time after starting the treatment).

The Hazard Ratios from PARADIGM-HF^{338,345} were multiplied by the different probabilities (hospital/ICU admissions and deaths) to calculate the parameters for sacubitril/valsartan. The values are shown in table 9.4.

Costs

Medicine costs

The cost difference between sacubitril/valsartan and enalapril is one of the main differentiators between both treatments. While the list price of sacubitril/valsartan is known in the Netherlands at this point (€5.25 daily), parties such as the department of health, hospitals and health insurance companies may still negotiate lower prices. For this reason, several additional daily price points of sacubitril/valsartan were considered in the analysis (€0.045; €1; €3; €10) in addition to €5.25 as the base case. For enalapril, the lowest price point as found on the Dutch database of medicine costs is used in the model, which is €16.42 for the 20mg dose package (730 tablets, taken twice daily for a year) or €0.045 per day¹⁰⁰. Additional medicine costs included were hydrochlorothiazide, digoxin, metoprolol and spironolactone, all of which were used by a subset of the population as described in PARADIGM-HF³³⁸. The specific costs of these additional drugs are summarized in table 9.5. All these costs include taxes and exclude the dispensing fee (€6 per three months), this fee was included separately in the model.

9

Hospital costs

The hospital length of stay (LoS) during PARADIGM-HF has been reported by Packer et al.³⁴⁵ The average ICU LoS for CHF in the Netherlands has been described in a study by Van Vliet et al.³⁸⁵ The LoS, as used in the model, is shown in supplementary table 9.1. Note that the LoS in the ICU model state is the same for the enalapril group and sacubitril/valsartan group and that these patients are actually treated on the normal ward for the majority of their stay. The hospital costs were calculated using the weighted average for both academic and general hospital per diem costs, which are €502.54 per day for the nursing ward and €2,400.53 per day for the ICU (including correction for inflation to 2015), as described in the Dutch manual for costs research^{386,387}.

Elderly care and general practitioner costs

To estimate the elderly care and general practitioner (GP) costs, the Dutch cost of illness website was used³⁷⁷. These costs were converted to the costs per patient by calculating the

Table 9.3. Transition Probabilities Used in the Markov Model

Transition	Probability	Dependences	Source
Death (all causes, except cardiovascular)	0.00086	Age ^a	383
Death (cardiovascular)	0.0089	-	338
Death (in hospital)	0.037	Age ^a	348
Death (in ICU)	0.11	-	384
Hospitalization	0.0119 0.199 (enalapril)	Time ^b	345
30-day rehospitalization	0.088 (sacubitil/valsartan)	-	349

^a probability displayed is at age 65^b probability displayed is in the first month

Table 9.4. Effects (Risk Ratios) of Sacubitil/valsartan Compared to Enalapril

Target of effect	Risk Ratio [95% confidence interval]	Distribution	Source
Hospitalization	0.77 [0.67-0.89]	Lognormal	345
ICU admission	0.82 [0.72-0.94]	Lognormal	345
Death	0.84 [0.76-0.93]	Lognormal	338

Table 9.5. Medicine Costs for the Included Drugs in the Model and Usage Among the Two Treatment Groups

Drug	Cost (€) per year ¹⁰⁰	Used by % of population for enalapril group ³³⁸	Used by % of population for LCZ696 group ³³⁸
Hydrochlorothiazide (25mg)	4.90	80.1	80.3
Digoxin (0.125 mg)	11.68	31.2	29.2
Metoprolol (25 mg, controlled release)	10.06	92.9	93.1
Spironolactone (25 mg)	12.12	57	54.2

total number of HF patients in the Netherlands, using the prevalence as described in the Rotterdam Study³⁸⁸ and the age tables provided by Statistics Netherlands (CBS)³⁸⁹. These data are age-dependent categories.

Unrelated medical costs in life years gained

The unrelated medical costs in life years gained from all diseases except HF were included in the Markov model³⁹⁰. Both the costs of the last year of life and all other years were taken into account. Due to some practical limitations of a Markov model, the costs in the last year of life were added when a person died and the previous costs of health care were subtracted from this amount. These costs were not included in the base case, but in a specific targeted scenario.

Health Outcomes

Utilities

Since the utilities were not available from PARADIGM-HF, the previously published EQ-5D (EuroQol 5 Dimensions data from the SHIFT (Systolic Heart failure treatment with the I₁-inhibitor ivabradine Trial) trial were used³⁹¹. Both trials included patients with an ejection fraction of 35% or less. These utility values differentiated between NYHA classes. However, PARADIGM-HF did not publish outcomes differentiated by NYHA class. Therefore, using the NYHA-class distribution as weights, the average value of utility scores was calculated^{391–393}. These utility scores were calculated using the population norms from the UK^{393,394}. The weighted averages (using data from PARADIGM-HF) were calculated for both the non-hospitalized and hospitalized patients and are shown in table 9.6. These utilities were used to calculate quality adjusted life months, which were converted into QALYs.

To take the uncertainty around the utilities into account, a triangular distribution was applied to these data for the probability sensitivity analysis. The point estimate was used as mode, 80% as the lower bound and 120% as the upper bound.

Discounting

All costs were discounted at 4% per year and health outcomes were discounted with 1.5% per year according to Dutch pharmacoeconomic guidelines³⁸⁶. Additionally, a sensitivity analysis was performed using equal discounting rates at 4% a year and included as an additional scenario.

Table 9.6. Yearly Utility Scores for Heart Failure Patients, Weighed Average for All NYHA Classes

Model state	Utility score ³⁹³ (lower bound – upper bound)	Distribution
No hospitalization	0.72 (0.576 – 0.864)	Triangular
Hospitalized (both ICU and non-ICU)	0.64 (0.512 – 0.768)	Triangular
Death	0	None

NYHA: New York Heart Association; ICU: Intensive Care Unit

Willingness-to-pay

Cost-effectiveness was assessed using the incremental cost-effectiveness ratio (ICER), expressed as the difference in health care costs, divided by the difference in QALYs. While there is no explicit cost-effectiveness threshold in the Netherlands, €20,000 - €50,000 per QALY have previously been reported as reference values and are therefore considered reasonable³⁹⁵. Therefore, €20,000 and €50,000 were used as lower and upper willingness-to-pay (WTP) limits per QALY in this article.

Sensitivity analyses

To investigate the effects of uncertainty in the model, univariate sensitivity analyses were performed, by changing the values to an 80-120% interval of their primary values. This interval was used since no 95% confidence intervals were available for all parameters. Subsequently, the individual effects on the ICER were recorded and displayed as a Tornado diagram.

In addition to this, a probabilistic sensitivity analysis was performed, to investigate the uncertainty around all parameter values simultaneously. This was done by calculating the results using random samples of the distribution of the different input parameters in 1000 replications. These results are shown on a Cost-effectiveness (CE) plane and were transformed into cost-effectiveness acceptability curves (CEACs).

Results

Sacubitril/valsartan costs

The list price of €5.25 yields an ICER of €19,133.33 /QALY, see table 9.8 for the detailed results. Considering €20,000 and €50,000 per QALY as reasonable WTP thresholds, sacubitril/valsartan can be priced up to €5.50 and €14.14, respectively.

Univariate sensitivity analysis

The results of the univariate sensitivity analysis are shown in the Tornado diagram in figure 9.6. The parameters are ordered with the most influential driver of the cost-effectiveness at the top to the least important driver of the results on the bottom. The effect of sacubitril/valsartan on death has the most influence on the ICER. The model responds less to changes in any other values, including the non-hospital utilities and minor changes in the price of sacubitril/valsartan.

Scenario analyses

In table 9.9, the different scenario analyses were compared to the base case. Shown are the maximum daily costs of sacubitril/valsartan, at WTP thresholds of both €20,000 and €50,000 per QALY.

CE plane and CEAC

The CE plane (figure 9.7) displays the distribution of the base case results of the probabilistic sensitivity analysis for different possible price points of sacubitril/valsartan. In figure 9.8, the CEACs of sacubitril/valsartan are displayed for different price points. The probability of sacubitril/valsartan to be cost-effective at €5.25 a day is over 95% at a WTP of €50,000/QALY and over 75% at €20,000/QALY. At the price point of €1 the probability of sacubitril/valsartan being cost-effective is almost 90% for the WTP threshold of €20,000/QALY. Considering a WTP threshold of €50,000/QALY the price point of €10 is cost-effective with 90%.

Table 9.8. Base Case Results

	Enalapril	Sacubitril/valsartan	Difference
Costs	€12,358.01	€17,918.22	€5,560.21
Life years	6.87	7.28	0.40
QALYs	4.93	5.22	0.29
ICER			€19,113.33

ICER: Incremental Cost-Effectiveness Ratio

Table 9.9. Maximum Daily Costs for Different Scenarios

Scenario	Maximum daily cost sacubitril/valsartan (WTP threshold: €20,000/QALY)	Maximum daily cost sacubitril/valsartan (WTP threshold: €50,000/QALY)
Base case	€5.50	€14.14
Extrapolated effect to 30 years	€6.04	€15.50
Included unrelated medical costs in life years gained	€4.05	€12.69
Applied equal discounting for costs and effects (4% annually)	€4.57	€11.81

WTP: willingness-to-pay

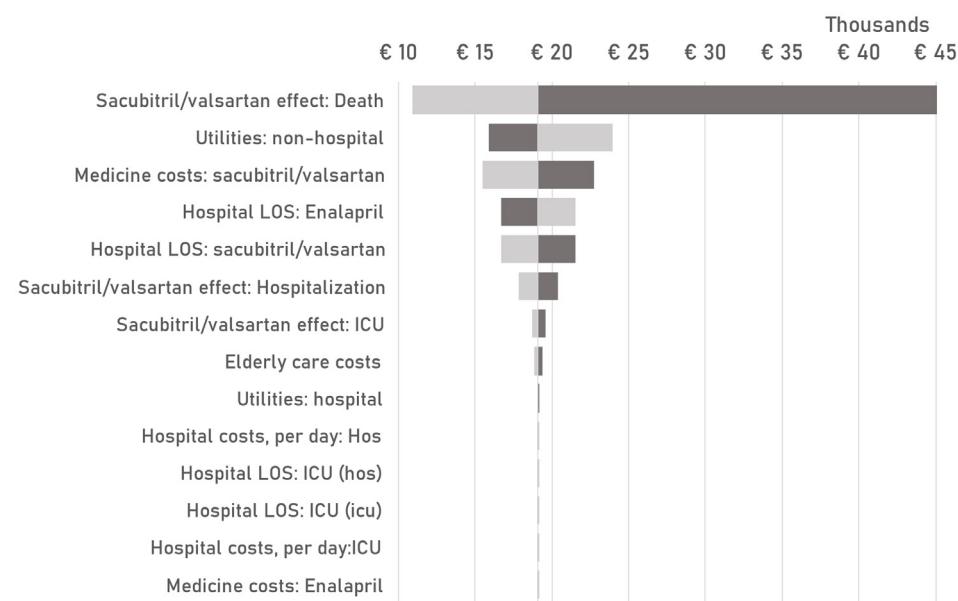


Figure 9.6. Tornado diagram showing the univariate sensitivity analysis of the Markov model simulation the range measured for the different parameters is 80%-120%
LoS: length of stay, ICU: intensive care unit, hos: hospital

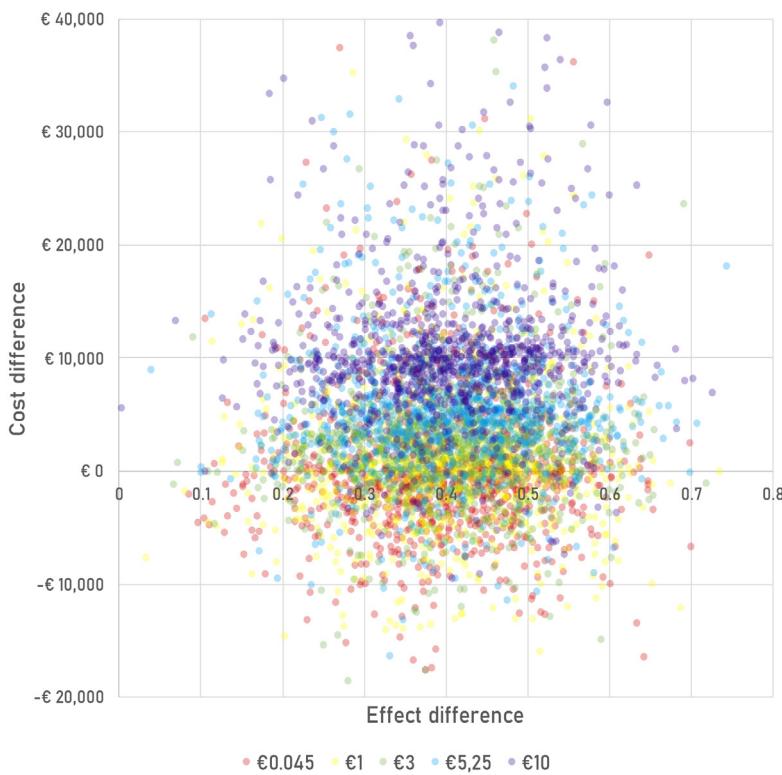


Figure 9.7. Cost-effectiveness plane displaying the results of the Monte Carlo simulation

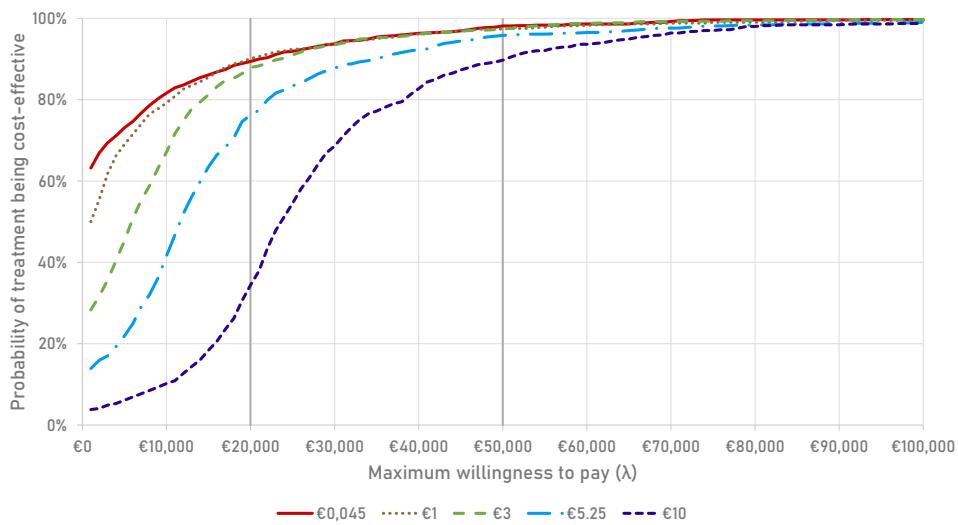


Figure 9.8. Cost-effectiveness acceptability curve, showing the maximum willingness to pay (or threshold ratio) and the corresponding probability of cost-effectiveness for both enalapril and sacubitril/valsartan

Discussion

The base case results of the Markov model show that sacubitril/valsartan, disregarding parameter uncertainty, can be considered cost-effective at €5.50 per day (WTP threshold of €20,000/QALY) or €14.14 (WTP threshold of €50,000/QALY). In this model, sacubitril/valsartan treatment was not likely to be cost-saving unless priced at the same level as the off-patent enalapril.

In the CE plane (figure 9.7) the distribution of the Monte Carlo analyses are shown for the different price points. This indicates a relatively small contribution to the overall treatment costs by these lower sacubitril/valsartan prices; even if sacubitril/valsartan is priced at the same level as enalapril, the probability of it being cost-saving is only 63%. This changes profoundly at the higher price points where the sacubitril/valsartan price became the major driver of the cost-effectiveness outcomes. The CEAC (figure 9.8) shows that the probability of cost-effectiveness of the price point of €5.25 is over 95% at a WTP threshold of €50,000/QALY. When a WTP threshold of €20,000 is considered, the calculated price points of €0.045 and €1 are likely to be cost-effective with 90% certainty.

The univariate sensitivity analysis (figure 9.6) shows that the uncertainty around the relative risk of dying for the sacubitril/valsartan group has the highest impact on the ICER: avoiding deaths in the sacubitril/valsartan treatment arm leads to considerably more QALYs compared to enalapril. Another important driver of the model outcomes was the utility of patients who are nonhospitalized due to the additional gained QALYs as patients that use sacubitril/valsartan tend to live longer. In addition, the minor changes in the sacubitril/valsartan price, in this case ranging from €4.20 to €6.30, seems impactful as well, although to a lesser extent.

The scenario in which the effects of the PARADIGM-HF were extrapolated to 30 years, results in higher maximum per diem costs of sacubitril/valsartan for both thresholds. This is mainly due to the increase in long-term effects, which are discounted less than the long-term decrease of costs.

In the scenario which incorporates unrelated medical costs in life years gained, the upper limits of the sacubitril/valsartan daily cost are €4.05 and €12.69 per day for €20,000/QALY and €50,000/QALY WTP thresholds, respectively. This is lower compared to the base case, which is mainly due to the extra costs that are added in the additional life years gained in the sacubitril/valsartan case and the increased end-of-life costs at a later age. While the inclusion of unrelated medical costs in life years gained essentially is a penalty for a beneficial outcome (life years gained), these are costs that have to be taken into account according to new Dutch guidelines⁴⁰. These results suggest that to achieve a high probability of cost-effectiveness, sacubitril/valsartan will need to be priced lower than the base case suggests. The sensitivity analysis in which equal discounting was applied, shows that the maximum daily costs of sacubitril/valsartan at both WTP thresholds benefit from differential discounting. Especially when the €50,000/QALY WTP threshold is considered, the maximum per diem costs are lower (down to €11.81 from €14.14 in the base case). The long-term effects of sacubitril/valsartan seem to play an important role in its cost-effectiveness.

The PARADIGM-HF trial was limited to patients with HF-REF and as such, data from this trial are only applicable to this group (death rates, hospitalization rates and sacubitril/valsartan effects)³³⁸. Other data sources used to create the Markov model in this article are for the general CHF patient population. The costs data are based on averages for all HF

patients in the Netherlands³⁷⁷. While it would be preferable to create an economic evaluation for the whole group of CHF patients, the model can only be used for patients with HF-REF. At the time of writing, an ejection fraction equal to or less than 35% is a requirement in the Netherlands to have sacubitril/valsartan reimbursed by health insurance¹⁰⁰. Other groups are being researched right now with a focus on patients with a Preserved Ejection Fraction (HF-PEF)^{396,397}. The results of the PARAMOUNT phase 2 trial, which compared sacubitril/valsartan to valsartan, are promising³⁹⁷, however we speculate that the beneficial effects of sacubitril/valsartan for these groups will be less pronounced, since HF-PEF is usually less severe than HF-REF, resulting in a lower maximum daily price compared to our results.

The data derived from the Kaplan Meier curves from PARADIGM-HF were used to calculate the hospitalization and cardiovascular death rate in the model. However, the trial data stop after 42 months^{338,345}. The results will need to be continually updated with the availability of more trials and longer follow-up data. Accordingly, the appropriate pricing of the drugs needs to be re-evaluated continually. Validation of the Markov model is reported in supplementary file 9.2, using a filled-in version of the model validation assessment tool AdViSHE (Assessment of the Validation Status of Health Economic decision models)³⁹⁸. Part of the model validation process, was a cross-validation with other published studies. The CE analysis created by Novartis for the Dutch market reports an ICER of €18.580/QALY, which is lower than, but close to, the € 19,113.33/QALY we found. A main difference here is that the effect of sacubitril/valsartan is extrapolated to 30 years (the time horizon). They also assume lower daily costs of sacubitril/valsartan (€4.83) and higher daily costs for enalapril (€0.14)³⁹⁹. King et al. published a CE analysis for the American market, using a daily price of sacubitril/valsartan of \$12.66, resulting in a ICER of \$50,959/QALY⁴⁰⁰. If a daily price of €12.66 is applied to our model, it results in an ICER of € 44,853.36 /QALY. They also used a Markov model, the main differences being the cycle length (three months) and a differentiation of different NYHA classes⁴⁰⁰.

The impact on the national health budget of treatment with sacubitril/valsartan instead of enalapril for HF-REF patients is also investigated. If 50% of the 140,000 HF patients in the Netherlands⁴⁰¹ would start sacubitril/valsartan treatment, an increase of €5.21 a day, assuming they already use enalapril, this would amount to €385,140 per diem, or €132,987,750 annually, 15% of all heart failure expenses or 0.16% of all health care expenses in the Netherlands³⁷⁷.

Right now, sacubitril/valsartan is only available for HF-REF patients that already are on an ACEi or ATB¹⁰⁰. While this is a good solution to keep the costs low in the short term, a health benefit for all HF-REF patients may be achieved when patients are prescribed sacubitril/valsartan immediately, lower costs of sacubitril/valsartan would enable this with less effects on the health budget. Additionally, new trials covering e.g. HF-PEF patients might enable sacubitril/valsartan to be prescribed to this group of patients^{396,397}.

The model was tailored to the Dutch situation as much as possible, which includes all costing data. However not all country specific data were available, such as the results from PARADIGM-HF.⁴⁰² However, the GP guidelines in the Netherlands are similar to those in the rest of Europe and the United States, which makes the CHF treatment comparable and the results applicable to the Netherlands^{378,379,403}. The LoS of PARADIGM-HF was used for the analyses, to be able to differentiate between the two treatments arms. The average LoS in the Netherlands is close to the PARADIGM-HF results and well within the ranges used for the sensitivity analysis^{338,404}.

Data collected during a trial are often not comparable to real life scenarios. During PARADIGM-HF there was a run-in phase at the start of the trial, to make sure that patients were able to tolerate both enalapril and sacubitril/valsartan. A well-known side effect of enalapril is cough and these patients were excluded from the trial, while they would still require treatment in daily practice. 12% of the patients were excluded from the trial due to side effects.³³⁸ However, more patients had to leave the trial due to adverse effects caused by enalapril than sacubitril/valsartan³³⁸.

Productivity losses are not taken into account for this simulation. Therefore, this study is from the healthcare payer's perspective and not from the societal perspective as recommended by Dutch authorities. However, since the vast majority of patients are likely to be retired when heart failure is diagnosed³⁷⁵, the effect of this is likely to be low.

Another limitation of the study was the estimation of elderly care costs. Sacubitril/valsartan was shown to improve quality of life and reduce the decline in heart failure class compared to enalapril^{338,345}. It would be fair to assume that the elderly care costs for these patients would be lower, since the need for home care later would be offset. However, in this study, the only differentiator for elderly care costs is age and it would have been better to be able to select patients with a certain class of heart failure in order to distribute the costs more accurately. Unfortunately, during the development of the model these data from PARADIGM-HF were not published. Lastly, the NYHA classification⁴⁰⁵ was not incorporated in the model since these data were not available as well. Hospitalization and death rates are affected by NYHA class, as has been described in the PARADIGM-HF trial.³³⁸ The beneficial effects of sacubitril/valsartan on the primary end point are more pronounced in NYHA class I and II patients than in class III and IV patients, which would probably also result in a lower ICER for class I and II patients compared to class III and IV patients. Unfortunately, there were no specific data available on the utilities for ICU hospitalized patients, as compared to the nursing ward.

In summary, with a WTP threshold of €20,000/QALY the base case results show that the maximum daily costs of sacubitril/valsartan is €5.50 per day. The CEAC shows a 90% certainty that sacubitril/valsartan is cost-effective when priced at €1 per day. When the WTP threshold of €50,000/QALY is considered, the base case results demonstrate its cost-effectiveness up to a price of €14.14 per day, or €5.25 with more than 95% certainty.

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS)⁴⁰⁶ checklist has been included as a separate table in supplementary file 9.3.

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CHAPTER

10

The Tripartite Insurance Model (TIM)

A Financial Incentive to Prevent Outbreaks of Infections due to Multi-drug Resistant Microorganisms in Hospitals

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Abstract

Healthcare-associated infections caused by multidrug-resistant organisms (MDROs) constitute a major challenge worldwide, but care providers are often not sufficiently incentivized to implement recommended infection prevention measures to prevent the spread of such infections. We propose a new approach which creates incentives for hospitals, external laboratories and insurers to collaborate on preventing MDRO outbreaks by testing more and implementing infection prevention measures. This tripartite insurance model (TIM) redistributes the costs of preventing and combating MDRO outbreaks in a way that all parties benefit from reducing the number of outbreaks.

See figure 10.1 for a graphical abstract.

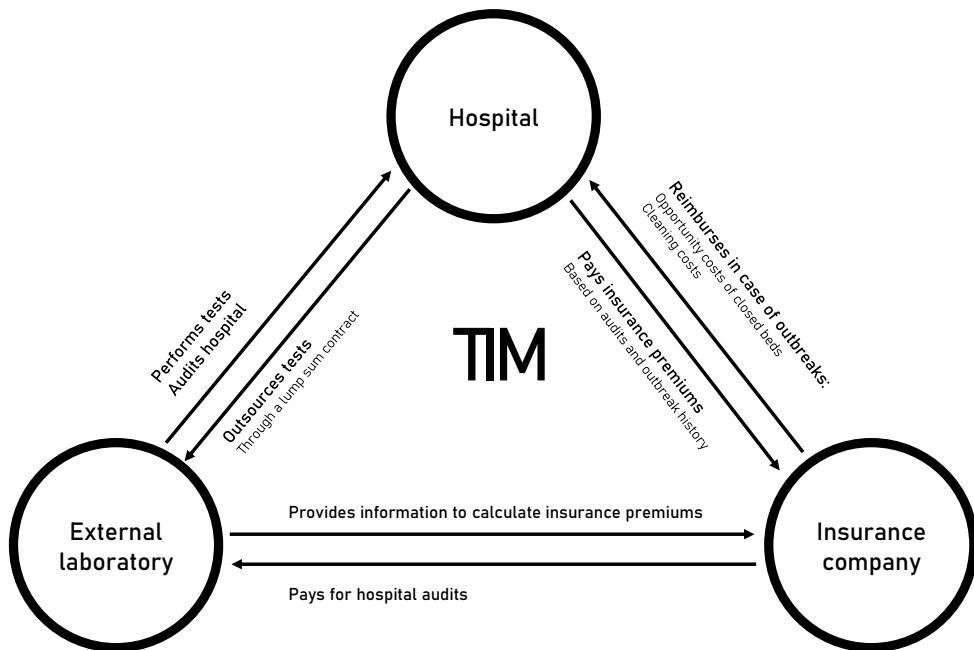


Figure 10.1. Graphical abstract Tripartite Insurance Model (TIM)

Introduction

Healthcare-associated infections (HAI), especially those caused by antimicrobial-resistant microorganisms, constitute a major challenge for medicine worldwide. This worldwide increase in multidrug-resistant microorganisms (MDRO) makes HAIs increasingly difficult to control, treat and cure. This causes a major rise in morbidity, mortality and healthcare costs^{11,12}. In 2015 alone, an estimated 33,110 deaths were caused by HAIs with MDROs in Europe¹¹. The occurrence and spread of MDROs vary between countries in Europe⁴⁰⁷. For example, in Scandinavian countries and the Netherlands, 1-2% of invasive *Staphylococcus aureus* isolates are resistant to methicillin (MRSA). In contrast, neighbouring countries such as Belgium, Germany and the United Kingdom measure MRSA rates of 10-15%, while in some countries in southern Europe 30% or more of invasive isolates are MRSA⁴⁰⁷.

Although many countries have implemented extensive measures to prevent the occurrence and spread of MDROs in recent years, antimicrobial resistance (AMR) levels are predicted to rise¹². One reason for this may be a lack of economic incentives to prevent AMR, further complicated by the fact that the impact of AMR is difficult to quantify in economic terms¹⁴. Other parties may benefit from preventing AMR than the parties that make the investments, complicating collaboration. We hypothesize that a system change is necessary by introducing not only medical but also economic incentives to reduce AMR. We propose a model of insurance against MDRO outbreaks that will incentivize infection prevention measures within the hospital, and with that, reduce the occurrence and spread of MDROs and in turn MDRO outbreaks.

Current situation

Outbreaks, during which MDRO spread quickly through hospitals, are a major financial risk: a study in a Dutch academic hospital estimated an average cost of €546 per infected patient per outbreak day⁴⁴. To prevent MDRO outbreaks and limit the further spread of MDROs, an integrated stewardship approach is necessary, comprising antimicrobial therapy, infection prevention and diagnostics to effectively combat AMR¹⁹. Core to this is an innovative approach for infection management, which closely links diagnostics and therapy to provide optimal diagnostics and treatment targeted to individual patients¹⁹. Additionally, screening for MDRO is important to identify patients that require additional precautions.

Key to such a screening approach is an adequate testing capacity, low barriers for clinicians to perform these tests and microbiological advice to interpret the test results. In some healthcare systems, incentives seem to have developed to save costs by reducing tests in hospitals. For example, there may be an incentive not to screen patients when high AMR levels are publicly reported, since positive tests would possibly drive patients to competing hospitals when seeking care. Secondly, if tests are outsourced, hospitals often pay per diagnostic test performed and the benefits from the economies of scale initially flow back to external microbiological laboratories. For external microbiological laboratories that are being contracted by healthcare providers, MDRO outbreaks can lead to an increase of the number of diagnostic tests and therefore to, albeit not actively desired, positive financial effects. The incentive to reduce the number of outbreaks could be in consequence solely medical and jeopardised by the underlying misdirecting economic incentive.

The tripartite-insurance model (TIM)

Most current economic constructs are production-driven and not able to support adequate preventive policies, complicating approaches to further reduce AMR⁴⁰⁸. Therefore, there is a clear need to develop a model in which clinicians and hospital management are not only driven by medical necessity but also by financial incentives to counteract AMR. We propose an insurance model which enables the redistribution of the various financial flows of MDRO preventive policies, tests and outbreaks⁴⁴. The model considers three parties, the hospital and an external laboratory as previously mentioned, and a new stakeholder: a casualty insurer. This is a conceptual model, which can be tailored to different healthcare systems, with the requirement that the parties act independently. In the TIM, we do not discern between public or private funding. Health insurers are not included in the model; we expect their role to remain unchanged (i.e., reimburse costs of care for individual patients).

Within the TIM, we differentiate between two different types of costs: constant costs and outbreak costs. Constant costs need to be paid regardless of an MDRO outbreak, including insurance premiums, the contract between the microbiological laboratory, hospital staff costs (e.g., hiring a full-time infection prevention specialist), and infection prevention measures. Outbreak costs include additional diagnostics, cleaning, personnel (hours spent on outbreaks by hospital staff and productivity losses of infected staff), patient isolation and opportunity costs due to closed beds (i.e., missed revenue)⁴⁴. Key in an insurance model is to transfer risks from a risk-averting party (in this case a hospital), to a party more willing to take on these risks (an insurer)⁴⁰⁹. Additionally, as it is unlikely that all hospitals signing up for the TIM suffer an outbreak simultaneously, the financial risks related to outbreaks are distributed more evenly, i.e., the risks are pooled⁴⁰⁹.

The hospital would negotiate a lump sum contract with an external laboratory, providing routine tests, tailored to the needs of the hospital. In case of an outbreak, all additional tests are covered by this contract. This will give the laboratory an incentive to aid in the prevention of outbreaks, for example by educating hospital staff on infection prevention strategies. In consequence, the laboratory will have a strong incentive to reduce costs and time to result of a diagnostic test which will encourage cost-effective diagnostic procedures.

The hospital also has a contract with the insurer covering the missed revenue of closed beds and cleaning costs caused by an outbreak⁹⁰. The insurance premium will be determined based on the number of beds, bed occupancy and risk modifying factors. Risk increasing factors include the prevalence of MDRO within the hospitals and the healthcare region, effective nursing staff to patient ratio, the number and size of previous outbreaks within the hospital, and a lack of action after admission screenings. Risk reducing factors include a high annual number of screened patients, an active stewardship programme, and a high compliance to hand hygiene and other infection prevention guidelines⁴¹⁰. In general, a bonus/malus seems critical: hospitals which perform well and effectively reduce AMR levels and the number of outbreaks will have lower premiums than hospitals with many outbreaks.

Finally, the external laboratory is contracted by the insurer to audit the hospital regarding the implementation of infection prevention measures, which in turn influences the insurance premium paid by the hospital. This integral collaboration between the hospital and laboratory regarding infection control is already implemented in some countries (e.g., the Netherlands): it stimulates the transfer of knowledge and improves the use of

diagnostics for clinical and preventive purposes. Additionally, the risks for the insurer will be reduced, as the outbreak risk decreases.

In the TIM, outbreak costs are for the largest part covered by the insurance and for a smaller part by the laboratory, which has to pay for additional tests. As more tests would increase costs of the laboratory but not the income, the laboratory has a clear incentive to reduce its operating costs related to performing the tests, as well as to help the healthcare provider to control the spread of AMR and prevent outbreaks. The hospital has an additional financial incentive not to run the risk of an increase of the insurance premium due to outbreaks caused by AMR. Finally, the insurer's profits increase if AMR is reduced and outbreaks are prevented, as the insurer will continue to receive premiums but does not need to reimburse as many outbreak costs. This preventive-economic approach changes the incentives on all three stakeholder sites towards the main interest of the patient.

Next steps

Before implementing the TIM, key questions remain to be answered; some of which have been raised in a stakeholder meeting where all three parties were represented. We believe it is vital to assess the willingness-to-pay of hospital management for this proposed system: what percentage of the hotel costs would they be willing to spend on insurance premiums? Additionally, a major hurdle is to convince insurers that this is a vital business model, especially since there is currently no sound and complete data to support this system. Risk models need to be developed to predict hospital outbreaks, to be used as a basis for the insurance premium calculation. Current projections of the prevalence of MDRO show an increasing trend¹², which can lead insurers to conclude risks are too difficult to curtail. To critically assess the investments required to implement the TIM, we believe it is vital to apply a broad, societal perspective, where not only the direct effects on hospital outbreaks are included, but also delays in care due to these outbreaks, the long-term loss of effective antibiotics due to AMR¹² and increased morbidity and mortality¹¹. Whether these long-term benefits outweigh the short-term investments, such as implementation costs and, potentially, increased spending on diagnostic tests for the hospital, remains to be investigated further. An implementation trial in several hospitals, combined with health-economic analyses, would be important to assess the incremental value of the TIM for the health system and its feasibility from an insurer's perspective. Although we focussed on hospitals in this commentary, it may also be possible to include other inpatient facilities, such as nursing homes in the model.

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CHAPTER

11

General Discussion

Principle findings of this thesis

Part I: aspects of tests in practice

In part I of this thesis I considered economic aspects of three different settings where tests play an important role. The School Health System (SHS) provides an important framework to reach children from a young age and screen them for various illnesses, as well as to educate them on health-related matters. Although the tasks of the SHS vary between countries, in almost all European countries school doctors and nurses screen for height, weight, vision, hearing and dental problems. The majority of countries also include vaccinations, infection control and hygiene⁵⁶. In a recent survey on the SHS, many professionals in this field indicated that a shortage of staff is a problem⁵⁶. In chapter 2, a survey was sent out to professionals in 31 countries to estimate the number of staff and their salaries, which were expected to be the main driver of SHS expenditure. Additionally, I looked at various online sources, such as published literature and online sources such as the system of health accounts⁶⁰. However, I was able to make an estimation on SHS expenditure on workforce for only five countries. Per 1,000 pupils, I estimated this to range from €43,000 in Estonia to €195,300 in Norway (corrected for purchasing power parities). This constitutes a minor part in total spending on healthcare: 0.16% - 0.69%. I conclude in chapter 2 that there is the major gap in knowledge regarding the spending on SHS in Europe, which may be problematic in light of the maintenance and further development of SHSs across Europe. Chapter 3 focusses on the costs associated with two outbreaks of vancomycin-resistant *Enterococci* (VRE) in the University Medical Center Groningen (UMCG). I used data from various sources in the hospital as well as interviews, to identify and quantify the costs resulting from tests, closed beds (opportunity costs), cleaning, additional personnel, and patient isolation. During the first outbreak, in 2017, tests were the major driver of the outbreak-related costs, constituting almost two thirds of the total costs. However, the second outbreak in 2018 was much shorter than the first: due to an early and aggressive screening, the outbreak was detected in an early stage and quickly controlled, reducing the clinical impact of the outbreak and the total costs. This illustrates the importance of using tests to have a good overview of the pathogens carried by patients. In chapter 4, I looked at a very specific case: periprocedural management for patients on vitamin K antagonists (VKAs). I combined various data sources in one model: INR changes, which are monitored intensively in these patients, and various risk scores for bleeding and strokes. These risk scores are applied commonly in clinical practice and combine data from various tests, such as blood pressure, INR and renal function, but also patient characteristics such as age and sex^{111,411}. Around five days before a surgical procedure, VKA treatment is interrupted if the procedure-related bleeding risk is high. Bridging therapy may aid in this period of interrupted treatment to prevent strokes, but also significantly increases the bleeding risk¹⁰⁹. I developed an easily interpretable matrix which can guide clinicians in their decision to bridge or not to bridge, considering the quality-adjusted life expectancy. The results predict that for patients at high risk of bleeding, bridging therapy is highly unlikely to be beneficial. For patients with a low risk of bleeding and a very high risk of strokes, I found a significant benefit of bridging. However, these patients are expected to be very rare, as most patients at a high risk of stroke will also have a high risk of bleeding. This modelling study is an example on how data gathered using various tests can be combined to optimize patient management.

Part II: methods to assess the value of diagnostics

The value of diagnostics, primarily of respiratory-tract infections, was the focus of part II. This includes the value for money, or the cost-effectiveness, but very specifically also

the value in containing, or even reducing, antimicrobial resistance (AMR). In chapter 5 I reviewed 70 health-economic analyses of diagnostics for infections of the respiratory tract, covering influenza, pneumonia, pharyngitis, and tuberculosis, among others. Most included studies used relatively simple models to assess the cost effectiveness, such as decision trees, with short time horizons and non-generalizable outcome measures, instead of quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs). AMR is also an important aspect in this area that was only included in a minority of the papers, mainly three approaches were used for this: adding a 'societal cost' to all antibiotic prescriptions; assuming a fixed percentage of infections were resistant; or dynamic resistance, varying over the modelled time horizon, e.g., using antibiotic consumption. Considering health-economic guidelines, there is room for improvements in the model design and reporting of CEAs of diagnostics⁵⁰. To aid in this process, I provided eight recommendations in chapter 6, which were linked to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist and reference case for economic evaluation^{50,238}. The symptoms patients experience, the clinical setting, locations of test sampling and analysis, and diagnostic algorithms should be clearly reported. The used time horizon should reflect the time horizon used to model the treatment after the diagnostic pathway. QALYs or DALYs should be used as the clinical outcomes, but may be combined with other relevant outcomes, such as real options value. If the number of tests using the same equipment can vary, the economy of scale should be considered. An understandable graphical representation of the various diagnostic algorithms should be provided to understand the results, such as an efficiency frontier. Finally, the budget impact and affordability should be considered. Many of these recommendations were applied in chapter 7, where I assessed the value of hypothetical POC tests in primary care in the Netherlands. Even though bacteria are estimated to cause a minority of community-acquired acute respiratory tract infections (CA-ARTI) cases in Europe, CA-ARTI are a major driver of antibiotic consumption in primary care, accounting for around 40% of all antibiotic prescriptions by general practitioners (GPs)²⁶². We aimed to quantify the investments required for a large-scale rollout of improved point-of-care diagnostics in Dutch primary care effective at reducing antibiotic prescriptions. We developed a model that simulates consultations for CA-ARTI at GP practices in the Netherlands and compared a scenario where GPs test all CA-ARTI patients with a hypothetical diagnostic strategy to continuing the current standard of care for the years 2020-2030. The simulation was run in the newly developed Modelling the Economics of Respiratory tract Infections and AMR (MERIAM) model, an individual-based simulation model for CA-ARTI. MERIAM is an innovative model which enabled forecasts of AMR, focussing specifically on predicting resistance of *Streptococcus pneumoniae* to penicillins, which are the most prevalent cause of bacterial CA-ARTI and most prescribed antibiotic^{17,263,266}. The diagnostic algorithm increased the total costs of GP consultations for CA-ARTI with 7.7% or with 18% over 10 years, at price points of €5 or €10 per consulting patient, respectively. In these simulations, the forecast increase in resistance of *S. pneumoniae* resistance against penicillins would be partly contained.

Part III: improving development, assessment, and financing

In part III, I considered the development, assessment, and financing of tests in the health-care system, partly by looking to other fields. Chapter 8 concerns a memorandum of initiative, which was submitted to the Dutch Tweede Kamer (Parliament) and minister of health by a member of parliament. This memorandum promoted the application of real option analysis (ROA) for strategies used to counter infectious diseases. Its primary focus was on new vaccines and antibiotics, but the proposed framework could be used to consider the development, assessment, and implementation of various microbiological

tests as well. ROA can aid decision makers in considering time and scenarios. Decisions in healthcare are rarely ‘yes’ or ‘no’ questions, they can be regarded as ‘right now’ or ‘maybe later’ questions. ROA can be used to value specific investments, even if they are not used or needed immediately. A common (and very Dutch) example would be a dike: dikes are not built for common water levels measured every year, they are built for extreme floods, which may occur once every millennium or even less frequently⁴¹². I argued that a similar perspective is required for the inherent uncertainty regarding infectious disease outbreaks, whether this concerns a pandemic or the development of multi-drug-resistant bacteria. For vaccines this means we should invest in the development of platform technologies which can be tailored to new diseases, regarding the assessment, we need to consider various scenarios regarding the incidence of the disease against which a vaccine protects, and regarding the procurement, we need to consider the availability of various types of vaccines during outbreaks. For novel antibiotics, we should incentivize the pharmaceutical industry to invest in research by offering subscription services to antibiotics that are ‘saved’ for when we need them. Finally, for our testing infrastructure, ROA can be used to assess the value of an AMR monitoring programme, an early-warning system for potential pandemic diseases or the value of being able to screen the whole population in case of a pandemic. In chapter 9, I considered the EF methodology, using a model for a novel drug to treat heart failure: sacubitril/valsartan. The EF approach is a method to assess the cost effectiveness of interventions; in Germany the EF is the primary method to decide whether a new intervention is cost effective^{323,324}. The EF has the advantage that, next to QALYs, many different types of outcomes can be used, and that the willingness-to-pay threshold is derived directly from the frontier, which means decision makers do not need to set a threshold. A major disadvantage of this technique was also illustrated in this chapter, which is the difficulty to compare a novel, innovative strategy (such as sacubitril/valsartan) to established, much less expensive, strategies. In this case, an EF could not be created, and the willingness-to-pay threshold could not be established. The main advantage of this method in the field of diagnostics is to compare and visualize various diagnostic algorithms, using various outcomes relevant to the decision problem. I believe this approach can be used in addition to the standard methods in health economics, such as the incremental cost-effectiveness ratio (ICER) and cost-effectiveness acceptability curves (CEACs). In Chapter 10, I proposed a tripartite insurance model (TIM) to create incentives to prevent outbreaks of resistant infections in the hospital setting, by connecting the hospitals, laboratories, and a casualty insurer. If the TIM is applied, the hospital negotiates a lump-sum contract with a laboratory to run the microbiological tests in the hospitals, including screening and diagnostics. This removes a barrier to run a test for clinicians, as they do not have to pay for each individual test. At the same time, the hospital acquires an insurance for the risk of outbreaks, so that part of the costs discussed in chapter 2, such as the opportunity costs of closed beds, are reimbursed in case of an outbreak. This introduces an incentive for the insurer to minimize this risk: the insurer contracts the laboratory to audit the hospital regarding the implementation of infection prevention measures. In this model, the laboratory is not just analysing the test samples, it also provides expertise regarding the interpretation of the results. As discussed in the chapter, many questions remain to be answered and an implementation trial would be beneficial to further develop the TIM.

Key messages

This thesis uses examples from a broad collection of tests to research the health-economic aspects of testing strategies: from simple tests at primary schools to advanced genetic tests

used in the hospital, to clinical algorithms used by clinicians which are basically free to implement. Screening can be used for the whole population, as is the case for the various tests included in the SHS, or for very specific groups, for example to prevent the spread of VRE through the hospital. When antibiotics are considered, diagnostic tests offer value as they can lead to more appropriate prescriptions²⁶⁷ and, in time, reduce AMR^{275,288}. Finally, monitoring can be done to optimise treatment for an individual patient, but also for the benefit of the whole population, where tests can inform public health decisions, for example related to AMR or infectious diseases capable of causing large-scale outbreaks. The testing infrastructure and organisation is an essential part of our healthcare system. To prioritize decisions and further improve this area, it is critical to have a better overview of these organisational aspects, regardless of whether this is performed within the SHS, at POC or within a large-scale laboratory.

As testing does not provide direct improvements for patient health in most cases, different ways to assess its value may be required. When considering the economic value of diagnostic testing using CEA, there are some specific issues to be addressed. CEA are usually used to assess mutually exclusive strategies; however, diagnostic algorithms offer a lot of flexibility not applicable to many other strategies in healthcare. Diagnostics within these algorithms can be combined in various ways, either sequentially or simultaneously, they can be sampled and analysed at various locations, e.g., at POC or within a large-scale laboratory, and they can be followed by several treatment options. The specifics of these algorithms can affect both the costs and the outcomes of the CEA and therefore, the characteristics should be reported in a transparent manner. To compare various diagnostic algorithms, the EF approach can be helpful.

New European regulations: risks and opportunities

In the next few years, we may see the effects of the new regulations from the European Union (EU) for market entry of non-pharmaceutical medical innovations: the medical device regulation (MDR) and in-vitro diagnostics regulation (IVDR). They aim to improve patient safety by requiring more robust clinical evidence before a new product can be brought to market. Patient safety is important - most would agree that the example in the introduction of this thesis should be avoided⁴⁵ - but these new barriers may also limit patient access to new technologies. The collection of clinical data can be expensive and takes time. During crises, adapting to new situations quickly is essential. An example is the PCR test developed by the University Medical Center Groningen during the VRE outbreak of 2017, as discussed in chapter 2. Initially, a commercial PCR device was used to sequence patient and environmental samples, however, this device only had 16 slots and required a lot of manual labour. During the outbreak, an alternative approach was developed, which could be analysed on regular PCR devices using an automated approach. Although the IVDR has an exception for diagnostics used solely within health institutions⁴¹³, whether this approach would still be feasible under the IVDR remains to be seen - this legal question certainly is outside of the scope of this thesis. For the COVID-19 pandemic, EU countries could approve the use of specific tests for use within their country as an emergency response⁴¹⁴. Very early in the COVID-19 pandemic, PCR tests were able to identify infected patients, but of course these methods had not gained market entry under the IVDR. Additionally, there was a global shortage of reagents required to perform the recommended tests, so various experimental, alternative approaches were developed to deal with the shortages and to be able to adequately treat patients presenting with respiratory complaints in hospitals^{4,415,416}. Later during the pandemic rapid antigen tests to detect

SARS-CoV-2 could enter the market before gaining EU market authorization, using national emergency procedures.

However, patient access regarding tests is broader than gaining market access: they should also be implemented in clinical practice. As the clinical evidence supporting the introduction of novel tests will be more extensive under the new regulations, this may be used to inform the implementation. As discussed in chapter 5, the long-term clinical evidence supporting economic evaluations of diagnostics is lacking. After the IVDR comes into effect, I expect more evidence to be available for decision makers regarding the benefits for clinical patient outcomes, as opposed to only technical evidence such as the sensitivity and specificity of tests. Using standard health-economic methods, the clinical effects can subsequently be extrapolated to longer time horizons³³⁰. In chapter 5, I also recommend companies to collect quality-of-life data during clinical trials to be able to calculate the costs per QALY. Just as in the market for pharmaceuticals, this enables policy makers and clinicians to compare the various available tests using CEAAs and to implement the most cost-effective options. Additionally, the use of CEAAs also enables comparisons between tests and other technologies, whether these are pharmaceuticals, medical implants, surgical procedures, or any other health technology.

Further considerations linked to health technology assessment

This thesis covered most topics that should be included in an health technology assessment (HTA) according to the domains of the HTA Core Model, as discussed in the introduction of this thesis (see Box 11.1 for a summary)³⁸. The first two points are rather straightforward; as described above, the technical characteristics have traditionally been the focus for new tests. Due to the beforementioned introduction of the IVDR, I expect the quality of safety and clinical effectiveness data to improve. The clinical effectiveness data should increasingly include relevant clinical outcomes for patients, such as QALYs. Chapter 4 focussed exclusively on optimizing clinical effectiveness, in this case using quality-adjusted life expectancy as an outcome measure. In chapter 6, several recommendations regarding the costs and economic evaluation are provided. Ethical aspects are highly relevant for the SHS, as described in chapter 2, where providing access to basic health care for all pupils, regardless the financial situation or health literacy of their parents, can aid in providing a more equitable start⁵³. Another ethical aspect is AMR^{20,417}. As mentioned in the introduction, AMR is both an inter-generational and a global issue²⁰. An inter-generational issue as AMR develops on the long term, I would argue current generations have a responsibility to not leave future generations with a plethora of multi-resistant bacteria which are difficult to treat. And also a global issue as resistant bacteria cross borders, carried by people, also countries that are doing relatively well, such as the Netherlands, should not ignore the resistance rates in other countries⁸⁵. Related to the availability of antibiotics, there needs to be a right balance between excess and access: still many people die globally because they do not have access to antibiotics¹⁴. I elaborate further on the inclusion of AMR in economic analyses below.

The organizational aspects of tests are rather complicated, and they should be explained well in CEAAs, as recommended in chapter 6. In chapter 2 the economic aspects of one of the most important systems for screening and early diagnosis is the focus: the SHS⁵⁶. The data availability regarding SHS staff and remuneration was lacking in most European countries, which I consider to be a risk for informed decision-making as these aspects need to be clear when performing an HTA. In chapter 10 I suggest how the organisation of tests in the hospital setting can be tailored to deal with AMR more adequately by incen-

Box 11.1. Domains HTA Core Model

1. Health problem and current use of technology
2. Description and technical characteristics
3. Safety
4. Clinical effectiveness
5. Costs and economic evaluation
6. Ethical analysis
7. Organizational aspects
8. Patient and social aspects

tivizing collaboration on this topic between various stakeholders.

The information gathered when testing is used to inform clinical decision-making. To maximize the impact, both the clinician and the patient need to be able to interpret the test result and to use the information to decide on the consecutive steps. Especially clinical studies focussed on the adequate

prescription of antibiotics consider this and, in some cases, combine the diagnostic intervention with professional training for clinicians¹³⁷. How does diagnostic-driven antibiotic prescribing affect care-seeking behaviour by patients on the long term? Does the additional information on the aetiology of a patient's complaints increase the likelihood to consult a physician in the future? Or will patients be less likely to seek care when the probability of being prescribed an antibiotic is lower? Decision making based on more informative diagnostics may have improve patient adherence to the treatment that follows: a specific element of value described elsewhere, but inconsistently used in CEA^s¹⁰⁵. The final HTA domain, legal aspects, was discussed previously.

Eventually, the aim of HTA should be to decide on the implementation of certain tests. By definition, this requires input from various scientific fields and as discussed above, there are various barriers and uncertainties to consider³⁷. The currently-running, EU-funded VALUE-Dx research project may set the stage for HTAs of diagnostics into the future⁴¹⁸. Within the consortium all factors of value are considered for various diagnostics used for patients with respiratory tract infections and are expected to reduce antibiotic prescribing. The technical characteristics of all relevant diagnostics are thoroughly reviewed. Two clinical trials assess the value for patients seeking care in the community setting, with adequate follow-up to include the major elements of value, such as health outcomes, productivity losses and adherence¹⁰⁵. A trial-based health-economic model closely follows the costs incurred during the trial, while a broader health-economic framework is used to calculate the cost effectiveness from the long-term, societal perspective. The organizational, patient, and social aspects related to changing clinical practice are thoroughly assessed using qualitative research methods and the regulatory issues are investigated using interviews with national authorities. MERIAM, the model described in chapter 7 of this thesis will form the basis of the health-economic framework of VALUE-Dx and can be used to assess patient outcomes, such as QALYs, and public-health outcomes, such as the development of AMR. In further research also the social aspects, such as future care-seeking behaviour, can be included in the model to inform decision makers and make strategic decisions to transform clinical practice⁴¹⁸.

Towards tailored testing

More frequent testing requires significant investments, as described in chapters 3 and 7. Especially when screening, testing more will result in more positive findings and even more costs, which negatively impact the cost effectiveness. Additionally, as discussed in

chapter 5, the cost-effectiveness of a diagnostic strategy is highly dependent on the disease incidence. To construct cost-effective testing strategies, it may be vital to look towards improved predictive models that aid in testing tailored populations that benefit from the test result, i.e., a population at increased risk of a certain condition. For example, the risk scores for stroke and bleeding used in chapter 4 are very inexpensive to apply and are used frequently in clinical decision-making to improve patient outcomes. Little *et al*, compared care-as-usual, a clinical score and an antigen test combined with a clinical score for patients consulting a GP for acute sore throat in England. They found that the clinical score reduced antibiotic prescribing with 29%, but did not find an additional benefit related to the use of the antigen test²⁷¹. Deciding whom to test may be very important for the testing strategy to remain cost-effective. In essence, testing is all about probabilities: test results change the probability of a patient having a specific condition, which in turn guides treatment decisions. Combining epidemiological data and patient characteristics may enable testing algorithms more tailored to the individual, and, as less tests need to be performed, improved cost effectiveness. As more health data become available and accessible, for example through large-scale cohort studies such as Lifelines⁴¹⁹ and data infrastructure such as Health-RI⁴²⁰, data scientists gain the tools to build better models to predict diseases. These models can be used to quantify the added value of specific tests for individual patients; using tests to fill in missing data points will change the probability of having the disease and be informative to estimate the effectiveness of specific treatment options.

For infections, the probability that a disease is caused by a certain virus, bacterium or parasite changes depending on the incidence within the community. Incidence data of different infections in the population can be incorporated in predictive models and combined with patient symptoms and characteristics to estimate the disease aetiology before any tests. This approach was researched for febrile illness in South-East Asia, where regional surveillance data for diseases like dengue, scrub typhus, influenza and leptospirosis were collected using a relatively expensive multiplex PCR in the hospital setting to inform empirical treatment in rural areas²⁴⁸. Although the use of surveillance data only was not deemed to be cost-effective, combining surveillance data with CRP testing was considered to be highly cost-effective and was estimated to prevent hundreds of deaths while reducing antibiotic prescribing²⁴⁸. Further research could focus on the development and implementation of flexible diagnostic algorithms for infectious disease that recommend tests and treatment in clinical practice based on the real-time aetiology of infections, while considering the overall cost effectiveness. This approach could also allow for more flexible antibiotic treatment options, as local resistance rates could feed into the system, preventing the use of antibiotics a patient is likely to be or become resistant to. Privacy of patients remains an important issue to consider in the context of large-scale data collection but should not be a major barrier as aggregated test results should not be traceable to individuals. Of course, there are costs associated with gathering sufficient surveillance data as well, but these data may serve several purposes, as they are important in informing policies regarding AMR and pandemic preparedness, which are described in more detail below.

Preventing a post-antibiotic era

In chapter 1, I introduced warnings from experts on a post-antibiotic era^{13,14}: a future which is difficult to predict, but would be detrimental to healthcare as we know it today. As can be seen from our forecasts of resistance of *pneumococci* to broad-spectrum penicil-

lins in chapter 6, this is not something that seems likely if only current trends are extrapolated in the Netherlands. Globally however, in some countries resistance rates for specific bacterium-antibiotic pairs exceed 90%⁴²¹. Considering the low number of new antibiotics in development^{422,423}, the development and spread of these resistant bacteria needs to be prevented. In many cases, AMR develops by chance, as random mutations introduce a benefit to survival to resistant organisms⁹. This is the case for tuberculosis, caused by *Mycobacterium tuberculosis*, for which already variants exist that are resistant to all known antibiotics^{9,424}. Surveillance of AMR is an important aspect to be able to act on changes in the population, e.g., by changing treatment guidelines. Looking at national resistance rates, the data used to support decision making currently is rather limited⁴²⁵: they are derived from a limited number of samples and primarily from the hospital setting. Implementing tests capable of detecting resistant organisms in a way where the collected data do not only benefit the individual patient but can also be used for AMR surveillance on the population level, can be highly beneficial. These data can be used to develop the personalized testing algorithms described earlier, to inform empirical treatment decisions, to develop improved AMR prediction models and to draft AMR-related policy.

In chapter 6 of this thesis, we discussed the value of diagnostics to combat AMR and advocated for a more strict adherence of CEAs of diagnostics to the reference case for economic evaluations⁵⁰: including that the main outcome should be an ICER expressed as costs per QALY or DALY. Apparently contradictory to our own recommendation, chapter 7 is a study that uses costs and reductions of AMR as the main outcome of interest. Here we used previously detailed methods to build a model which forecasts the effects of CRP testing on AMR^{12,284}. However, the assumption was made that there was no change in QALYs between the CRP-testing scenario and the current standard-of-care, meaning that an ICER is impossible to calculate as the denominator is zero. Two approaches could have worked to be able to enable the calculation of an ICER: firstly, previous research has shown that it is possible to express lost health due to AMR in DALYs^{11,254} and cost-effectiveness outcomes²⁸⁴, so this approach could be followed. However, as this approach is focussed on the hospital setting, it may not be a valid approach for the community setting. Secondly, clinical trials could show differences in QALYs, albeit marginal, which is an approach tried in the VALUE-Dx project, the results of which will be incorporated in the health-economic model in the future. Still, I would argue that the ethical considerations discussed in the part on HTA warrant the approach taken in chapter 7. There is inherent value in reducing AMR, as this contributes to preventing the worst-case scenario, a post-antibiotic era. Dorgali *et al.* previously estimated that the willingness to pay for containing AMR in the United Kingdom was around £8.35 billion annually²⁹³. To account for the uncertainty in the future development of AMR, I suggest the use of ROA. Performing a ROA for any new intervention that affects antibiotic consumption may not be a feasible approach for HTAs, hence I would suggest a two-step approach. Start with a ROA: consider scenario analyses regarding the long-term effects of AMR, quantify the associated costs, and use this to develop a long-term mission on AMR. Similar to the Paris climate agreement, where the international community agreed to limit global warming to 1.5 °C above pre-industrial levels⁴²⁶, specific goals to contain AMR should be set. Within this mission-oriented approach, budgets should be structured in a way so that the long-term AMR goals can be reached²¹. Any innovative intervention that aids in reaching these goals should be assessed based on its relative contribution and investment, i.e., the AMR reduction in relation to the additional costs. The analysis performed in chapter 7 would fit in such a framework and similar methods could be incorporated in other CEAs without too much effort. Additionally, the EF approach as used in Germany, discussed in chapter

9, inherently considers outcome measures other than QALYs and could be used to relate costs to changes in AMR for various strategies.

Preparing for the next pandemic

This thesis started with the massive impact of the COVID-19 pandemic on health and the economy. Next to the recommendations related to ROA in chapter 8, what can the findings in this thesis contribute to preparing for the next pandemic? As mentioned, having an adequate testing infrastructure is an important aspect of pandemic preparedness, while this infrastructure can also be used during “inter-pandemic” times. In the coming years, the EU is expected to invest heavily in cross-border health and pandemic preparedness⁴²⁷. At the time of writing, the EU is working on the Health Emergency preparedness and Response Authority (HERA), an organization to “improve Europe’s capacity and readiness to respond to cross-border health threats and emergencies”⁴²⁸. Although this plan is expected to have a broad scope, one of the aspects is expected to be an intensive collaboration with the European Centre for Disease Prevention and Control (ECDC) to improve surveillance of potential pandemic pathogens⁴²⁷. During the COVID-19 pandemic, the ECDC already played an important role in drafting guidelines¹²⁹ and sharing relevant data⁴²⁹. One of the ECDC’s strategic goals for the coming years is to enhance surveillance and emergency preparedness by streamlining epidemiological information from existing systems⁴³⁰. If innovative, widely applied microbiological tests would feed into these surveillance systems, this can be used to identify potential threats faster, enabling authorities to hit hard and early to potentially prevent the next pandemic and related economic and health damage.

Concluding remarks

In this thesis, I covered many aspects related to the economics of testing strategies in healthcare, from the organization of screening tests to the use of diagnostics to combat AMR. It is important to consider the testing infrastructure: where should testing take place, close to the patient or in specialized laboratories; who should perform the test and how are these health professionals organized; and what value do the test results have for public health and how are these data shared? These are some of the issues to be considered for HTAs of tests. From a cost-effectiveness perspective, the underlying clinical data should be sufficient to compare the testing strategy to other health technologies, by using generalizable health outcomes, such as QALYs, and by using sufficiently long time horizons. In a CEA, the costs for society are related to the clinical benefits for patients, but for microbiological tests, the clinical value is broader than that, especially if tests can identify specific pathogens. The collected data can be used to make public health decisions, for example by updating treatment guidelines for infectious disease and by responding to AMR and potentially pandemic pathogens. These data could feed into decision models that are able to support clinical decision making by tailoring testing strategies to individual patients, thereby improving the cost-effectiveness.

Back matter



References

1. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis.* 2020;20(5):533-534. doi:10.1016/S1473-3099(20)30120-1
2. Centers for Disease Control and Prevention (U.S.), ed. Interim pre-pandemic planning guidance : community strategy for pandemic influenza mitigation in the United States : early, targeted, layered use of nonpharmaceutical interventions. Published online February 2007. <https://stacks.cdc.gov/view/cdc/11425>
3. World Health Organization. Transmission of SARS-CoV-2: implications for infection prevention precautions. Published July 9, 2020. Accessed May 26, 2021. <https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions>
4. van Ark E, Strop JH. Hoe "testen, testen, testen" stukliep op een muur van eigenbelang. *Follow the Money - Platform voor onderzoeksjournalistiek.* <https://www.ftm.nl/artikelen/coronatesten-belangen-arts-microbiologen>. Published September 11, 2020. Accessed September 11, 2020.
5. Kochańczyk M, Lipniacki T. Pareto-based evaluation of national responses to COVID-19 pandemic shows that saving lives and protecting economy are non-trade-off objectives. *Sci Rep.* 2021;11(1):2425. doi:10.1038/s41598-021-81869-2
6. Postma MJ. Wat kost de coronacrisis Nederland? Rijksuniversiteit Groningen. Published January 26, 2021. Accessed June 22, 2021. <https://www.rug.nl/letta/blog/wat-kost-de-coronacrisis-nederland-26-01-2021>
7. Centraal Bureau voor de Statistiek. Economie krimpt met 0,1 procent in vierde kwartaal 2020. Centraal Bureau voor de Statistiek. Accessed May 31, 2021. <https://www.cbs.nl/nl-nl/nieuws/2021/07/economie-krimpt-met-0-1-procent-in-vierde-kwartaal-2020>
8. Dohmen J. Coronacrisis kost jaarlijks €12 mrd aan verloren groei. Financieel Dagblad. Published August 20, 2021. Accessed October 21, 2021. <https://fd.nl/economie-politiek/1408631/coronacrisis-kost-jaarlijks-12-mrd-aan-verloren-groei>
9. Davies J, Davies D. Origins and Evolution of Antibiotic Resistance. *Microbiol Mol Biol Rev MMBR.* 2010;74(3):417-433. doi:10.1128/MMBR.00016-10
10. OECD. OECD Health Statistics. Accessed May 26, 2021. <https://stats.oecd.org/Index.aspx?ThemeTreeId=9>
11. Cassini A, Höglberg LD, Plachouras D, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect Dis.* 2019;19(1):56-66. doi:10.1016/S1473-3099(18)30605-4
12. Hashiguchi TCO, Ouakrim DA, Padgett M, Cassini A, Cecchini M. Resistance proportions for eight priority antibiotic-bacterium combinations in OECD, EU/EEA and G20 countries 2000 to 2030: a modelling study. *Eurosurveillance.* 2019;24(20):1800445. doi:10.2807/1560-7917.ES.2019.24.20.1800445
13. Smith R, Coast J. The true cost of antimicrobial resistance. *BMJ.* 2013;346:f1493. doi:10.1136/bmj.f1493
14. Roope LSJ, Smith RD, Pouwels KB, et al. The challenge of antimicrobial resistance: What economics can contribute. *Science.* 2019;364(6435):eaau4679. doi:10.1126/science.aau4679
15. Outterson K, Rex JH. Evaluating for-profit public benefit corporations as an additional structure for antibiotic development and commercialization. *Transl Res.* 2020;220:182-190. doi:10.1016/j.trsl.2020.02.006
16. Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC Infect Dis.* 2014;14(1):13. doi:10.1186/1471-2334-14-13
17. Ieven M, Coenen S, Loens K, et al. Aetiology of lower respiratory tract infection in adults in primary care: a prospective study in 11 European countries. *Clin Microbiol Infect.* 2018;24(11):1158-1163. doi:10.1016/j.cmi.2018.02.004
18. World Health Organization. *Global Action Plan on Antimicrobial Resistance;* , 2016. Accessed April 27, 2021. <https://www.who.int/publications-detail-redirect/9789241509763>
19. Dik JWH, Poelman R, Friedrich AW, et al. An integrated stewardship model: antimicrobial, infection prevention and diagnostic (AID). *Future Microbiol.* 2015;11(1):93-102. doi:10.2217/fmb.15.99
20. Coast J, Smith RD. Distributional Considerations in Economic Responses to Antimicrobial Resistance. *Public Health Ethics.* 2015;8(3):225-237. doi:10.1093/phe/phv004
21. Mazzucato M. *Mission Economy: A Moonshot Guide to Changing Capitalism.* Allen Lane, an imprint of Penguin Books; 2021.
22. Keizer J, Braakman-Jansen LMA, Kampmeier S, et al. Cross-border comparison of antimicrobial resistance (AMR) and AMR prevention measures: the healthcare workers' perspective. *Antimicrob Resist Infect Control.* 2019;8(1):123. doi:10.1186/s13756-019-0577-4
23. Vereniging Innovatieve Geneesmiddelen. *Boston by the North Sea;* , 2021. Accessed September 7, 2021. <https://vig-platform-axazmkc.netdna-ssl.com/production/documents/Boston-by-the-North-Sea.pdf.pdf>
24. Wald N, Law M. Medical screening. In: *Oxford Textbook of Medicine.* Oxford University Press; 2010:94-108. doi:10.1093/med/9780199204854.003.030302_update_002
25. Nederlands Huisartsen Genootschap (NHG). Cardiovasculair risicomangement. NHG-Richtlijnen. Accessed May 31, 2021. <https://richtlijnen.nhg.org/standaarden/cardiovasculair-risicomangement>
26. Merriam-Webster. Definition of DIAGNOSIS. Merriam-Webster. Accessed March 2, 2020. <https://www.merriam-webster.com/dictionary/diagnosis>
27. van der Pol S, Garcia PR, Postma MJ, Villar FA, van Asselt ADI. Economic Analyses of Respiratory Tract Infection Diagnostics: A Systematic Review. *Pharmacoeconomics.* Published online July 15, 2021. doi:10.1007/s40273-021-01054-1
28. Wells P, Hirsh J, Anderson D, et al. Accuracy of clinical assessment of deep-vein thrombosis. *The Lancet.* 1995;345(8961):1326-1330. doi:[https://doi.org/10.1016/S0140-6736\(95\)92535-X](https://doi.org/10.1016/S0140-6736(95)92535-X)
29. Doble B, Tan M, Harris A, Lorgelly P. Modeling companion diagnostics in economic evaluations of targeted oncology therapies: systematic review and methodological checklist. *Expert Rev Mol Diagn.* 2015;15(2):235-254. doi:10.1586/14737159.2014.929499
30. Goble JA, Rocafort PT. Point-of-Care Testing: Future of Chronic Disease State Management? *J Pharm Pract.* 2017;30(2):229-237. doi:10.1177/0897190015587696
31. Plebani M. Clinical laboratories: production industry or medical services? *Clin Chem Lab Med CCLM.* 2015;53(7):995-1004. doi:10.1515/cclm-2014-1007
32. Plexus. *Business Case Ersteljinsdiagnostiek.* Accessed June 2, 2021. https://www.eumonitor.eu/9353000/1/j4nvg5kjg27kof_j9vvik7m-1c3gyxp/vj7xno0hbwm/f/blg213597.pdf
33. Kelsey FO. Thalidomide update: regulatory aspects. *Teratology.* 1988;38(3):221-226.

34. College ter Beoordeling van Geneesmiddelen. CBG viert 900e Collegevergadering - Nieuwsbericht - College ter Beoordeling van Geneesmiddelen. Published April 6, 2018. Accessed June 2, 2021. <https://www.cbg-meb.nl/actueel/nieuws/2018/04/06/cbg-viert-900e-collegevergadering>
35. Chang AY, Cowling K, Micah AE, et al. Past, present, and future of global health financing: a review of development assistance, government, out-of-pocket, and other private spending on health for 195 countries, 1995–2050. *The Lancet*. 2019;393(10187):2233-2260. doi:10.1016/S0140-6736(19)30841-4
36. Rascati K. *Essentials of Pharmacoconomics*. Wolters Kluwer; 2013. Accessed June 2, 2021. <http://ebookcentral.proquest.com/lib/rug/detail.action?docID=4625043>
37. O'Rourke B, Oortwijn W, Schuller T, Group the IJT. The new definition of health technology assessment: A milestone in international collaboration. *Int J Technol Assess Health Care*. 2020;36(3):187-190. doi:10.1017/S0266462320000215
38. Kristensen FB, Lampe K, Wild C, Cerbo M, Goettsch W, Becla L. The HTA Core Model®—10 Years of Developing an International Framework to Share Multidimensional Value Assessment. *Value Health*. 2017;20(2):244-250. doi:10.1016/j.jval.2016.12.010
39. Gabbay J, Walley T. Introducing new health interventions. *BMJ*. 2006;332(7533):64-65.
40. Zorginstituut Nederland. *Richtlijn Voor Het Uitvoeren van Economische Evaluaties in de Gezondheidszorg*; 2015. Accessed January 3, 2018. <https://www.zorginstituutnederland.nl/over-ons/werkwijzen-en-procedures/adviseren-over-en-verduidelijken-van-het-basispakket-aan-zorg/beoordeling-van-geneesmiddelen/richtlijnen-voor-economische-evaluatie>
41. Miller MB, Atrazadeh F, Burnham CAD, et al. Clinical Utility of Advanced Microbiology Testing Tools. *J Clin Microbiol*. 2019;57(9):e00495-19. doi:10.1128/JCM.00495-19
42. Gopalakrishna G, Leeflang MMG, Davenport C, et al. Barriers to making recommendations about medical tests: a qualitative study of European guideline developers. *BMJ Open*. 2016;6(9):e010549. doi:10.1136/bmjopen-2015-010549
43. Abel L, Shinkins B, Smith A, et al. Early Economic Evaluation of Diagnostic Technologies: Experiences of the NIHR Diagnostic Evidence Co-operatives. *Med Decis Mak Int J Soc Med Decis Mak*. 2019;39(7):857-866. doi:10.1177/0272989X19866415
44. Dik JWH, Dinkelacker AG, Vemer P, et al. Cost-Analysis of Seven Nosocomial Outbreaks in an Academic Hospital. *PLOS ONE*. 2016;11(2):e0149226. doi:10.1371/journal.pone.0149226
45. Stoltenberg L. *All Meshed up: From Manderin Bag to Medical Implant*. AVROTROS; 2018. Accessed April 26, 2021. https://www.youtube.com/watch?v=X4gX9z5O_dE
46. Dick K. *The Bleeding Edge*. Netflix; 2018. Accessed June 7, 2021. <https://www.netflix.com/nl-en/title/80170862>
47. Ministerie van Algemene Zaken. Handreiking medische hulpmiddelen. Published November 30, 2018. Accessed June 7, 2021. <https://www.rijksoverheid.nl/documenten/publicaties/2017/12/12/handreiking-medische-hulpmiddelen>
48. Melvin T, Torre M. New medical device regulations: the regulator's view. *EFORT Open Rev*. 2019;4(6):351-356. doi:10.1302/2058-5241.4.180061
49. Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement. *PharmacoEconomics*. 2013;31(5):361-367. doi:10.1007/s40273-013-0032-y
50. Wilkinson T, Sculpher MJ, Claxton K, et al. The International Decision Support Initiative Reference Case for Economic Evaluation: An Aid to Thought. *Value Health*. 2016;19(8):921-928. doi:10.1016/j.jval.2016.04.015
51. Case A, Fertig A, Paxson C. The lasting impact of childhood health and circumstance. *J Health Econ*. 2005;24(2):365-389. doi:10.1016/j.jhealeco.2004.09.008
52. Arpino B, Gumà J, Julià A. Early-life conditions and health at older ages: The mediating role of educational attainment, family and employment trajectories. *PLOS ONE*. 2018;13(4):e0195320. doi:10.1371/journal.pone.0195320
53. Lantz PM, House JS, Mero RP, Williams DR. Stress, Life Events, and Socioeconomic Disparities in Health: Results from the Americans' Changing Lives Study. *J Health Soc Behav*. 2005;46(3):274-288. doi:10.1177/002214650504600305
54. UN General Assembly. *UN Convention on the Rights of the Child (UNCRC)*; 1989. Accessed April 18, 2018. <https://www.unicef.org.uk/what-we-do/un-convention-child-rights/>
55. Venkataramani AS, Brigelj R, O'Brien R, Chatterjee P, Kawachi I, Tsai AC. Economic opportunity, health behaviours, and health outcomes in the USA: a population-based cross-sectional study. *Lancet Public Health*. 2016;1(1):e18-e25. doi:10.1016/S2468-2667(16)30005-6
56. Jansen DEMC, Visser A, Vervoort JPM, et al. *School and Adolescent Health Services in 30 European Countries: A Description of Structure and Functioning, and of Health Outcomes and Costs*; 2018. http://mocha.cci.ac.uk/wp-content/uploads/Deliverable-173.1_Final-report-on-the-description-of-the-various-models-of-school-health-services-and-adolescent-health-services-1.pdf
57. Blair M, Alexander D, Rigby M. The MOCHA Project: Origins, Approach and Methods. In: *Issues and Opportunities in Primary Health Care for Children in Europe*. Emerald Publishing Limited; 2019:1-12. doi:10.1108/978-1-78973-351-820191001
58. Jansen D, Vervoort JPM, Visser A, et al. School Health Services. In: *Issues and Opportunities in Primary Health Care for Children in Europe*. Emerald Publishing Limited; 2019:219-236. doi:10.1108/978-1-78973-351-820191015
59. OECD. Health expenditure indicators. Published online 2019. doi:10.1787/data-00349-en
60. OECD, WHO, Eurostat. *A System of Health Accounts*. OECD Publishing; 2011. doi:10.1787/9789264116016-en
61. Langford R, Bonell CP, Jones HE, et al. The WHO Health Promoting School framework for improving the health and well-being of students and their academic achievement. *Cochrane Database Syst Rev*. 2014;(4):CD008958. doi:10.1002/14651858.CD008958.pub2
62. Ran T, Chattopadhyay SK, Hahn RA. Economic Evaluation of School-Based Health Centers: A Community Guide Systematic Review. *Am J Prev Med*. 2016;51(1):129-138. doi:10.1016/j.amepre.2016.01.017
63. Wang LY, O'Brien MJ, Maughan ED. An Excel Spreadsheet Model for States and Districts to Assess the Cost-Benefit of School Nursing Services. *NASN Sch Nurse*. 2016;31(6):354-363. doi:10.1177/1942602X16659349
64. Guo JJ, Wade TJ, Pan W, Keller KN. School-Based Health Centers: Cost-Benefit Analysis and Impact on Health Care Disparities. *Am J Public Health*. 2010;100(9):1617-1623. doi:10.2105/AJPH.2009.185181
65. Conesa M, Llauradó E, Aceves-Martíns M, et al. Cost-Effectiveness of the EdAI (Educació en Alimentació) Program: A Primary School-Based Study to Prevent Childhood Obesity. *J Epidemiol*. 2018;28(12):477-481. doi:10.2188/jea.JE20170111
66. Keszytus D, Lauer R, Keszytus T, Kilian R, Steinacker JM, "Join the Healthy Boat" Study Group. Costs and effects of a state-wide health promotion program in primary schools in Germany - the Baden-Württemberg Study: A cluster-randomized, controlled trial. *PloS One*. 2017;12(2):e0172332. doi:10.1371/journal.pone.0172332



67. te Velde SJ, Lennert Veerman J, Tak NI, Bosmans JE, Klepp KI, Brug J. Modeling the long term health outcomes and cost-effectiveness of two interventions promoting fruit and vegetable intake among schoolchildren. *Econ Hum Biol.* 2011;9(1):14-22. doi:10.1016/j.ehb.2010.09.001
68. Sköld UM, Petersson LG, Birkhed D, Norlund A. Cost-analysis of school-based fluoride varnish and fluoride rinsing programs. *Acta Odontol Scand.* 2008;66(5):286-292. doi:10.1080/00016350802293978
69. Sayal K, Taylor JA, Valentine A, et al. Effectiveness and cost-effectiveness of a brief school-based group programme for parents of children at risk of ADHD: a cluster randomised controlled trial. *Child Care Health Dev.* 2016;42(4):521-533. doi:10.1111/ccb.12349
70. Vrijen SMC, van Baal PHM, Hoogenveen RT, de Wit GA, Feenstra TL. Cost-effectiveness analyses of health promotion programs: a case study of smoking prevention and cessation among Dutch students. *Health Educ Res.* 2008;23(2):310-318. doi:10.1093/her/cym024
71. Cooper K, Shepherd J, Picot J, et al. AN ECONOMIC MODEL OF SCHOOL-BASED BEHAVIORAL INTERVENTIONS TO PREVENT SEXUALLY TRANSMITTED INFECTIONS. *Int J Technol Assess Health Care.* 2012;28(4):407-414. doi:10.1017/S0266462312000475
72. Trotter CL, Edmunds WJ. Modelling cost effectiveness of meningococcal serogroup C conjugate vaccination campaign in England and Wales. *BMJ.* 2002;324(7341):809. doi:10.1136/bmj.324.7341.809
73. Joint Committee on Vaccination and Immunisation. Statement on HPV Vaccination. Joint Committee on Vaccination and Immunisation; 2018. Accessed March 5, 2019. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/726319/JCVI_Statement_on HPV_vaccination_2018.pdf
74. the European Union for School and University Health and Medicine. EUSUHM - Members. Accessed May 2, 2019. <http://eusuhm.org/index.php/members>
75. Eurostat. Population by age group (tps00010). Published 2019. Accessed January 30, 2019. https://ec.europa.eu/eurostat/data/database?p_p_id=NavTreeportletprod_WAR_NavTreeportletprod_INSTANCE_nPqeVbPXRMnWQ&p_p_lifecycle=0&p_p_state=normal&p_p_mode=view&p_p_col_id=column-2&p_p_col_pos=1&p_p_col_count=2
76. OECD. Inflation (CPI). Published online 2019. doi:10.1787/eee82e6e-en
77. OECD. Purchasing power parities (PPP). Published online 2019. doi:10.1787/1290ee5a-en
78. Eurostat. Wages and labour costs. Published 2018. Accessed February 5, 2019. https://ec.europa.eu/eurostat/statistics-explained/index.php/Wages_and_labour_costs#Gross_wages.2Fearnings
79. Microsoft. Excel.; 2018. Accessed April 10, 2018. <https://www.office.com/>
80. Levinson J, Kohl K, Baltag V, Ross DA. Investigating the effectiveness of school health services delivered by a health provider: A systematic review of systematic reviews. *PLOS ONE.* 2019;14(6):e0212603. doi:10.1371/journal.pone.0212603
81. Thokala P, Devlin N, Marsh K, et al. Multiple Criteria Decision Analysis for Health Care Decision Making—An Introduction: Report 1 of the ISPOR MCDA Emerging Good Practices Task Force. *Value Health.* 2016;19(1):1-13. doi:10.1016/j.jval.2015.12.003
82. Marsh K, IJzerman M, Thokala P, et al. Multiple Criteria Decision Analysis for Health Care Decision Making—Emerging Good Practices: Report 2 of the ISPOR MCDA Emerging Good Practices Task Force. *Value Health.* 2016;19(2):125-137. doi:10.1016/j.jval.2015.12.016
83. OECD. Health Status. OECD.stat. Accessed May 27, 2019. https://stats.oecd.org/index.aspx?DataSetCode=HEALTH_STAT
84. Ahmed MO, Baptiste KE. Vancomycin-Resistant Enterococci: A Review of Antimicrobial Resistance Mechanisms and Perspectives of Human and Animal Health. *Microb Drug Resist.* 2018;24(5):590-606. doi:10.1089/mdr.2017.0147
85. European Centre for Disease Prevention and Control. Antimicrobial resistance. Surveillance Atlas of Infectious Diseases. Published March 19, 2021. Accessed March 19, 2021. <https://atlas.ecdc.europa.eu/public/index.aspx?Dataset=27&HealthTopic=4>
86. Lee AS, White E, Monahan LG, Jensen SO, Chan R, Hal SJ van. Defining the Role of the Environment in the Emergence and Persistence of vanA Vancomycin-Resistant Enterococcus (VRE) in an Intensive Care Unit: A Molecular Epidemiological Study. *Infect Control Hosp Epidemiol.* 2018;39(6):668-675. doi:10.1017/ice.2018.29
87. Kramer A, Schwebke I, Kampf G. How long do nosocomial pathogens persist on inanimate surfaces? A systematic review. *BMC Infect Dis.* 2006;6:130. doi:10.1186/1471-2334-6-130
88. Gast KB, van Oudheusden AJG, Murk JL, Stohr JJJM, Buiting AG, Verweij JJ. Successful containment of two vancomycin-resistant Enterococcus faecium (VRE) outbreaks in a Dutch teaching hospital using environmental sampling and whole-genome sequencing. *J Hosp Infect.* 2021;111:132-139. doi:10.1016/j.jhin.2021.02.007
89. Arend van Wijngaarden. Crisisfeer in het UMC Groningen. *Dagblad van het Noorden.* <https://www.dvhn.nl/groningen/Crisisfeer-in-het-UMC-Groningen-21975899.html>. Published February 4, 2017. Accessed April 30, 2019.
90. Sandmann FG, Robotham JV, Deeny SR, Edmunds WJ, Jit M. Estimating the opportunity costs of bed-days. *Health Econ.* 2018;27(3):592-605. doi:10.1002/hec.3613
91. Hakkaart-van Roijen L, Van der Linden N, Bouwmans C, Kanters T, Tan S. Kostenhandleiding: methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. Zorginstituut Nederland; 2015. Accessed April 15, 2021. [https://www.zorginstituutnederland.nl/binaries/zinl/documenten/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg/Richtlijn-voor-het-uitvoeren-van+economische+evaluaties+in+de+gezondheidszorg+\(verdiepingsmodules\).pdf](https://www.zorginstituutnederland.nl/binaries/zinl/documenten/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg/Richtlijn-voor-het-uitvoeren-van+economische+evaluaties+in+de+gezondheidszorg+(verdiepingsmodules).pdf)
92. Centraal Bureau voor de Statistiek. Consumer price Index. Statline. Accessed August 2, 2021. <https://opendata.cbs.nl/statline/#/CBS/nl/dataset/83131NED/table?ts=1627889467468>
93. NFU. Cao universitair medische centra 2018-2020. Published November 29, 2019. Accessed August 6, 2021. https://www.nfu.nl/sites/default/files/2020-07/19.9945_Umc_Cao_umc_2018-2020_per_1-1-2020_v8_0.pdf
94. Hyndman RJ, Athanasopoulos G. *Forecasting: Principles and Practice (3rd Ed).* 3rd edition. OTexts; 2021. Accessed March 19, 2021. <https://Otextst.com/fpp3/>
95. Hyndman RJ, Khandakar Y. Automatic Time Series Forecasting: The forecast Package for R. *J Stat Softw.* 2008;27(1):1-22. doi:10.18637/jss.v027.i03
96. R Core Team. *R: A Language and Environment for Statistical Computing.* R Foundation for Statistical Computing; 2021. <https://www.R-project.org/>
97. Wickham H, François R, Henry L, Müller K. *Dplyr: A Grammar of Data Manipulation.*; 2021. <https://CRAN.R-project.org/package=dplyr>
98. O'Hara-Wild M, Hyndman R, Wang E. *Fable: Forecasting Models for Tidy Time Series.*; 2021. <https://CRAN.R-project.org/package=fable>
99. Escaut L, Bouam S, Frank-Soltysiak M, et al. Eradication of an outbreak of vancomycin-resistant Enterococcus (VRE): the cost of a

- failure in the systematic screening. *Antimicrob Resist Infect Control.* 2013;2:18. doi:10.1186/2047-2994-2-18
100. Zorginstituut Nederland. Medicijnkosten. Accessed April 15, 2021. <https://www.medicijnkosten.nl/>
101. Prematunge C, MacDougall C, Johnstone J, et al. VRE and VSE Bacteremia Outcomes in the Era of Effective VRE Therapy: A Systematic Review and Meta-analysis. *Infect Control Hosp Epidemiol.* 2016;37(1):26-35. doi:10.1017/ice.2015.228
102. Puchter L, Chaberry IF, Schwab F, Vonberg RP, Bang FC, Ebadi E. Economic burden of nosocomial infections caused by vancomycin-resistant enterococci. *Antimicrob Resist Infect Control.* 2018;7:1. doi:10.1186/s13756-017-0291-z
103. MacDougall C, Johnstone J, Prematunge C, et al. Economic evaluation of vancomycin-resistant enterococci (VRE) control practices: a systematic review. *J Hosp Infect.* 2020;105(1):53-63. doi:10.1016/j.jhin.2019.12.007
104. Mac S, Fitzpatrick T, Johnstone J, Sander B. Vancomycin-resistant enterococci (VRE) screening and isolation in the general medicine ward: a cost-effectiveness analysis. *Antimicrob Resist Infect Control.* 2019;8(1):168. doi:10.1186/s13756-019-0628-x
105. Lakdawalla DN, Doshi JA, Garrison LP, Phelps CE, Basu A, Danzon PM. Defining Elements of Value in Health Care—A Health Economics Approach: An ISPOR Special Task Force Report [3]. *Value Health.* 2018;21(2):131-139. doi:10.1016/j.jval.2017.12.007
106. van der Pol S, Dik JWH, Glasner C, Postma MJ, Sinha B, Friedrich AW. The tripartite insurance model (TIM): a financial incentive to prevent outbreaks of infections due to multidrug-resistant microorganisms in hospitals. *Clin Microbiol Infect.* 2021;27(5):665-667. doi:10.1016/j.cmi.2021.01.019
107. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J.* 2016;37(38):2893-2962. doi:10.1093/euroheartj/ehw210
108. Committee PM of AW, Doherty JU, Gluckman TJ, et al. 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation. *J Am Coll Cardiol.* Published online January 9, 2017;23217. doi:10.1016/j.jacc.2016.11.024
109. Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation. *N Engl J Med.* 2015;373(9):823-833. doi:10.1056/NEJMoa1501035
110. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of Clinical Classification Schemes for Predicting Stroke: Results From the National Registry of Atrial Fibrillation. *JAMA.* 2001;285(22):2864-2870. doi:10.1001/jama.285.22.2864
111. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest.* 2010;137(2):263-272. doi:10.1378/chest.09-1584
112. Dunn AS, Wisnivesky J, Ho W, Moore C, McGinn T, Sacks HS. Perioperative Management of Patients on Oral Anticoagulants: A Decision Analysis. *Med Decis Making.* 2005;25(4):387-397. doi:10.1177/0272989X05278432
113. Pappas MA, Barnes GD, Vijan S. Personalizing Bridging Anticoagulation in Patients with Nonvalvular Atrial Fibrillation—a Micro-simulation Analysis. *J Gen Intern Med.* 2017;32(4):464-470. doi:10.1007/s11606-016-3932-7
114. Schulman S, Angerås U, Bergqvist D, et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. *J Thromb Haemost.* 2010;8(1):202-204. doi:10.1111/j.1538-7836.2009.03678.x
115. R Core Team. *R: A Language and Environment for Statistical Computing.* R Foundation for Statistical Computing; 2017. <https://www.R-project.org/>
116. Friberg L, Rosenvist M, Lip GYH. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur Heart J.* 2012;33(12):1500-1510. doi:10.1093/eurheartj/ehr488
117. Omran H, Bauersachs R, Rübenacker S, Goss F, Hammerstingl C. The HAS-BLED score predicts bleedings during bridging of chronic oral anticoagulation. *Thromb Haemost.* 2012;108(1):65-73. doi:10.1160/TH11-12-0827
118. Beck JR, Kassirer JP, Pauker SG. A convenient approximation of life expectancy (the “DEALE”). *Am J Med.* 1982;73(6):883-888. doi:10.1016/0002-9343(82)90786-0
119. Chiu HT, Wang YH, Jeng JS, Chen BB, Pan SL. Effect of Functional Status on Survival in Patients With Stroke: Is Independent Ambulation a Key Determinant? *Arch Phys Med Rehabil.* 2012;93(3):527-531. doi:10.1016/j.apmr.2011.10.018
120. Heuzey JYL, Ammentorp B, Darius H, et al. Differences among western European countries in anticoagulation management of atrial fibrillation. *Thromb Haemost.* 2014;111(05):833-841. doi:10.1160/TH13-12-1007
121. De Jong JS, Vink R, Henny CP, Levi M, Van Den Brink RBA, Kamphuisen PW. Perioperatieve onderbreking van antistollingsmiddelen. *Ned Tijdschr Geneesk.* 2009;153(33):1622-1628.
122. Haustein KO. Pharmacokinetic and Pharmacodynamic Properties of Oral Anticoagulants, Especially Phenprocoumon. *Semin Thromb Hemost.* 1999;25(01):5-11. doi:10.1055/s-2007-996417
123. Palomäki A, Kiviniemi T, Hartikainen JEK, et al. Postoperative Strokes and Intracranial Bleeds in Patients With Atrial Fibrillation: The FibStroke Study: Postoperative strokes in patients with AF. *Clin Cardiol.* 2016;39(8):471-476. doi:10.1002/clc.22554
124. Sorensen SV, Kansal AR, Connolly S, et al. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: A Canadian payer perspective. *Thromb Haemost.* 2011;105(5):908-919. doi:10.1160/TH11-02-0089
125. Andersen LV, Vestergaard P, Deichgraeber P, Lindholm JS, Mortensen LS, Frost L. Warfarin for the prevention of systemic embolism in patients with non-valvular atrial fibrillation: a meta-analysis. *Heart.* 2008;94(12):1607-1613. doi:10.1136/heart.2007.135657
126. Pobre M, Riley R, Predmore Z, Horvitz-Lennon M, Mattke Z. Potential Cost Savings of A Point-Of-Care Diagnostic Test Measuring Antipsychotic Plasma Levels for Treatment of Patients with Schizophrenia in Spain. *Value Health.* 2016;19(7):694. doi:<https://doi.org/10.1016/j.jval.2016.09.1993>
127. Salech F, Mery V, Larrondo F, Rada G. Estudios que evalúan un test diagnóstico: interpretando sus resultados. *Rev Médica Chile.* 2008;136(9). doi:10.4067/S0034-98872008000900018
128. Di Sanzo M, Cipolloni L, Borro M, et al. Clinical Applications of Personalized Medicine: A New Paradigm and Challenge. *Curr Pharm Biotechnol.* 2017;18(3):194-203. doi:10.2174/138920101866170224105600
129. European Centre for Disease Prevention and Control. *COVID-19 Testing Strategies and Objectives.*; 2020:22. <https://www.ecdc.europa.eu/en/publications-data/covid-19-testing-strategies-and-objectives#copy-to-clipboard>
130. Kretzschmar ME, Rozhnova G, Bootsma MCJ, Boven M van, Wijgert JHHM, Bonten MJM. Impact of delays on effectiveness of contact tracing strategies for COVID-19: a modelling study. *Lancet Public Health.* 2020;5(8):e452-e459. doi:10.1016/S2468-2667(20)30157-2
131. Marca AL, Capuzzo M, Paglia T, Roli L, Trenti T, Nelson SM. Testing for SARS-CoV-2 (COVID-19): a systematic review and clinical guide

- to molecular and serological in-vitro diagnostic assays. *Reprod Biomed Online*. 2020;41(3):483-499. doi:10.1016/j.rbmo.2020.06.001
132. Ji T, Liu Z, Wang G, et al. Detection of COVID-19: A review of the current literature and future perspectives. *Biosens Bioelectron*. 2020;166:112455. doi:10.1016/j.bios.2020.112455
 133. Sheridan C. COVID-19 spurs wave of innovative diagnostics. *Nat Biotechnol*. 2020;38(7):769-772. doi:10.1038/s41587-020-0597-x
 134. Antibiotic resistance. Key facts. World Health Organization. Published 2018. <https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance>
 135. Cassini A, Höglberg LD, Plachouras D, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect Dis*. 2018;0(0). doi:10.1016/S1473-3099(18)30605-4
 136. Cals JWJ, Butler CC, Hopstaken RM, Hood K, Dinant GJ. Effect of point of care testing for C reactive protein and training in communication skills on antibiotic use in lower respiratory tract infections: cluster randomised trial. *BMJ*. 2009;338:b1374. doi:10.1136/bmj.b1374
 137. Anthierens S, Tonkin-Crine S, Cals JW, et al. Clinicians' views and experiences of interventions to enhance the quality of antibiotic prescribing for acute respiratory tract infections. *J Gen Intern Med*. 2015;30(4):408-416. doi:10.1007/s11606-014-3076-6
 138. Llor C, Hernández S. Enfermedad infecciosa en atención primaria: estudio prospectivo efectuado durante todo un año. *Enfermedades Infect Microbiol Clínica*. 2010;28(4):222-226. doi:10.1016/j.eimc.2009.03.014
 139. Llor C. Uso prudente de antibióticos y propuestas de mejora desde la atención primaria. *Enfermedades Infect Microbiol Clínica*. 2010;28:17-22. doi:10.1016/S0213-005X(10)70037-9
 140. Akehurst RL, Abadie E, Renaudin N, Sarkozy F. Variation in Health Technology Assessment and Reimbursement Processes in Europe. *Value Health*. 2017;20(1):67-76. doi:10.1016/j.jval.2016.08.725
 141. Van den Bruel A, Cleemput I, Aertgeerts B, Ramaekers D, Buntinx F. The evaluation of diagnostic tests: evidence on technical and diagnostic accuracy, impact on patient outcome and cost-effectiveness is needed. *J Clin Epidemiol*. 2007;60(11):1116-1122. doi:10.1016/j.jclinepi.2007.03.015
 142. European Parliament and Council. *In Vitro Diagnostic Medical Devices*; 2017. Accessed October 12, 2020. <https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0746&from=EN>
 143. Moher D, Liberati A, Tetzlaff J, Altman DG, for the PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339(jul21 1):b2535-b2535. doi:10.1136/bmj.b2535
 144. R Core Team (2017). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing Accessed June 3, 2020. <https://www.R-project.org/>
 145. Wickham H, François R, Henry L, Müller K. *Dplyr: A Grammar of Data Manipulation*; 2020. <https://CRAN.R-project.org/package=dplyr>
 146. Iannone R, Cheng J, Schloerke B. *Gt: Easily Create Presentation-Ready Display Tables*; 2020. <https://CRAN.R-project.org/package=gt>
 147. Nicholson KG, Abrams KR, Batham S, et al. Randomised controlled trial and health economic evaluation of the impact of diagnostic testing for influenza, respiratory syncytial virus and Streptococcus pneumoniae infection on the management of acute admissions in the elderly and high-risk 18- to 64-year-olds. *Health Technol Assess*. 2014;18(36). doi:10.3310/hta18360
 148. Oppong R, Jit M, Smith RD, et al. Cost-effectiveness of point-of-care C-reactive protein testing to inform antibiotic prescribing decisions. *Br J Gen Pract*. 2013;63(612):e465-e471. doi:10.3399/bjgp13X69185
 149. Oppong R, Smith RD, Little P, et al. Cost-effectiveness of internet-based training for primary care clinicians on antibiotic prescribing for acute respiratory tract infections in Europe. *J Antimicrob Chemother*. 2018;73(11):3189-3198. doi:10.1093/jac/dky309
 150. Stankiewicz JA, Chow JM. Cost analysis in the diagnosis of chronic rhinosinusitis. *Am J Rhinol*. 2003;17(3):139-142.
 151. Dinh A, Duran C, Davido B, et al. Cost effectiveness of pneumococcal urinary antigen in Emergency Department: a pragmatic real-life study. *Intern Emerg Med*. 2018;13(1):69-73. doi:10.1007/s11739-016-1586-4
 152. Van Rie A, Page-Shipp L, Hanrahan CF, et al. Point-of-care Xpert® MTB/RIF for smear-negative tuberculosis suspects at a primary care clinic in South Africa. *Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis*. 2013;17(3):368-372. doi:10.5588/ijtld.12.0392
 153. Böhmer W, Loos U, Heissenberg A, Kullmann KH. Guideline-driven infectiological quality management on a general medical ward in patients with community-acquired pneumonia [Leitliniengesteuertes infektiologisches qualitätsmanagement auf einer internistischen allgemeinstation bei Patienten mit ambulant erworbener Pneumonie]. *Chestnother J*. 2002;11(2):83-86.
 154. Pooran A, Theron G, Zijenah L, et al. Point of care Xpert MTB/RIF versus smear microscopy for tuberculosis diagnosis in southern African primary care clinics: a multicentre economic evaluation. *Lancet Glob Health*. 2019;7(6):e798-e807. doi:10.1016/S2214-109X(19)30164-0
 155. Wang SQ, Sun Q, Jiang GL, et al. [Incremental cost-effectiveness of the second Xpert MTB/RIF assay for detection of Mycobacterium tuberculosis]. *Zhonghua Jie He He Hu Xi Za Zhi Zhonghua Jiehe He Huxi Zazhi Chin J Tuberc Respir Dis*. 2019;42(6):432-437. doi:10.3760/cma.j.issn.1001-0939.2019.06.006
 156. Jha S, Ismail N, Clark D, et al. Cost-Effectiveness of Automated Digital Microscopy for Diagnosis of Active Tuberculosis. Subbian S, ed. *PLOS ONE*. 2016;11(6):e0157554. doi:10.1371/journal.pone.0157554
 157. Naidoo P, Dunbar R, du Toit E, et al. Comparing laboratory costs of smear/culture and Xpert® MTB/RIF-based tuberculosis diagnostic algorithms. *Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis*. 2016;20(10):1377-1385. doi:10.5588/ijtld.16.0081
 158. Yakeleff N, Audibert M, Varaine F, et al. Is introducing rapid culture into the diagnostic algorithm of smear-negative tuberculosis cost-effective? *Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis*. 2014;18(5):541-546. doi:10.5588/ijtld.13.0630
 159. Hoch JS, Rockx MA, Krahn AD. Using the net benefit regression framework to construct cost-effectiveness acceptability curves: an example using data from trial of external loop recorders versus Holter monitoring for ambulatory monitoring of "community acquired" syncope. *BMC Health Serv Res*. 2006;6:68. doi:10.1186/1472-6963-6-68
 160. Rautenberg T, Gerritsen A, Downes M. Health Economic Decision Tree Models of Diagnostics for Dummies: A Pictorial Primer. *Diagn Basel Switz*. 2020;10(3). doi:10.3390/diagnostics10030158
 161. Bonnet M, Tajahmad Y, Hepple P, et al. Added value of bleach sedimentation microscopy for diagnosis of tuberculosis: a cost-effectiveness study. *Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis*. 2010;14(5):571-577.
 162. Cowan JF, Chandler AS, Kracen E, et al. Clinical Impact and Cost-effectiveness of Xpert MTB/RIF Testing in Hospitalized Patients With Presumptive Pulmonary Tuberculosis in the United States. *Clin Infect Dis*. 2016;64(4):482-489. doi:10.1093/cid/ciw803
 163. You JHS, Lui G, Kam KM, Lee NLS. Cost-effectiveness analysis of the Xpert MTB/RIF assay for rapid diagnosis of suspected tuberculo-

- sis in an intermediate burden area. *J Infect.* 2015;70(4):409-414. doi:10.1016/j.jinf.2014.12.015
164. Vassall A, van Kampen S, Sohn H, et al. Rapid Diagnosis of Tuberculosis with the Xpert MTB/RIF Assay in High Burden Countries: A Cost-Effectiveness Analysis. *PLOS Med.* 2011;8(11):e1001120. doi:10.1371/journal.pmed.1001120
165. Herrárez Ó, Asencio-Egea MA, Huertas-Vaqueira M, et al. Cost-effectiveness study of the microbiological diagnosis of tuberculosis using geneXpert MTB/RIF®. 2017. 2017;35(7):403-410. doi:10.1016/j.eimce.2017.06.007
166. Pinto M, Steffen RE, Cobelens F, van den Hof S, Entrirringer A, Trajman A. Cost-effectiveness of the Xpert® MTB/RIF assay for tuberculosis diagnosis in Brazil. *Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis.* 2016;20(5):611-618. doi:10.5588/ijtld.15.0455
167. Walusimbi S, Kwesiga B, Rodrigues R, et al. Cost-effectiveness analysis of microscopic observation drug susceptibility test versus Xpert MTB/Rif test for diagnosis of pulmonary tuberculosis in HIV patients in Uganda. *BMC Health Serv Res.* 2016;16(1):563. doi:10.1186/s12913-016-1804-9
168. Abimbola TO, Marston BJ, Date AA, Blandford JM, Sangrujee N, Wiktor SZ. Cost-Effectiveness of Tuberculosis Diagnostic Strategies to Reduce Early Mortality Among Persons With Advanced HIV Infection Initiating Antiretroviral Therapy: *JAIDS J Acquir Immune Defic Syndr.* 2012;60(1):e1-e7. doi:10.1097/QAI.0b013e318246538f
169. Shah M, Dowdy D, Joloba M, et al. Cost-effectiveness of novel algorithms for rapid diagnosis of tuberculosis in HIV-infected individuals in Uganda: *AIDS.* 2013;27(18):2883-2892. doi:10.1097/QAD.0000000000000008
170. Ang M, Nguyen HV, Kiew SY, Chen S, Chee SP, Finkelstein E. Cost-effectiveness of alternative strategies for interferon- γ release assays and tuberculin skin test in tuberculous uveitis. *Br J Ophthalmol.* 2015;99(7):984-989. doi:10.1136/bjophthalmol-2014-306285
171. Takwoingi Y, Whitworth H, Rees-Roberts M, et al. Interferon gamma release assays for Diagnostic Evaluation of Active tuberculosis (IDEA): test accuracy study and economic evaluation. *Health Technol Assess Winch Engl.* 2019;23(23):1-152. doi:10.3310/hta23230
172. You JHS, Chan ESK, Leung MYK, Ip M, Lee NLS. A Cost-Effectiveness Analysis of “Test” versus “Treat” Patients Hospitalized with Suspected Influenza in Hong Kong. Semple MG, ed. *PLoS ONE.* 2012;7(3):e33123. doi:10.1371/journal.pone.0033123
173. Dugas AF, Coleman S, Gaydos CA, Rothman RE, Frick KD. Cost-Utility of Rapid Polymerase Chain Reaction-Based Influenza Testing for High-Risk Emergency Department Patients. *Ann Emerg Med.* 2013;62(1):80-88. doi:10.1016/j.annemergmed.2013.01.005
174. Nelson RE, Stockmann C, Hersh AL, et al. Economic Analysis of Rapid and Sensitive Polymerase Chain Reaction Testing in the Emergency Department for Influenza Infections in Children: *Pediatr Infect Dis J.* 2015;34(6):577-582. doi:10.1097/INF.00000000000000703
175. Cals JWJ, Ament AJHA, Hood K, et al. C-reactive protein point of care testing and physician communication skills training for lower respiratory tract infections in general practice: economic evaluation of a cluster randomized trial: Economic evaluation IMPAC3T trial. *J Eval Clin Pract.* 2011;17(6):1059-1069. doi:10.1111/j.1365-2753.2010.01472.x
176. Holmes E, Harris S, Hughes A, Craine N, Hughes D. Cost-Effectiveness Analysis of the Use of Point-of-Care C-Reactive Protein Testing to Reduce Antibiotic Prescribing in Primary Care. *Antibiotics.* 2018;7(4):106. doi:10.3390/antibiotics7040106
177. Oostenbrink R, Oostenbrink JB, Moons KGM, et al. Cost-utility analysis of patient care in children with meningeal signs. *Int J Technol Assess Health Care.* 2002;18(3):485-496.
178. Harris JR, Marston BJ, Sangrujee N, DuPlessis D, Park B. Cost-Effectiveness Analysis of Diagnostic Options for Pneumocystis Pneumonia (PCP). Chaturvedi V, ed. *PLoS ONE.* 2011;6(8):e23158. doi:10.1371/journal.pone.0023158
179. Michaelidis CI, Zimmerman RK, Nowalk MP, Fine MJ, Smith KJ. Cost-Effectiveness of Procalcitonin-Guided Antibiotic Therapy for Outpatient Management of Acute Respiratory Tract Infections in Adults. *J Gen Intern Med.* 2014;29(4):579-586. doi:10.1007/s11606-013-2679-7
180. Mewes JC, Pulia MS, Mansour MK, Broyles MR, Nguyen HB, Steuten LM. The cost impact of PCT-guided antibiotic stewardship versus usual care for hospitalised patients with suspected sepsis or lower respiratory tract infections in the US: A health economic model analysis. *PLoS One.* 2019;14(4):e0214222. doi:10.1371/journal.pone.0214222
181. Stojanovic I, Schneide JE, Wei L, Hong Z, Keane C, Schuetz P. Economic evaluation of procalcitonin-guided antibiotic therapy in acute respiratory infections: a Chinese hospital system perspective. *Clin Chem Lab Med CCLM.* 2017;55(4). doi:10.1515/cclm-2016-0349
182. Schuetz P, Balk R, Briel M, et al. Economic evaluation of procalcitonin-guided antibiotic therapy in acute respiratory infections: a US health system perspective. *Clin Chem Lab Med CCLM.* 2015;53(4). doi:10.1515/cclm-2014-1015
183. Van der Maas M, Kip M, Mantjes G, Steuten L. A procalcitonin algorithm used in adult ICU patients with sepsis saves costs by reducing antibiotic resistance and C. difficile infections. *Milan Italy 71115 - 111115.*
184. Van Howe RS. Diagnosis and Management of Pharyngitis in a Pediatric Population Based on Cost-Effectiveness and Projected Health Outcomes. *PEDIATRICS.* 2006;117(3):609-619. doi:10.1542/peds.2005-0879
185. Giraldez-Garcia C, Rubio B, Gallegos-Braun JF, Imaz I, Gonzalez-Enriquez J, Sarria-Santamera A. Diagnosis and management of acute pharyngitis in a paediatric population: a cost-effectiveness analysis. *Eur J Pediatr.* 2011;170(8):1059-1067. doi:10.1007/s00431-011-1410-0
186. Maizia A, Letrilliart L, Colin C. Stratégies de diagnostic de l'angine aiguë en France : une étude coût-efficacité. *Presse Médicale.* 2012;41(4):e195-e203. doi:10.1016/j.jpm.2011.10.021
187. Behnamfar Z, Shahkarami V, Sohrabi S, Aghdam AS, Afzali H. Cost and effectiveness analysis of the diagnostic and therapeutic approaches of group A Streptococcus pharyngitis management in Iran. *J Fam Med Prim Care.* 2019;8(9):2942-2949. doi:10.4103/jfmpc.jfmpc_487_19
188. Lathia N, Sullivan K, Tam K, et al. Cost-minimization analysis of community pharmacy-based point-of-care testing for strep throat in 5 Canadian provinces. *Can Pharm J Rev Pharm Can.* 2018;151(5):322-331. doi:10.1177/1715163518790993
189. Perone N, Humair JP. [Diagnosis and management of pharyngitis]. *Rev Med Suisse.* 2007;3(96):286-290.
190. Bertrán MJ, Trilla A, Codina C, Carné X, Ribas J, Asenjo MA. [Analysis of the cost-effectiveness relationship in the empirical treatment in patients with infections of the lower respiratory tract acquired in the community]. *Enferm Infect Microbiol Clin.* 2000;18(9):445-451.
191. Ost DE, Hall CS, Joseph G, et al. Decision Analysis of Antibiotic and Diagnostic Strategies in Ventilator-associated Pneumonia. *Am J Respir Crit Care Med.* 2003;168(9):1060-1067. doi:10.1164/rccm.200302-199OC
192. Xie X, Sinclair A, Dendukuri N. Evaluating the accuracy and economic value of a new test in the absence of a perfect reference test. *Res Synth Methods.* 2017;8(3):321-332. doi:10.1002/rsm.1243
193. de Bock GH, van Erkel AR, Springer MP, Kievit J. Antibiotic prescription for acute sinusitis in otherwise healthy adults. Clinical cure in relation to costs. *Scand J Prim Health Care.* 2001;19(1):58-63. doi:10.1080/028134301300034729
194. González-Canudas J, Iglesias-Chiesa JM, Romero-Antonio Y, Chávez-Cortes C, Gay-Molina JG, Rivas-Ruiz R. [Cost-effectiveness in the detection of influenza H1N1: clinical data versus rapid tests]. *Rev Panam Salud Pública Pan Am J Public Health.* 2011;29(1):1-8.



195. Schwarzinger M, Housset B, Carrat F. Bedside Rapid Flu Test and Zanamivir Prescription in Healthy Working Adults: A Cost-Benefit Analysis. *PharmacoEconomics*. 2003;21(3):215-224. doi:10.2165/00019053-200321030-00006
196. Smith KJ, Roberts MS. Cost-effectiveness of newer treatment strategies for influenza. *Am J Med*. 2002;113(4):300-307. doi:10.1016/S0002-9343(02)01222-6
197. Siddiqui MR, Edmunds WJ. Cost-effectiveness of Antiviral Stockpiling and Near-Patient Testing for Potential Influenza Pandemic. *Emerg Infect Dis*. 2008;14(2):267-274. doi:10.3201/eid1402.070478
198. Tillekeratne LG, Bodinayake C, Nagahawatte A, et al. Use of clinical algorithms and rapid influenza testing to manage influenza-like illness: a cost-effectiveness analysis in Sri Lanka. *BMJ Glob Health*. 2019;4(2):e001291. doi:10.1136/bmigh-2018-001291
199. Neuner JM, Hamel MB, Phillips RS, Bona K, Aronson MD. Diagnosis and Management of Adults with Pharyngitis: A Cost-Effectiveness Analysis. *Ann Intern Med*. 2003;139(2):113. doi:10.7326/0003-4819-139-2-200307150-00011
200. Rothberg MB, He S, Rose DN. Management of influenza symptoms in healthy adults: Cost-effectiveness of rapid testing and antiviral therapy. *J Gen Intern Med*. 2003;18(10):808-815. doi:10.1046/j.1525-1497.2003.20822.x
201. Lavelle TA, Uyeki TM, Prosser LA. Cost-Effectiveness of Oseltamivir Treatment for Children with Uncomplicated Seasonal Influenza. *J Pediatr*. 2012;160(1):67-73.e6. doi:10.1016/j.jpeds.2011.07.001
202. Shen K, Xiong T, Tan SC, Wu J. Oseltamivir Treatment for Children with Influenza-Like Illness in China: A Cost-Effectiveness Analysis. Gantti S, ed. *PLOS ONE*. 2016;11(4):e0153664. doi:10.1371/journal.pone.0153664
203. Rothberg MB, Fisher D, Kelly B, Rose DN. Management of Influenza Symptoms in Healthy Children: Cost-effectiveness of Rapid Testing and Antiviral Therapy. *Arch Pediatr Adolesc Med*. 2005;159(11):1055. doi:10.1001/archpedi.159.11.1055
204. You JHS, Tam L pui, Lee NLS. Cost-effectiveness of molecular point-of-care testing for influenza viruses in elderly patients at ambulatory care setting. Qiu C, ed. *PLOS ONE*. 2017;12(7):e0182091. doi:10.1371/journal.pone.0182091
205. Rothberg MB, Bellantonio S, Rose DN. Management of Influenza in Adults Older than 65 Years of Age: Cost-Effectiveness of Rapid Testing and Antiviral Therapy. *Ann Intern Med*. 2003;139(5):321. doi:10.7326/0003-4819-139-5_Part_1-200309020-00007
206. Durski KN, Kuntz KM, Yasukawa K, Virnig BA, Meya DB, Boulware DR. Cost-Effective Diagnostic Checklists for Meningitis in Resource-Limited Settings. *JAIDS J Acquir Immune Defic Syndr*. 2013;63(3):e101-e108. doi:10.1097/QAI.0b013e31828e1e56
207. Rodriguez-Martinez CE, Sossa-Briceño MP, Castro-Rodriguez JA. Cost-effectiveness of the utilization of "good practice" or the lack thereof according to a bronchiolitis evidence-based clinical practice guideline. *J Eval Clin Pract*. 2019;25(4):682-688. doi:10.1111/jep.13157
208. Haeuusler K, den Hout A van, Baio G. A dynamic Bayesian Markov model for health economic evaluations of interventions in infectious disease. *BMC Med Res Methodol*. 2018;18(1):82. doi:10.1186/s12874-018-0541-7
209. Ball E, Zucker DR, Engels EA, Wong JB, Williams JW, Lau J. Strategies for diagnosing and treating suspected acute bacterial sinusitis: A cost-effectiveness analysis. *J Gen Intern Med*. 2001;16(10):701-711. doi:10.1111/j.1525-1497.2001.00429.x
210. Hunter R. Cost-Effectiveness of Point-of-Care C-Reactive Protein Tests for Respiratory Tract Infection in Primary Care in England. *Adv Ther*. 2015;32(1):69-85. doi:10.1007/s12325-015-0180-x
211. Briggs AH, Claxton K, Sculpher MJ. *Decision Modelling for Health Economic Evaluation*. Oxford University Press; 2006.
212. Nshimiyumukiza L, Douville X, Fournier D, et al. Cost-effectiveness analysis of antiviral treatment in the management of seasonal influenza A: point-of-care rapid test versus clinical judgment. *Influenza Other Respir Viruses*. 2016;10(2):113-121. doi:10.1111/irv.12359
213. Mears J, Vynnycky E, Lord J, et al. The prospective evaluation of the TB strain typing service in England: a mixed methods study. *Thorax*. 2016;71(8):734-741. doi:10.1136/thoraxjnl-2014-206480
214. Menzies NA, Cohen T, Lin HH, Murray M, Salomon JA. Population Health Impact and Cost-Effectiveness of Tuberculosis Diagnosis with Xpert MTB/RIF: A Dynamic Simulation and Economic Evaluation. Rosen S, ed. *PLoS Med*. 2012;9(11):e1001347. doi:10.1371/journal.pmed.1001347
215. Suen S chuan, Bendavid E, Goldhaber-Fiebert JD. Cost-Effectiveness of Improvements in Diagnosis and Treatment Accessibility for Tuberculosis Control in India. *Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis*. 2015;19(9):1115-xv. doi:10.5588/ijtld.15.0158
216. Wikman-Jorgensen PE, Llenas-García J, Pérez-Porcuna TM, et al. Microscopic observation drug-susceptibility assay vs . Xpert® MTB/RIF for the diagnosis of tuberculosis in a rural African setting: a cost-utility analysis. *Trop Med Int Health*. 2017;22(6):734-743. doi:10.1111/tmi.12879
217. Sohn H, Kasaie P, Kendall E, et al. Informing decision-making for universal access to quality tuberculosis diagnosis in India: an economic-epidemiologic model. *BMC Med*. 2019;17(1):155. doi:10.1186/s12916-019-1384-8
218. Langley I, Lin HH, Egwaga S, et al. Assessment of the patient, health system, and population effects of Xpert MTB/RIF and alternative diagnostics for tuberculosis in Tanzania: an integrated modelling approach. *Lancet Glob Health*. 2014;2(10):e581-e591. doi:10.1016/S2214-109X(14)70291-8
219. Lee DJ, Kumarasamy N, Resch SC, et al. Rapid, point-of-care diagnosis of tuberculosis with novel Truenat assay: Cost-effectiveness analysis for India's public sector. Subbian S, ed. *PLOS ONE*. 2019;14(7):e0218890. doi:10.1371/journal.pone.0218890
220. Bogdanova EN, Mariandyshov AO, Balantcev GA, et al. Cost minimization analysis of line probe assay for detection of multidrug-resistant tuberculosis in Arkhangelsk region of Russian Federation. Furin J, ed. *PLOS ONE*. 2019;14(1):e0211203. doi:10.1371/journal.pone.0211203
221. Oostenbrink R, Oostenbrink JB, Moons KGM, et al. APPLICATION OF A DIAGNOSTIC DECISION RULE IN CHILDREN WITH MENINGEAL SIGNS: A COST-MINIMIZATION STUDY. *Int J Technol Assess Health Care*. 2003;19(4):698-704. doi:10.1017/S0266462303000667
222. Oppong R, Smith RD, Little P, et al. Cost effectiveness of amoxicillin for lower respiratory tract infections in primary care: an economic evaluation accounting for the cost of antimicrobial resistance. *Br J Gen Pr*. 2016;66(650):e633-e639. doi:10.3399/bjgp16X686533
223. Center for Disease Dynamics, Economics & Policy. ResistanceMap - Antibiotic Resistance. Accessed May 5, 2021. <https://resistancemap.cddcp.org/>
224. Nickbakhsh S, Thorburn F, Wissmann BV, McMENAMIN J, Gunson RN, Murcia PR. Extensive multiplex PCR diagnostics reveal new insights into the epidemiology of viral respiratory infections. *Epidemiol Infect*. 2016;144(10):2064-2076. doi:10.1017/S0950268816000339
225. Vassall A, Sweeney S, Kahn JG, et al. Reference Case for Estimating the Costs of Global Health Services and Interventions. *Global Health Cost Consortium*. Published online 2017.
226. Garfield S, Polisena J, S. Spinner D, et al. Health Technology Assessment for Molecular Diagnostics: Practices, Challenges, and

- Recommendations from the Medical Devices and Diagnostics Special Interest Group. *Value Health*. 2016;19(5):577-587. doi:10.1016/j.jval.2016.02.012
227. Wetstein DJ, Boes S. Effectiveness of National Pricing Policies for Patent-Protected Pharmaceuticals in the OECD: A Systematic Literature Review. *Appl Health Econ Health Policy*. 2019;17(2):143-162. doi:10.1007/s40258-018-0437-z
228. Vogler S, Haasis MA, Dede G, Lam J, Pedersen HB. *Medicines Reimbursement Policies in Europe*. World Health Organization; 2018. Accessed January 4, 2021. <https://www.euro.who.int/en/publications/abstracts/medicines-reimbursement-policies-in-europe>
229. Garattini L, Curto A, Freemantle N. Pharmaceutical Price Schemes in Europe: Time for a 'Continental' One? *PharmacoEconomics*. 2016;34(5):423-426. doi:10.1007/s40273-015-0377-5
230. Bellomi A, Morgan D, Paris V. Pharmaceutical Expenditure And Policies: Past Trends And Future Challenges. Published online April 21, 2016. doi:<https://doi.org/10.1787/5jm0q1f4cdq7-en>
231. Blair ED, Stratton EK, Kaufmann M. The economic value of companion diagnostics and stratified medicines. *Expert Rev Mol Diagn*. 2012;12(8):791-794. doi:10.1586/erm.12.129
232. Fischer S, Vogler S, Windisch F, Zimmermann N. *HTA, Reimbursement and Pricing of Diagnostic Tests for CA-ARTI: An International Overview of Policies*. Gesundheit Österreich; 2021. Accessed September 27, 2021. https://www.value-dx.eu/wp-content/uploads/2021/04/VALUE-DX_Report_Task5.5_Deliverable5.2_Final.pdf
233. Vogler S, Habimana K, Fischer S, Haasis MA. *Novel Policy Options for Reimbursement, Pricing and Procurement of AMR Health Technologies*. Gesundheit Österreich; 2021. Accessed September 27, 2021. https://globalamrhub.org/wp-content/uploads/2021/03/GOe_FP_AMR_Report_final.pdf
234. European Parliament and Council. *Regulation on in Vitro Diagnostic Medical Devices*. Accessed November 30, 2020. <http://data.europa.eu/eu/eli/reg/2017/746/2017-05-05>
235. European Commission. Factsheet for Authorities in non-EU/EEA States on Medical Devices and in vitro Diagnostic Medical Devices. Published online February 5, 2019. Accessed November 30, 2020. <https://ec.europa.eu/docsroom/documents/33863>
236. European Parliament and Council. *Regulation on Medical Devices*. Accessed February 19, 2021. <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A2017R0745-20200424>
237. Rojas García P, van der Pol S, van Asselt ADI, et al. Efficiency of Diagnostic Testing for Helicobacter pylori Infections—A Systematic Review. *Antibiotics*. 2021;10(1):55. doi:10.3390/antibiotics10010055
238. Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement. *PharmacoEconomics*. 2013;31(5):361-367. doi:10.1007/s40273-013-0032-y
239. Gilbert R, Logan S, Moyer VA, Elliott EJ. Assessing diagnostic and screening tests. *West J Med*. 2001;174(6):405-409.
240. Definition of MONITORING. Accessed June 10, 2021. <https://www.merriam-webster.com/dictionary/monitoring>
241. Payne K, Gavan SP, Wright SJ, Thompson AJ. Cost-effectiveness analyses of genetic and genomic diagnostic tests. *Nat Rev Genet*. 2018;19(4):235-246. doi:10.1038/nrg.2017.108
242. Kroneman MW, Maarse H, van der Zee J. Direct access in primary care and patient satisfaction: a European study. *Health Policy Amst Neth*. 2006;76(1):72-79. doi:10.1016/j.healthpol.2005.05.003
243. Hordijk PM, Broekhuizen BDL, Butler CC, et al. Illness perception and related behaviour in lower respiratory tract infections—a European study. *Fam Pract*. 2015;32(2):152-158. doi:10.1093/fampra/cmu075
244. Drummond M. *Methods for the Economic Evaluation of Health Care Programmes*. Fourth edition. Oxford University Press; 2015.
245. Incerti D, Thom H, Baio G, Jansen JP. R You Still Using Excel? The Advantages of Modern Software Tools for Health Technology Assessment. *Value Health*. 2019;22(5):575-579. doi:10.1016/j.jval.2019.01.003
246. Watts RD, Li IW, Geelhoed EA, Sanfilippo FM, John AS. Economic Evaluations of Pathology Tests, 2010-2015: A Scoping Review. *Value Health*. 2017;20(8):1210-1215. doi:10.1016/j.jval.2017.04.023
247. Giusepi I, John AS, Jülicher P. Who Conducts Health Economic Evaluations of Laboratory Tests? A Scoping Review. *J Appl Lab Med*. 2020;5(5):954-966. doi:10.1093/jalm/jfaa107
248. Chandna A, White LJ, Pongvongsra T, et al. Accounting for aetiology: can regional surveillance data alongside host biomarker-guided antibiotic therapy improve treatment of febrile illness in remote settings? *Wellcome Open Res*. 2019;4:1. doi:10.12688/wellcomeopen-res.14976.1
249. Attema AE, Lugnér AK, Feenstra TL. Investment in antiviral drugs: a real options approach. *Health Econ*. 2010;19(10):1240-1254. doi:10.1002/hec.1549
250. Schey C, Postma MJ, Krabbe PFM, Topachevskyi O, Volovyk A, Connolly M. Assessing the Preferences for Criteria in Multi-Criteria Decision Analysis in Treatments for Rare Diseases. *Front Public Health*. 2020;8:162. doi:10.3389/fpubh.2020.00162
251. Langley I, Lin HH, Egwaga S, et al. Assessment of the patient, health system, and population effects of Xpert MTB/RIF and alternative diagnostics for tuberculosis in Tanzania: an integrated modelling approach. *Lancet Glob Health*. 2014;2(10):e581-e591. doi:10.1016/S2214-109X(14)70291-8
252. van der Pol S, de Jong LA, Verner P, Jansen DEMC, Postma MJ. Cost-Effectiveness of Sacubitril/Valsartan in Germany: An Application of the Efficiency Frontier. *Value Health*. 2019;22(10):1119-1127. doi:10.1016/j.jval.2019.06.007
253. Sullivan SD, Mauskopf JA, Augustovski F, et al. Budget Impact Analysis—Principles of Good Practice: Report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. *Value Health*. 2014;17(1):5-14. doi:10.1016/j.jval.2013.08.2291
254. Murray CJ, Ikuta KS, Sharara F, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet*. Published online January 19, 2022. doi:10.1016/S0140-6736(21)02724-0
255. Aryee A, Price N. Antimicrobial stewardship – can we afford to do without it? *Br J Clin Pharmacol*. 2015;79(2):173-181. doi:10.1111/bcp.12417
256. Coast J, Smith RD, Millar MR. Superbugs: Should antimicrobial resistance be included as a cost in economic evaluation? *Health Econ*. 1996;5(3):217-226. doi:10.1002/(SICI)1099-1050(199605)5:3<217::AID-HEC200>3.0.CO;2-5
257. Atkins KE, Lafferty El, Deeny SR, Davies NG, Robotham JV, Jit M. Use of mathematical modelling to assess the impact of vaccines on antibiotic resistance. *Lancet Infect Dis*. 2018;18(6):e204-e213. doi:10.1016/S1473-3099(17)30478-4
258. Mauskopf J, Standaert B, Connolly MP, et al. Economic Analysis of Vaccination Programs: An ISPOR Good Practices for Outcomes Research Task Force Report. *Value Health*. 2018;21(10):1133-1149. doi:10.1016/j.jval.2018.08.005

259. Birkegård AC, Halasa T, Toft N, Folkesson A, Graesbøll K. Send more data: a systematic review of mathematical models of antimicrobial resistance. *Antimicrob Resist Infect Control.* 2018;7(1):117. doi:10.1186/s13756-018-0406-1
260. Pezzani MD, Tornimbene B, Pessoa-Silva C, et al. Methodological quality of studies evaluating the burden of drug-resistant infections in humans due to the WHO Global Antimicrobial Resistance Surveillance System target bacteria. *Clin Microbiol Infect.* 2021;0(0). doi:10.1016/j.cmi.2021.01.004
261. Goossens H. Antibiotic consumption and link to resistance. *Clin Microbiol Infect.* 2009;15:12-15. doi:10.1111/j.1469-0991.2009.02725.x
262. van den Broek d'Obrenan J, Verheij TJM, Numans ME, van der Velden AW. Antibiotic use in Dutch primary care: relation between diagnosis, consultation and treatment. *J Antimicrob Chemother.* 2014;69(6):1701-1707. doi:10.1093/jac/dku005
263. Dolk FCK, Pouwels KB, Smith DRM, Robotham JV, Smieszek T. Antibiotics in primary care in England: which antibiotics are prescribed and for which conditions? *J Antimicrob Chemother.* 2018;73(suppl_2):ii2-ii10. doi:10.1093/jac/dkx504
264. European Centre for Disease Prevention and Control. Antimicrobial consumption database (ESAC-Net). European Centre for Disease Prevention and Control. Accessed April 15, 2021. <https://www.ecdc.europa.eu/en/antimicrobial-consumption/surveillance-and-dis-ease-data/database>
265. Butler CC, Hood K, Verheij T, et al. Variation in antibiotic prescribing and its impact on recovery in patients with acute cough in primary care: prospective study in 13 countries. *BMJ.* 2009;338:b2242. doi:10.1136/bmj.b2242
266. Velden A van der, Pol AC van de, Bongard E, et al. Point of care testing, antibiotic prescribing and prescribing confidence for respiratory tract infections in primary care: Prospective audit in 18 European countries. *BJGP Open.* Published online December 17, 2021. doi:10.3399/BJGPO.2021.0212
267. Martínez-González NA, Keizer E, Plate A, et al. Point-of-Care C-Reactive Protein Testing to Reduce Antibiotic Prescribing for Respiratory Tract Infections in Primary Care: Systematic Review and Meta-Analysis of Randomised Controlled Trials. *Antibiotics.* 2020;9(9):610. doi:10.3390/antibiotics9090610
268. Cohen JF, Pauchard JY, Hjelm N, Cohen R, Chalumeau M. Efficacy and safety of rapid tests to guide antibiotic prescriptions for sore throat. *Cochrane Database Syst Rev.* 2020;(6). doi:10.1002/14651858.CD012431.pub2
269. Bruning AHL, de Kruijf WB, van Weert HCPM, et al. Diagnostic performance and clinical feasibility of a point-of-care test for respiratory viral infections in primary health care. *Fam Pract.* 2017;34(5):558-563. doi:10.1093/fampra/cmx019
270. Rothberg MB, Bellantonio S, Rose DN. Management of Influenza in Adults Older than 65 Years of Age: Cost-Effectiveness of Rapid Testing and Antiviral Therapy. *Ann Intern Med.* 2003;139(5_Part_1):321. doi:10.7326/0003-4819-139-5_Part_1-200309020-00007
271. Little P, Hobbs FDR, Moore M, et al. Clinical score and rapid antigen detection test to guide antibiotic use for sore throats: randomised controlled trial of PRISM (primary care streptococcal management). *BMJ.* 2013;347:f5806. doi:10.1136/bmj.f5806
272. R Core Team. *R: A Language and Environment for Statistical Computing.*; 2020. <https://www.R-project.org/>
273. European Commission. Eurostat. Accessed April 12, 2021. <https://ec.europa.eu/eurostat>
274. European Centre for Disease Prevention and Control. The European Surveillance System (TESSy). European Centre for Disease Prevention and Control. Accessed April 12, 2021. <https://www.ecdc.europa.eu/en/publications-data/european-surveillance-system-tessy>
275. Cecchini M, Lee S. Low-value health care with high stakes: Promoting the rational use of antimicrobials. Published online January 10, 2017;115-158. doi:10.1787/9789264266414-6-en
276. Jombart T, Kamvar ZN, FitzJohn R, et al. *Incidence: Compute, Handle, Plot and Model Incidence of Dated Events.*; 2020. Accessed April 15, 2021. <https://CRAN.R-project.org/package=incidence>
277. Wright MN, Ziegler A. ranger: A Fast Implementation of Random Forests for High Dimensional Data in C++ and R. *J Stat Softw.* 2017;77(1):1-17. doi:10.18637/jss.v077.i01
278. Chen T, Guestrin C. XGBoost: A Scalable Tree Boosting System. *Proc 22nd ACM SIGKDD Int Conf Knowl Discov Data Min.* Published online August 13, 2016:785-794. doi:10.1145/2939672.2939785
279. Certe. Price list. Certe. Accessed April 19, 2021. <https://www.certe.nl/over-certe/organisatie/tarieven-certe/de-nza-tarieven>
280. European Commission. Harmonised Indices of Consumer Prices. Eurostat. Accessed April 15, 2021. <https://ec.europa.eu/eurostat/web/hicp>
281. Zorginstituut Nederland. *Guideline for Economic Evaluations in Healthcare.*; 2016. Accessed January 3, 2018. <https://english.zorginstituutnederland.nl/publications/reports/2016/06/16/guideline-for-economic-evaluations-in-healthcare>
282. van der Pol S, Rojas García P, Postma MJ, Villar FA, van Asselt ADI. Economic Analyses of Respiratory Tract Infection Diagnostics: A Systematic Review. *PharmacoEconomics.* 2021;39(12):1411-1427. doi:10.1007/s40273-021-01054-1
283. Rojas García P, van der Pol S, van Asselt ADI, et al. Diagnostic Testing for Sepsis: A Systematic Review of Economic Evaluations. *Antibiotics.* 2022;11(1):27. doi:10.3390/antibiotics11010027
284. OECD. *Stemming the Superbug Tide: Just A Few Dollars More.* OECD; 2018. doi:10.1787/9789264307599-en
285. European Centre for Disease Prevention and Control, World Health Organization. Influenza Surveillance Country, Territory and Area Profiles 2019. Published 2019. Accessed November 17, 2021. https://www.euro.who.int/__data/assets/pdf_file/0016/402082/InfluenzaSurveillanceProfiles_2019_en.pdf
286. Nederlands Huisartsen Genootschap (NHG). ICPC-online. Published April 2021. Accessed November 17, 2021. <https://www.nhg.org/themas/artikelen/icpc-online>
287. European Centre for Disease Prevention and Control. *Country Summaries - Antimicrobial Resistance in the EU/EEA 2019.*; 2020. Accessed November 17, 2021. [https://www.ecdc.europa.eu/sites/default/files/documents/Country%20summaries-AER-EARS-Net%20202019.pdf](https://www.ecdc.europa.eu/sites/default/files/documents/Country%20summaries-AER-EARS-Net%2020202019.pdf)
288. Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *The Lancet.* 2005;365(9459):579-587. doi:10.1016/S0140-6736(05)17907-0
289. Minnaard MC, van de Pol AC, Hopstaken RM, et al. C-reactive protein point-of-care testing and associated antibiotic prescribing. *Fam Pract.* 2016;33(4):408-413. doi:10.1093/fampra/cmw039
290. European Commission. *A European One Health Action Plan against Antimicrobial Resistance.*; 2017. https://ec.europa.eu/health/sites/health/files/antimicrobial_resistance/docs/amr_2017_action-plan.pdf
291. Department of Health and Social Care. *Contained and Controlled: The UK's 20-Year Vision for Antimicrobial Resistance.* British Government; 2019-19. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/773065/uk-20-year-vision-for-antimicrobial-resistance.pdf

292. Centers for Disease Control and Prevention (U.S.). *Antibiotic Resistance Threats in the United States, 2019*. Centers for Disease Control and Prevention (U.S.); 2019. doi:10.15620/cdc:82532
293. Dorgali MV, Longo A, Vass C, et al. A General Public Study on Preferences and Welfare Impacts of Antimicrobial Resistance in the United Kingdom. *PharmacoEconomics*. Published online August 30, 2021. doi:10.1007/s40273-021-01076-9
294. van de Pol AC, Boeijen JA, Venekamp RP, et al. Impact of the COVID-19 Pandemic on Antibiotic Prescribing for Common Infections in The Netherlands: A Primary Care-Based Observational Cohort Study. *Antibiot Basel Switz*. 2021;10(2). doi:10.3390/antibiotics10020196
295. Rothery C, Woods B, Schmitt L, Claxton K, Palmer S, Sculpher M. Framework for value assessment of new antimicrobials. *Policy Res Unit Econ Eval Health Care Interv N Y NY USA*. Published online 2018.
296. Colson AR, Megiddo I, Alvarez-Uria G, et al. Quantifying uncertainty about future antimicrobial resistance: Comparing structured expert judgment and statistical forecasting methods. *PLoS ONE*. 2019;14(7):e0219190. doi:10.1371/journal.pone.0219190
297. Galicia A, Talavera-Llames R, Troncoso A, Koprinska I, Martínez-Alvarez F. Multi-step forecasting for big data time series based on ensemble learning. *Knowl-Based Syst*. 2019;163:830-841. doi:10.1016/j.knosys.2018.10.009
298. Breiman L. Random Forests. *Mach Learn*. 2001;45(1):5-32. doi:10.1023/A:1010933404324
299. Honaker J, King G, Blackwell M. Amelia II: A Program for Missing Data. *J Stat Softw*. 2011;45(1):1-47. doi:10.18637/jss.v045.i07
300. Probst P, Wright M, Boulesteix AL. Hyperparameters and Tuning Strategies for Random Forest. *Wiley Interdiscip Rev Data Min Knowl Discov*. 2019;9(3). doi:10.1002/widm.1301
301. Eurostat. Population on 1st January by age, sex and type of projection. Eurostat. Published February 8, 2021. Accessed March 19, 2021. https://ec.europa.eu/eurostat/databrowser/view/proj_19np/default/table?lang=en
302. Eurostat. Population on 1 January by age and sex. Eurostat. Published March 12, 2021. Accessed March 19, 2021. https://ec.europa.eu/eurostat/databrowser/view/demo_pjan/default/table?lang=en
303. OECD. Long-term baseline projections, No. 103. Published online August 2018. doi:10.1787/68465614-en
304. The World Bank. GDP per capita, PPP (constant 2017 international \$). The World Bank Data. Accessed March 19, 2021. <https://data.worldbank.org/indicator/NY.GDP.PCAP.PP.KD>
305. Cheng VCC, Lau SKP, Woo PCY, Yuen KY. Severe Acute Respiratory Syndrome Coronavirus as an Agent of Emerging and Reemerging Infection. *Clin Microbiol Rev*. 2007;20(4):660-694. doi:10.1128/CMR.00023-07
306. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). Antibioticaresistentie | RIVM. Accessed February 21, 2022. <https://www.rivm.nl/antibioticaresistentie>
307. Ferriman A. BMJ readers choose the “sanitary revolution” as greatest medical advance since 1840. *BMJ*. 2007;334(7585):111-111. doi:10.1136/bmj.39097.611806.DB
308. Riley JC. *Rising Life Expectancy: A Global History*. Cambridge University Press; 2001. doi:10.1017/CBO9781316036495
309. OECD. Health expenditure and financing. Published April 26, 2018. Accessed April 26, 2018. <http://stats.oecd.org/viewhtml.aspx?datascode=SHA&lang=en#>
310. Gouglas D, Hoyt K, Peacock E, Kaloudis A, Ottersen T, Røttingen JA. Setting Strategic Objectives for the Coalition for Epidemic Preparedness Innovations: An Exploratory Decision Analysis Process. *Inf J Appl Anal*. 2019;49(6):430-446. doi:10.1287/inte.2019.1011
311. Gezondheidsraad. *Het individuele, collectieve en publieke belang van vaccinatie*. Gezondheidsraad; 2013.
312. Gezondheidsraad. *Vaccinatie tegen rotavirus - Advies*. Ministerie van Volksgezondheid, Welzijn en Sport; 2017. Accessed March 15, 2022. <https://www.gezondheidsraad.nl/documenten/adviezen/2017/09/27/vaccinatie-tegen-rotavirus>
313. Gezondheidsraad. *Vaccinatie Tegen Meningokokken*. Gezondheidsraad; 2018.
314. Gezondheidsraad. *Vaccinatie tegen gordelroos - Advies*. Ministerie van Volksgezondheid, Welzijn en Sport; 2019. Accessed March 15, 2022. <https://www.gezondheidsraad.nl/documenten/adviezen/2019/07/15/vaccinatie-tegen-gordelroos>
315. Zaken M van A. Kamerbrief over Europese gezamelijke aankoop pandemisch griepvaccin - Kamerstuk - Rijksoverheid.nl. Published March 29, 2019. Accessed March 25, 2020. <https://www.rijksoverheid.nl/documenten/kamerstukken/2019/03/29/kamerbrief-over-europese-gezamelijke-aankoop-pandemisch-griepvaccin>
316. Tweede Kamer der Staten-Generaal. Overeenkomst kansrijk vaccin - Kamerstuk 25 295 nr 421. Published online June 13, 2020. Accessed February 22, 2022. <https://zoek.officielebekendmakingen.nl/kst-25295-421.html>
317. Option Value - Explanation and examples. Conceptually. Accessed March 25, 2020. <https://conceptually.org/option-value>
318. Bos F, Zwaneveld P. Reële opties en de waarde van flexibiliteit bij investeringen in natte infrastructuur, samenvatting en conclusies | CPB.nl. CBS. Published May 21, 2014. Accessed May 12, 2020. <https://www.cpb.nl/publicatie/reelle-opties-en-de-waarde-van-flexibiliteit-bij-investeringen-in-natte-infrastructuur-samenvatting-en-conclusies>
319. Shaw AR, Feinberg MB. 90 - Vaccines. In: Rich RR, Fleisher TA, Shearer WT, Schroeder HW, Frew AJ, Weyand CM, eds. *Clinical Immunology (Fourth Edition)*. Content Repository Only!; 2013:1095-1121. doi:10.1016/B978-0-7234-3691-1.00103-3
320. Gerber-Grote A, Sandmann FG, Zhou M, et al. Decision making in Germany: Is health economic evaluation as a supporting tool a sleeping beauty? *Z Für Evidenz Fortbild Qual Im Gesundheitswesen*. 2014;108(7):390-396. doi:10.1016/j.zefq.2014.06.018
321. Lauenroth VD, Stargardt T. Pharmaceutical Pricing in Germany: How Is Value Determined within the Scope of AMNOG? *Value Health*. 2017;20(7):927-935. doi:10.1016/j.jval.2017.04.006
322. Angelis A, Lange A, Kanavos P. Using health technology assessment to assess the value of new medicines: results of a systematic review and expert consultation across eight European countries. *Eur J Health Econ*. 2018;19(1):123-152. doi:10.1007/s10198-017-0871-0
323. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. *General Methods*. 5.0.; 2017. Accessed July 17, 2018. <https://www.iqwig.de/en/methods/methods-paper.3020.html>
324. Caro JJ, Nord E, Siebert U, et al. The efficiency frontier approach to economic evaluation of health-care interventions. *Health Econ*. 2010;19(10):1117-1127. doi:10.1002/hec.1629
325. Ryen L, Svensson M. The Willingness to Pay for a Quality Adjusted Life Year: A Review of the Empirical Literature. *Health Econ*. 2015;24(10):1289-1301. doi:10.1002/hec.3085
326. Sculpher M, Claxton K. Sins of omission and obfuscation: IQWIG's guidelines on economic evaluation methods. *Health Econ*. 2010;19(10):1132-1136. doi:10.1002/hec.1645
327. Brouwer WBF, Rutten FFH. The efficiency frontier approach to economic evaluation: will it help German policy making? *Health*

- Econ.* 2010;19(10):1128-1131. doi:10.1002/hec.1644
328. Sandmann FG, Mostardt S, Lhachimi SK, Gerber-Grote A. The efficiency-frontier approach for health economic evaluation versus cost-effectiveness thresholds and internal reference pricing: combining the best of both worlds? *Expert Rev Pharmacoecon Outcomes Res.* 2018;18(5):475-486. doi:10.1080/14737167.2018.1497976
329. Drummond MF, ed. *Methods for the Economic Evaluation of Health Care Programmes.* 3. ed., reprint. Oxford Univ. Press; 2007.
330. Briggs AH, Claxton K, Sculpher MJ. *Decision Modelling for Health Economic Evaluation.* Oxford University Press; 2006.
331. Bobinac A, van Exel NJA, Rutten FFH, Brouwer WBF. Willingness to Pay for a Quality-Adjusted Life-Year: The Individual Perspective. *Value Health.* 2010;13(8):1046-1055. doi:10.1111/j.1524-4733.2010.00781.x
332. Eichler HG, Kong SX, Gerth WC, Mavros P, Jönsson B. Use of Cost-Effectiveness Analysis in Health-Care Resource Allocation Decision-Making: How Are Cost-Effectiveness Thresholds Expected to Emerge? *Value Health.* 2004;7(5):518-528. doi:10.1111/j.1524-4733.2004.75003.x
333. Ohlmeier C, Mikolajczyk R, Frick J, Prütz F, Haverkamp W, Garbe E. Incidence, prevalence and 1-year all-cause mortality of heart failure in Germany: a study based on electronic healthcare data of more than six million persons. *Clin Res Cardiol.* 2015;104(8):688-696. doi:10.1007/s00392-015-0841-4
334. Peters-Klimm F, Halmer A, Flessa S, Szecsenyi J, Ose D. What drives the costs of heart failure care in Germany? A health services cost analysis. *J Public Health.* 2012;20(6):653-660. doi:10.1007/s10389-012-0501-3
335. Statistisches Bundesamt. Krankenhauspatienten (Hauptdiagnosen, Deutschland). Destatis. Published 2019. Accessed February 28, 2019. <https://www-genesis.destatis.de/genesis/online/>
336. Statistisches Bundesamt. Krankheitskostenrechnung (Herzinsuffizienz). Destatis. Published 2019. Accessed February 28, 2019. <https://www-genesis.destatis.de>
337. European Medicines Agency (EMA). Entresto. European Medicines Agency. Published September 17, 2018. Accessed March 7, 2019. <https://www.ema.europa.eu/en/medicines/human/EPAR/entresto>
338. McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med.* 2014;371(11):993-1004. doi:10.1056/NEJMoa1409077
339. van der Pol S, Degener F, Postma MJ, Vemer P. An Economic Evaluation of Sacubitril/Valsartan for Heart Failure Patients in the Netherlands. *Value Health.* 2017;20(3):388-396. doi:10.1016/j.jval.2016.10.015
340. Ademi Z, Pfeil AM, Hancock E, et al. Cost-effectiveness of sacubitril/valsartan in chronic heart-failure patients with reduced ejection fraction. *Swiss Med Wkly.* 2017;147:w14533. doi:10.4414/smw.2017.14533
341. D'Angiolella LS, Cortesi PA, Pitto C, Ritrovato D, Mantovani LG, Senni M. Sacubitril/valsartan in heart failure with reduced ejection fraction: cost and effectiveness in the Italian context. *Eur J Heart Fail.* 2017;19(11):1551-1553. doi:10.1002/ejhf919
342. Ramos IC, Versteegh MM, de Boer RA, et al. Cost Effectiveness of the Angiotensin Receptor Neprilysin Inhibitor Sacubitril/Valsartan for Patients with Chronic Heart Failure and Reduced Ejection Fraction in the Netherlands: A Country Adaptation Analysis Under the Former and Current Dutch Pharmacoeconomic Guidelines. *Value Health.* 2017;20(10):1260-1269. doi:10.1016/j.jval.2017.05.013
343. McMurray J JV, Trueman D, Hancock E, et al. Cost-effectiveness of sacubitril/valsartan in the treatment of heart failure with reduced ejection fraction. *Heart Br Card Soc.* 2018;104(12):1006-1013. doi:10.1136/heartjnl-2016-310661
344. Gandjour A, Ostwald DA. Sacubitril/Valsartan (LCZ696): A Novel Treatment for Heart Failure and its Estimated Cost Effectiveness, Budget Impact, and Disease Burden Reduction in Germany. *PharmacoEconomics.* Published online July 27, 2018:1-12. doi:10.1007/s40273-018-0688-4
345. Packer M, McMurray J JV, Desai AS, et al. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. *Circulation.* 2015;131(1):54-61. doi:10.1161/CIRCULATIONAHA.114.013748
346. Safavi KC, Dharmarajan K, Kim N, et al. Variation exists in rates of admission to intensive care units for heart failure patients across hospitals in the United States. *Circulation.* 2013;127(8):923-929. doi:10.1161/CIRCULATIONAHA.112.001088
347. Statistisches Bundesamt. Gestorbene: Deutschland, Jahre, Todesursachen, Altersgruppen. Destatis. Accessed September 12, 2017. https://www-genesis.destatis.de/genesis/online/?ejessionid=9954CD4EB335B7C6302FE2B91455B386.tomcat_GO_1_1?operation=prevous&levelIndex=2&levelId=1505205518177&step=2
348. Corrao G, Ghirardi A, Ibrahim B, Merlini L, Maggioni AP. Short- and long-term mortality and hospital readmissions among patients with new hospitalization for heart failure: A population-based investigation from Italy. *Int J Cardiol.* 2015;181:81-87. doi:10.1016/j.ijcardiol.2014.12.004
349. Desai AS, Claggett BL, Packer M, et al. Influence of Sacubitril/Valsartan (LCZ696) on 30-Day Readmission After Heart Failure Hospitalization. *J Am Coll Cardiol.* 2016;68(3):241-248. doi:10.1016/j.jacc.2016.04.047
350. Arzneimittelkommission Der Deutschen Apotheker, Arzneimittelkommission Der Deutschen Ärzteschaft, Deutsche Arbeitsgemeinschaft Selbsthilfegruppen E. V., et al. *NVL Chronische Herzinsuffizienz – Kurzfassung.* 2. Auflage. Bundesärztekammer (BÄK); Kassenärztliche Bundesvereinigung (KBV); Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF); 2017. doi:10.6101/AZQ/000393
351. The SOLVD Investigators. Effect of Enalapril on Survival in Patients with Reduced Left Ventricular Ejection Fractions and Congestive Heart Failure. *N Engl J Med.* 1991;325(5):293-302. doi:10.1056/NEJM199108013250501
352. Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *The Lancet.* 2003;362(9386):772-776. doi:10.1016/S0140-6736(03)14284-5
353. McMurray J, Packer M, Desai A, et al. A putative placebo analysis of the effects of LCZ696 on clinical outcomes in heart failure. *Eur Heart J.* 2015;36(7):434-439. doi:10.1093/euroheartj/ehu455
354. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol.* 1997;50(6):683-691. doi:10.1016/S0895-4356(97)00049-8
355. Martin-Broto J. Indirect comparisons in cost-effectiveness analysis: are we being naïve? *Clin Transl Oncol.* 2015;17(1):85-86. doi:10.1007/s12094-014-1256-9
356. Gemeinsamer Bundesausschuss. *Zusammenfassende Dokumentation über eine Änderung der Arzneimittel Anlage XII Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGBV - Sacubitril/Valsartan.* Gemeinsame Bundesausschuss; 2016. Accessed July 19, 2018. https://www.g-ba.de/downloads/40-268-4037/2016-06-16_AM-RL-XII_Sacubitril_Valsartan_D-207_ZD.pdf
357. Deutsches Institut für Medizinische Dokumentation und Information. ABDA Festbetragsrecherche. DIMDI. Accessed August 24, 2018.

- <https://portal.dimdi.de/festbetragsrecherche/>
358. Institut für das Entgeltsystem im Krankenhaus. Fallpauschalen Katalog 2018. Published November 24, 2017. Accessed September 4, 2018. https://www.g-drg.de/G-DRG-System_2018/Fallpauschalen-Katalog/Fallpauschalen-Katalog_2018
359. Schmidt S, Hendricks V, Griebenow R, Riedel R. Demographic change and its impact on the health-care budget for heart failure inpatients in Germany during 1995–2025. *Herz.* 2013;38(8):862-867. doi:10.1007/s00059-013-3955-3
360. GKV-Spitzenverband. Landesbasisfallwerte. Accessed September 4, 2018. <https://www.gkv-spitzenverband.de/krankenversicherung/krankenhaeuser/budgetverhandlungen/landesbasisfallwerte/landesbasisfallwerte.jsp>
361. Hendricks V, Schmidt S, Vogt A, et al. Case Management Program for Patients With Chronic Heart Failure. *Dtsch Arztebl Int.* 2014;111(15):264-270. doi:10.3238/arztebl.2014.0264
362. Neumann A, Mostard S, Biermann J, et al. Cost-effectiveness and cost-utility of a structured collaborative disease management in the Interdisciplinary Network for Heart Failure (INH) study. *Clin Res Cardiol.* 2015;104(4):304-309. doi:10.1007/s00392-014-0781-4
363. OECD. *Pensions at a Glance 2017*; 2017. https://www.oecd-ilibrary.org/content/publication/pension_glance-2017-en
364. Statistisches Bundesamt. Consumer price indices - Consumer prices. Destatis. Accessed December 5, 2017. https://www.destatis.de/EN/FactsFigures/NationalEconomyEnvironment/Prices/ConsumerPriceIndices/Tables/_ConsumerPricesCategories.html?cms_gtp=151232_list%253D1%2526151228_list%253D1%2526151230_list%253D2%2526151226_slot%253D1&https=1
365. Trueman D, Kapetanakis V, Briggs A, et al. P3373 Better health-related quality of life in patients treated with sacubitril/valsartan compared with enalapril, irrespective of NYHA class: Analysis of EQ-5D in PARADIGM-HF. *Eur Heart J.* 2017;38(suppl_1). doi:10.1093/euroheartj/exh504.P3373
366. National institute for health care excellence. *Single Technology Appraisal: Sacubitril Valsartan for Treating Heart Failure with Systolic Dysfunction*. National institute for health care excellence Accessed December 5, 2017. <https://www.nice.org.uk/guidance/ta388/documents/committee-papers-2>
367. Stollenwerk B, Lhachimi SK, Briggs A, et al. Communicating the Parameter Uncertainty in the IQWiG Efficiency Frontier to Decision-Makers. *Health Econ.* 2015;24(4):481-490. doi:10.1002/hec.3041
368. Edelmann F, Knosalla C, Mörike K, Muth C, Prien P, Störk S. Chronic Heart Failure. *Dtsch Aerzteblatt Online*. Published online February 23, 2018. doi:10.3238/arztebl.2018.0124
369. Facey KM, Bedlington N, Berglas S, Bertelsen N, Single ANV, Thomas V. Putting Patients at the Centre of Healthcare: Progress and Challenges for Health Technology Assessments. *Patient - Patient-Centered Outcomes Res.* 2018;11(6):581-589. doi:10.1007/s40271-018-0325-5
370. Solomon SD, Rizkala AR, Gong J, et al. Angiotensin Receptor Neprilysin Inhibition in Heart Failure With Preserved Ejection Fraction: Rationale and Design of the PARAGON-HF Trial. *JACC Heart Fail.* 2017;5(7):471-482. doi:10.1016/j.jchf.2017.04.013
371. U.S. National Library of Medicine. Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction. ClinicalTrials. Published March 1, 2019. Accessed March 1, 2019. <https://clinicaltrials.gov/ct2/show/NCT01920711>
372. Seferovic JP, Claggett B, Seidelmann SB, et al. Effect of sacubitril/valsartan versus enalapril on glycaemic control in patients with heart failure and diabetes: a post-hoc analysis from the PARADIGM-HF trial. *Lancet Diabetes Endocrinol.* 2017;5(5):333-340. doi:10.1016/S2213-8587(17)30087-6
373. Kristensen SL, Preiss DH, Jhund PS, et al. Risk Related to Pre-Diabetes Mellitus and Diabetes Mellitus in Heart Failure With Reduced Ejection Fraction. *Circ Heart Fail.* 2016;9(1). doi:10.1161/CIRCHEARTFAILURE.115.002560
374. Smith KR, Hsu CC, Berei TJ, et al. PARADIGM-HF Trial: Secondary Analyses Address Unanswered Questions. *Pharmacother J Hum Pharmacol Drug Ther.* 2018;38(2):284-298. doi:10.1002/phar.2075
375. Engelfriet PM, Hoogenveen RT, Poos MJJC, Blokstra A, van Baal PHM, Verschuren WMM. *Hartfalen: epidemiologie, risicofactoren en toekomst*. Rijksinstituut voor Volksgezondheid en Milieu (RIVM); 2012. http://www.rivm.nl/Documenten_en_publicaties/Wetenschappelijk/Rapporten/2012/maart/Hartfalen_epidemiologie_risicofactoren_en_toekomst
376. Lloyd-Jones DM, Larson MG, Leip EP, et al. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation.* 2002;106(24):3068-3072.
377. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). Costs of Illness Tool. Published November 12, 2017. Accessed January 10, 2019. <https://statline.rivm.nl/#/RIVM/nl/dataset/50040NED/table?graphType=Table&ts=1512975518824>
378. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* Published online May 20, 2015;ehw128. doi:10.1093/eurheartj/ehw128
379. Nederlands Huisartsen Genootschap (NHG). Hartfalen. Nederlands Huisartsen Genootschap. Accessed July 12, 2015. <https://www.nhg.org/standaarden/samenvatting/hartfalen>
380. European Medicines Agency (EMA). Opinions on annual re-assessments, renewals of marketing authorisations and accelerated assessment procedures. Published November 20, 2014. Accessed July 12, 2015. http://www.ema.europa.eu/docs/en_GB/document_library/Annex_to_CHMP_highlights/2014/11/WC500177877.pdf
381. European Medicines Agency - Find medicine - Entresto. Accessed January 12, 2016. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004062/human_med_001929.jsp&mid=WC0b01ac058001d124
382. DigitizedL. DigitizedL - Graph Digitizer Software. Digitize graphs, charts and math data. Accessed July 12, 2015. <http://www.digitizedl.de/>
383. Statistics Netherlands. CBS StatLine - Overledenen; belangrijke doodsoorzaken (kontakte lijst), leeftijd, geslacht. Statline. Accessed July 12, 2015. http://statline.cbs.nl/Statweb/publication/?DM=SLNL&PA=7052_95&D1=0,42&D2=0&D3=a&D4=61&HDR=G2,G1,G3&ST-B=1&VW=1
384. Adams KF, Fonarow GC, Emerman CL, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J.* 2005;149(2):209-216. doi:10.1016/j.ahj.2004.08.005
385. van Vliet M, Verburg IWM, van den Boogaard M, et al. Trends in admission prevalence, illness severity and survival of haematological patients treated in Dutch intensive care units. *Intensive Care Med.* 2014;40(9):1275-1284. doi:10.1007/s00134-014-3373-x
386. Hakkaart - van Roijen I, Tan SS, Bouwmans CAM. *Handleiding Voor Kostenonderzoek*. College van Zorgverzekeringen; 2010.
387. Statistics Netherlands. CBS StatLine - Consumentenprijzen; inflatie vanaf 1963. Statline. Accessed July 12, 2015. <http://statline.cbs.nl/Statweb/publication/?DM=SLNL&PA=70936NED&D1=0&D2=597,610,623,636,649,662,675&HDR=T&STB=G1&VW=T>



388. Mosterd A, Hoes AW, de Bruyne MC, et al. Prevalence of heart failure and left ventricular dysfunction in the general population; The Rotterdam Study. *Eur Heart J.* 1999;20(6):447-455.
389. Statistics Netherlands. CBS StatLine - Bevolking; geslacht, leeftijd en burgerlijke staat, 1 januari. Accessed July 12, 2015. <http://statline.cbs.nl/Statweb/publication/?DM=SLNL&PA=7461BEV&D1=0&D2=1-2&D3=1-100&D4=61&HDR=T,G3&STB=G1,G2&VW=T>
390. van Baal PHM, Wong A, Slobbe LCJ, Polder JJ, Brouwer WBF, de Wit GA. Standardizing the inclusion of indirect medical costs in economic evaluations. *PharmacoEconomics.* 2011;29(3):175-187. doi:10.2165/11586130-000000000-00000
391. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *The Lancet.* 2010;376(9744):875-885. doi:10.1016/S0140-6736(10)61198-1
392. Griffiths A, Paracha N, Davies A, Branscombe N, Cowie MR, Sculpher M. The cost effectiveness of ivabradine in the treatment of chronic heart failure from the U.K. National Health Service perspective. *Heart Br Card Soc.* 2014;100(13):1031-1036. doi:10.1136/heart-jnl-2013-304598
393. Kourlaba G, Parisissis J, Karavidas A, et al. Economic evaluation of ivabradine in the treatment of chronic heart failure in Greece. *BMC Health Serv Res.* 2014;14:631. doi:10.1186/s12913-014-0631-0
394. Kind P, Hardman G, Macran S. *UK Population Norms for EQ-5D.* Centre for Health Economics, University of York; 1999. Accessed December 10, 2015. <https://ideas.repec.org/p/chy/respap/172chdp.html>
395. Zorginstituut Nederland. *Kosteneffectiviteit in de Praktijk.*; 2015. Accessed April 25, 2016. <https://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/actueel/nieuws/2015/zorginstituut-stelt-rapport-%E2%80%99kosteneneffectiviteit-in-de-praktijk-%E2%80%99-vast/zinl%3ADocument/1506-kosteneneffectiviteit-in-de-praktijk/Kosteneneffectiviteit+in+de+praktijk.pdf>
396. Filippatos G, Farmakis D, Parisissis J, Lekakis J. Drug therapy for patients with systolic heart failure after the PARADIGM-HF trial: in need of a new paradigm of LCZ696 implementation in clinical practice. *BMC Med.* 2015;13:35. doi:10.1186/s12916-015-0272-0
397. Solomon SD, Zile M, Pieske B, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *The Lancet.* 2012;380(9851):1387-1395. doi:10.1016/S0140-6736(12)61227-6
398. Vemer P, Corro Ramos I, van Voorn GAK, Al MJ, Feenstra TL. AdViSHE: A Validation-Assessment Tool of Health-Economic Models for Decision Makers and Model Users. *PharmacoEconomics.* 2016;34(4):349-361. doi:10.1007/s40273-015-0327-2
399. Zorginstituut Nederland. *GVS-rapport 16/04 sacubitril/valsartan (Entresto®).*; 2016. Accessed July 5, 2016. [https://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/publicaties/genesesmiddelbeoordelingen/2016/1604-sacubitril-valsartan-entresto/sacubitril-valsartan-\(Entresto\).pdf](https://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/publicaties/genesesmiddelbeoordelingen/2016/1604-sacubitril-valsartan-entresto/sacubitril-valsartan-(Entresto).pdf)
400. King JB, Shah RU, Bress AP, Nelson RE, Bellows BK. Cost-Effectiveness of Sacubitril-Valsartan Combination Therapy Compared With Enalapril for the Treatment of Heart Failure With Reduced Ejection Fraction. *JACC Heart Fail.* 2016;4(5):392-402. doi:10.1016/j.jchf.2016.02.007
401. Hoe vaak komt hartfalen voor en hoeveel mensen sterven eraan? - Nationaal Kompass Volksgezondheid. Accessed December 8, 2015. <http://www.nationalkompass.nl/gezondheid-en-ziekte/ziekten-en-aandoeningen/hartvaatstelsel/hartfalen/omvang/>
402. McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure (protocol). *N Engl J Med.* 2014;371(11):993-1004. doi:10.1056/NEJMoa1409077
403. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013;62(16):e147-239. doi:10.1016/j.jacc.2013.05.019
404. Vaartjes I, Koopman C, van Dis I, Visseren FLJ, Bots ML. *Hart-En Vaatziekten in Nederland 2013, Cijfers over Leefstijl, Risicofactoren, Ziekte En Sterfte.* Hartstichting; 2013.
405. American Heart Association. Classification of Functional Capacity and Objective Assessment. Published 1994. Accessed July 27, 2015. http://my.americanheart.org/professional/StatementsGuidelines/ByPublicationDate/PreviousYears/Classification-of-Functional-Capacity-and-Objective-Assessment_UCM_423811_Article.jsp
406. Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *Eur J Health Econ.* 2013;14(3):367-372. doi:10.1007/s10198-013-0471-6
407. European Centre for Disease Prevention and Control. *Antimicrobial Resistance Surveillance in Europe 2015: Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net).* Accessed October 10, 2018. <https://www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/antimicrobial-resistance-europe-2015.pdf>
408. Anderson DJ, Kirkland KB, Kaye KS, et al. Underresourced Hospital Infection Control and Prevention Programs: Penny Wise, Pound Foolish? *Infect Control Hosp Epidemiol.* 2007;28(7):767-773. doi:10.1086/518518
409. Cutler D, Zeckhauser R. *The Anatomy of Health Insurance.* National Bureau of Economic Research; 1999:w7176. doi:10.3386/w7176
410. Drew RH. Antimicrobial Stewardship Programs: How to Start and Steer a Successful Program. *J Manag Care Pharm.* 2009;15(2 Supp A):18-23. doi:10.18553/jmcp.2009.15.s2.18
411. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (has-bled) to assess 1-year risk of major bleeding in patients with atrial fibrillation: The euro heart survey. *Chest.* 2010;138(5):1093-1100. doi:10.1378/chest.10-0134
412. Ministerie van Binnenlandse Zaken en Koninkrijksrelaties. Waterwet. Accessed July 26, 2021. <https://wetten.overheid.nl/BWBRO025458/2021-07-01>
413. European Parliament and Council. *In Vitro Diagnostic Medical Devices.*; 2017. Accessed October 12, 2020. <https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0746&from=EN>
414. European Commission. *Guidelines on COVID-19 in Vitro Diagnostic Tests and Their Performance.*; 2020. Accessed July 26, 2021. [https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52020XC0415\(04\)&from=NL](https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52020XC0415(04)&from=NL)
415. Esbin MN, Whitney ON, Chong S, Maurer A, Darzaeq X, Tjian R. Overcoming the bottleneck to widespread testing: a rapid review of nucleic acid testing approaches for COVID-19 detection. *RNA.* 2020;26(7):771-783. doi:10.1261/rna.076232.120
416. Venter M, Richter K. Towards effective diagnostic assays for COVID-19: a review. *J Clin Pathol.* 2020;73(7):370-377. doi:10.1136/jclinpath-2020-206685
417. Herten J van, Bovenkerk B, Verweij M. One Health as a moral dilemma: Towards a socially responsible zoonotic disease control. *Zoonoses Public Health.* 2019;66(1):26-34. doi:<https://doi.org/10.1111/zph.12536>
418. VALUE-Dx. Homepage. value-dx. Published September 7, 2021. Accessed September 7, 2021. <https://www.value-dx.eu/>

419. Lifelines. Lifelines maakt onderzoek naar gezonder oud worden mogelijk. Accessed July 27, 2021. <https://www.lifelines.nl/>
420. Health-RI. Data Driven Health: Connect, Share and Reuse | Health-RI. Accessed July 27, 2021. <https://www.health-ri.nl/data-driven-health-connect-share-and-reuse>
421. Center for Disease Dynamics, Economics & Policy. Antibiotic Resistance. ResistanceMap. Accessed July 27, 2021. <https://resistancemap.cddep.org/>
422. Fernandes P, Martens E. Antibiotics in late clinical development. *Biochem Pharmacol.* 2017;133:152-163. doi:10.1016/j.bcp.2016.09.025
423. Clancy CJ, Nguyen MH. Buying Time: The AMR Action Fund and the State of Antibiotic Development in the United States 2020. *Open Forum Infect Dis.* 2020;7(11):ofaa464. doi:10.1093/ofid/ofaa464
424. Velayati AA, Masjedi MR, Farnia P, et al. Emergence of new forms of totally drug-resistant tuberculosis bacilli: super extensively drug-resistant tuberculosis or totally drug-resistant strains in iran. *Chest.* 2009;136(2):420-425. doi:10.1378/chest.08-2427
425. Schnall J, Rajkhowa A, Ikuta K, Rao P, Moore CE. Surveillance and monitoring of antimicrobial resistance: limitations and lessons from the GRAM project. *BMC Med.* 2019;17(1):176. doi:10.1186/s12916-019-1412-8
426. Hulme M. 1.5 °C and climate research after the Paris Agreement. *Nat Clim Change.* 2016;6(3):222-224. doi:10.1038/nclimate2939
427. Wellcome Trust, Federation of European Academies of Medicine (FEAM). *EU Health and Emergency Preparedness and Response Authority: How Should the EU Prepare and Respond to Future Cross Border Health Threats?;* 2021. Accessed July 28, 2021. <https://cms.wellcome.org/sites/default/files/2021-05/EU-HERA-report-How-should-the-EU-prepare-and-respond-to-future-cross-border-health-threats.pdf>
428. European Commission. Health emergency preparedness and response authority (HERA): European Commission launches public consultation. *Press release.* https://ec.europa.eu/commission/presscorner/api/files/document/print/en/IP_21_1522/IP_21_1522_EN.pdf. Published April 6, 2021. Accessed July 28, 2021.
429. European Centre for Disease Prevention and Control. COVID-19 Situation Dashboard. Accessed July 28, 2021. <https://qap.ecdc.europa.eu/public/extensions/COVID-19/COVID-19.html#global-overview-tab>
430. European Centre for Disease Prevention and Control. *ECDC Strategy 2021-2027; 2021.* Accessed July 28, 2021. <https://www.ecdc.europa.eu/sites/default/files/documents/ECDC-Strategy-2021-2027.pdf>

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Summary

Tests are an essential aspect of health systems: not only are they necessary for the decision process in individual patients, but they are also an important component of public health policy making. In this thesis, three goals are defined for testing. First, screening, which involves population-wide testing to detect people suffering from a particular condition. Second, diagnosing, in which the most likely cause of a patient's complaints is determined and, in some cases, the optimal treatment for the complaints. Finally, monitoring, in which certain metrics of a patient are followed for a longer period to adjust the treatment plan if necessary. In infectious diseases, testing policy and infrastructure are very important. For example, for screening patients for the presence of resistant bacteria, identifying pathogens and mitigating outbreaks. Health-economic methods are important in decisions about investments in various tests and the implementation, considering both the interests of individual patients and the broad societal perspective.

School health care is important to screen children from an early age for various diseases; in **Chapter 2**, a survey was sent to experts in 31 countries to estimate the number of staff and their salaries. This is expected to be the main driver of spending on school health. It was possible to estimate expenditures for only five countries. Per 1,000 pupils, I estimated it to be between €43,000 in Estonia and €195,300 in Norway (adjusted for purchasing power differences between countries). This constitutes a small part of total health care expenditures: 0.16% - 0.69%.

Chapter 3 focuses on the costs associated with two outbreaks of vancomycin-resistant enterococci (VRE) in the University Medical Center Groningen (UMCG). Using different hospital data sources and interviews, I estimated the outbreak costs. During the first outbreak in 2017, tests were the main driver of the outbreak costs: almost two-thirds of the total costs. The second outbreak in 2018 was shorter than the first possibly due to proactive screening that allowed early detection and control of the outbreak. As a result, the total cost was roughly halved. This illustrates the importance of fine-grained testing, as it aids in the surveillance of the pathogens that patients are carrying.

In **Chapter 4**, I looked at the treatment of patients taking vitamin K antagonists (VKAs) around a surgical procedure. I combined several risk scores commonly used in clinical practice and combined them with data from various tests, such as blood pressure, INR, and renal function. About five days before a surgical procedure, VKA treatment is interrupted if the bleeding risk is high. Bridging therapy can help during this period of interrupted treatment to prevent strokes, but also significantly increases the risk of bleeding. I have developed a matrix that can help clinicians decide whether or not to bridge, taking into account quality-adjusted life expectancy. The results predict that for patients at high risk of bleeding, bridging therapy will most likely have no beneficial effect. For patients at low risk of bleeding and at very high risk of stroke, I found a significant benefit of bridging. However, these patients are expected to be very rare, as most patients at high risk of stroke will also have a high bleeding risk.

In **Chapter 5**, I reviewed 70 health-economic analyses of diagnostics for respiratory infections. Most studies used relatively simple models to assess cost-effectiveness, such as decision trees, with short time spans and non-generalizable outcome measures, rather than quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs). Antimicrobial resistance (AMR) was included in a minority of articles. Three approaches were primarily used for this purpose: adding a "social cost" to all antibiotic prescriptions; assuming a fixed percentage of infections are resistant; or dynamic resistance, varying over

the modelled time horizon, e.g., according to antibiotic use. Given the health-economic guidelines, there is room for improvement in the model design and reporting of cost-effectiveness analyses of diagnostics.

To help with these potential improvements, there are eight recommendations in **Chapter 6**. The symptoms experienced by patients, the clinical setting, sites of test sampling and analysis, and diagnostic algorithms should be clearly reported. The time horizon used should match the time horizon used to model treatment after the diagnostic pathway. QALYs or DALYs should be used as clinical outcomes, but these can be combined with other relevant outcomes, such as the value of real options. If the number of trials using the same equipment may vary, economies of scale should be considered. For a good understanding of the results, an understandable graphical representation of the different diagnostic algorithms should be provided, such as an efficiency frontier (EF). Finally, the budget impact and affordability must be considered.

Many of these recommendations were applied in **Chapter 7**, where I assessed the value of hypothetical testing in primary care in the Netherlands. Although bacteria are estimated to cause only a minority of respiratory infections in primary care, they are a major driver of antibiotic use, accounting for about 40% of all antibiotic prescriptions by general practitioners. I quantified the investments required for a large-scale rollout of improved point-of-care diagnostics in Dutch primary care and the effect on the number of antibiotic prescriptions. I developed a model that simulates consultations for respiratory infections in Dutch primary care and compared a scenario in which general practitioners test all patients with a hypothetical diagnostic strategy versus continuing the current standard of care for the years 2020-2030. The simulation was performed in the newly developed Modeling the Economics of Respiratory tract Infections and AMR (MERIAM) model, a simulation model for consultations of patients with respiratory tract infections. MERIAM is an innovative model that enables predictions of AMR; in this case, resistance of *Streptococcus pneumoniae* to broad-spectrum penicillins, which are the most common cause of bacterial respiratory tract infections and the most prescribed antibiotic, respectively. The diagnostic algorithm increased the total cost of GP consultations for CA-ARTI by 9% or by 19% over a 10-year period, at a cost of €5 or €10 per patient consultation, respectively. In these simulations, the predicted increase in resistance of *S. pneumoniae* to penicillins would be partially contained.

Chapter 8 concerns a memorandum of initiative, submitted by a member of Parliament to the House of Representatives and the Minister of Health. This note proposed the application of real options analysis (ROA) in strategies to control infectious diseases. The primary focus was on new vaccines and antibiotics, but the proposed framework can also be used in decisions related to the development, assessment, and implementation of microbiological tests. ROA can help policymakers consider time and scenarios. Health policy dilemmas rarely require a choice between “yes” or “no,” a choice can also be made between “right now” or “maybe later. ROA can be used to value specific investments, even if they are highly uncertainty. Given the inherent uncertainty surrounding infectious disease outbreaks, whether it is a pandemic or the development of resistant bacteria, ROA is an appropriate method for making informed decisions. For vaccines, this means investing in the development of platform technologies that can be tailored to new diseases; considering different scenarios about the incidence of the disease against which a vaccine offers protection; and considering the availability of different types of vaccines during outbreaks when procuring. For our testing infrastructure, the ROA can be used to assess the value of

an AMR monitoring program, an early warning system for potential pandemic diseases, or the value of being able to screen the entire population in the event of a pandemic.

In **Chapter 9**, I applied the EF method using a model for a new drug for the treatment of heart failure: sacubitril/valsartan. The EF approach is a method for assessing the cost-effectiveness of interventions that is standard in Germany. The EF has the advantage that, in addition to QALYs, many different types of outcomes can be used, and the willingness to pay for an investment is derived directly from the frontier, so policymakers do not need to set a threshold. A major drawback of this technique was also illustrated in this chapter, namely the difficulty of comparing a new, innovative strategy (such as sacubitril/valsartan) with established, much less expensive, strategies. In this case, no EF could be created and the threshold for cost-effectiveness could not be established. The main advantage of this method in the field of diagnostics is that different diagnostic algorithms can be compared and visualized, with different outcomes relevant to the decision problem. I believe that this approach can be used to complement standard methods in health economics, such as the incremental cost-effectiveness ratio (ICER) and cost-effectiveness acceptance curves (CEACs).

In **Chapter 10**, I proposed a tripartite insurance model (TIM) to create incentives to prevent outbreaks of drug-resistant infections in the hospital setting by linking hospitals, laboratories, and a claims insurer. If the TIM is implemented, the hospital negotiates with a laboratory to perform the hospitals' microbiology testing, including screening and diagnostics, for a fixed fee. This removes a barrier for clinicians to request tests, as they do not have to pay for each individual test. At the same time, the hospital takes out insurance for the risk of outbreaks, so that some of the costs discussed in Chapter 3, such as the opportunity cost of closed beds, are reimbursed in the event of an outbreak. This introduces an incentive for the insurer to minimize this risk: the insurer contracts the laboratory to monitor the hospital for implementation of infection prevention measures. Part of the TIM is that the laboratory not only analyses the test samples, but also provides expertise to interpret the results.

In this thesis, I covered many aspects related to the economics of testing strategies in healthcare, from the organization of screening tests to the use of diagnostics to combat AMR. It is important to consider the testing infrastructure: where should testing take place, close to the patient or in specialized laboratories; who should perform the test and how are these health professionals organized; and what value do the test results have for public health and how are these data shared? These are some of the issues to be considered for HTAs of tests. From a cost-effectiveness perspective, the underlying clinical data should be sufficient to compare the testing strategy to other health technologies, by using generalizable health outcomes, such as QALYs, and by using sufficiently long time horizons. In a CEA, the costs for society are related to the clinical benefits for patients, but for microbiological tests, the clinical value is broader than that, especially if tests can identify specific pathogens. The collected data can be used to make public health decisions, for example by updating treatment guidelines for infectious disease and by responding to AMR and potentially pandemic pathogens.

Nederlandse Samenvatting

Tests vormen een essentiële schakel in het gezondheidssysteem: niet alleen zijn ze noodzakelijk voor het beslisproces bij individuele patiënten, ze zijn ook een belangrijk onderdeel voor het maken van beleid op het gebied van de publieke gezondheid. In deze thesis worden drie doelen gedefinieerd voor tests. Allereerst screenen, waarbij populatie-breed wordt getest om mensen op te sporen die aan een bepaalde aandoening lijden. Ten tweede diagnosticeren, waarbij de oorzaak van klachten bij een patiënt wordt achterhaald en in sommige gevallen ook de optimale behandeling voor de desbetreffende klachten. Als laatste monitoren, waarbij bepaalde waarden van de patiënt voor een langere periode worden gevolgd om het behandelplan bij te stellen indien nodig. Bij infectieziekten zijn het testbeleid en de -infrastructuur zeer belangrijk, bijvoorbeeld voor het screenen van patiënten op de aanwezigheid van resistente bacteriën, het identificeren van ziekteverwekkers en het mitigeren van uitbraken. Gezondheids-economische methodes zijn van belang bij beslissingen over de investering en implementatie van tests, waarbij zowel het belang van de individuele patiënt wordt meegewogen, als een breed maatschappelijk perspectief.

De schoolgezondheidszorg is belangrijk om kinderen vanaf jonge leeftijd te screenen op verschillende ziektes, in **hoofdstuk 2** werd een enquête verstuurd naar experts in 31 landen om een schatting te maken van het aantal personeelsleden en hun salarissen. Dit is naar verwachting de belangrijkste drijvende kracht voor uitgaven aan de schoolgezondheid. Van slechts vijf landen was het mogelijk de uitgaven te schatten. Per 1.000 leerlingen schatte ik deze tussen €43.000 in Estland en €195.300 in Noorwegen (gecorrigeerd voor koopkrachtverschillen tussen landen). Dit vormt een klein deel van de totale uitgaven voor gezondheidszorg: 0,16% - 0,69%.

Hoofdstuk 3 richt zich op de kosten die samenhangen met twee uitbraken van vancomycine-resistente enterokokken (VRE) in het Universitair Medisch Centrum Groningen (UMCG). Door gebruik te maken van verschillende data-bronnen in het ziekenhuis en interviews, heb ik de uitbraakkosten geschat. Tijdens de eerste uitbraak in 2017 waren tests de belangrijkste aanjager van de uitbraakkosten: bijna twee derde van de totale kosten. De tweede uitbraak in 2018 was korter dan de eerste dankzij een proactieve screening waardoor de uitbraak vroeg werd ontdekt en onder controle was. De totale kosten zijn hierdoor ongeveer gehalveerd. Dit illustreert het belang van fijnmazig testen, omdat hiermee goed overzicht gehouden kan worden op de ziekteverwekkers die patiënten bij zich dragen.

In **hoofdstuk 4** heb ik gekeken naar de behandeling van patiënten die vitamine K-antagonisten (VKA's) gebruiken rondom een chirurgische ingreep. Ik combineerde verschillende risicoscores die in de klinische praktijk vaak worden toegepast en gecombineerd met gegevens van verschillende tests, zoals bloeddruk, INR en nierfunctie. Ongeveer vijf dagen voor een chirurgische ingreep wordt de VKA-behandeling onderbroken als het bloedingsrisico hoog is. Overbruggingstherapie kan helpen in deze periode van onderbroken behandeling om beroertes te voorkomen, maar verhoogt ook aanzienlijk het risico op bloedingen. Ik heb een matrix ontwikkeld die clinici kan helpen bij hun beslissing om al dan niet te overbruggen, rekening houdend met de voor kwaliteit gecorrigeerde levensverwachting. De resultaten voorspellen dat voor patiënten met een hoog risico op bloedingen, overbruggingstherapie hoogstwaarschijnlijk geen gunstig effect zal hebben. Voor patiënten met een laag risico op bloedingen en een zeer hoog risico op beroertes, vond ik een significant voordeel van overbrugging. Deze patiënten zullen echter naar

verwachting zeer zeldzaam zijn, aangezien de meeste patiënten met een hoog risico op een beroerte ook een hoog bloedingsrisico zullen hebben.

In **hoofdstuk 5** heb ik 70 gezondheids-economische analyses van diagnostica voor infecties van de luchtwegen beoordeeld. De meeste studies gebruikten relatief eenvoudige modellen om de kosteneffectiviteit te beoordelen, zoals beslisbomen, met korte tijdsperiodes en niet-generaliseerbare uitkomstmaten, in plaats van voor kwaliteit gecorrigeerde levensjaren (*quality-adjusted life years*, QALY's) of voor invaliditeit gecorrigeerde levensjaren (*disability-adjusted life years*, DALY's). Antimicrobiële resistentie (AMR) werd in een minderheid van de artikelen meegenomen. Hiervoor werden hoofdzakelijk drie benaderingen gebruikt: toevoeging van een “maatschappelijke kostenpost” aan alle antibioticavoorschriften; de veronderstelling dat een vast percentage infecties resistent is; of dynamische resistentie, variërend over de gemodelleerde tijdshorizon, bv. aan de hand van het antibioticagebruik. Gelet op de gezondheids-economische richtlijnen is er ruimte voor verbeteringen in de modelopzet en de rapportage van de kosten-effectiviteitsanalyses van diagnostica.

Om hierbij te helpen heb ik in **hoofdstuk 6** acht aanbevelingen gedaan. De symptomen die patiënten ervaren, de klinische setting, locaties van testbemonstering en -analyse, en diagnostische algoritmen moeten duidelijk worden gerapporteerd. De gebruikte tijdshorizon moet overeenkomen met de tijdshorizon die wordt gebruikt om de behandeling na het diagnostische traject te modelleren. Als klinische uitkomsten moeten QALY's of DALY's worden gebruikt, maar deze kunnen worden gecombineerd met andere relevante uitkomsten, zoals de waarde van reële opties. Als het aantal tests met dezelfde apparatuur kan variëren, moet rekening worden gehouden met schaalvoordelen. Voor een goed begrip van de resultaten moet een begrijpelijke grafische voorstelling van de verschillende diagnostische algoritmen worden gegeven, zoals een efficiëntiefrontier (EF). Ten slotte moet rekening worden gehouden met de budget impact en de betaalbaarheid.

Veel van deze aanbevelingen zijn toegepast in **hoofdstuk 7**, waar ik de waarde van hypothetische tests in de eerstelijnszorg in Nederland heb beoordeeld. Hoewel bacteriën naar schatting slechts een minderheid van de luchtweginfecties in de eerste lijn veroorzaken, zijn ze een belangrijke drijvende kracht achter het antibioticagebruik, goed voor ongeveer 40% van alle antibioticavoorschriften door huisartsen. Ik heb de investeringen gekwantificeerd die nodig zijn voor een grootschalige uitrol van verbeterde point-of-care diagnostiek in de Nederlandse eerstelijnszorg en het effect op het aantal antibioticavoorschriften. Ook ontwikkelde ik een model dat consulten voor luchtweginfecties in de Nederlandse eerstelijnszorg simuleert en vergeleken een scenario waarin huisartsen alle patiënten testen met een hypothetische diagnostische strategie ten opzichte van het voortzetten van de huidige standaard van zorg voor de jaren 2020-2030. De simulatie werd uitgevoerd in het nieuw ontwikkelde Modelling the Economics of Respiratory tract Infections and AMR (MERIAM)-model, een simulatiemodel voor consulten van patiënten met luchtweginfecties. MERIAM is een innovatief model dat voorspellingen van AMR mogelijk maakt; in dit geval resistentie van *Streptococcus pneumoniae* tegen breedspectrumpenicillines, die respectievelijk de meest voorkomende oorzaak van bacteriële luchtweginfecties en het meest voorgeschreven antibioticum zijn. Het diagnostisch algoritme verhoogde de totale kosten van huisartsconsulten voor CA-ARTI met 9% of met 19% over een periode van 10 jaar, bij een prijs van respectievelijk €5 of €10 per patiëntconsult. In deze simulaties zou de voorspelde toename van resistentie van *S. pneumoniae* tegen penicillines gedeeltelijk worden ingedamd.

Hoofdstuk 8 betreft een initiatiefnota, die door een Kamerlid is aangeboden aan de Tweede Kamer en de minister van Volksgezondheid. Deze nota stelt de toepassing voor van reële optie analyse (ROA) bij strategieën ter bestrijding van infectieziekten. De nadruk lag in de eerste plaats op nieuwe vaccins en antibiotica, maar het voorgestelde kader kan ook worden gebruikt bij beslissingen in het kader van de ontwikkeling, beoordeling en uitvoering van microbiologische tests. ROA kan beleidmakers helpen bij het overwegen van tijd en scenario's. Bij dilemma's in gezondheidsbeleid moet er zelden tussen 'ja' of 'nee' worden gekozen, er kan ook worden gekozen voor 'nu meteen' of 'misschien later'. ROA kan worden gebruikt om specifieke investeringen te waarderen, ook als deze met veel onzekerheid gepaard gaan. Gezien de inherente onzekerheid over uitbraken van infectieziekten, of het nu gaat om een pandemie of om de ontwikkeling van resistente bacteriën, is ROA een geschikte methode om onderbouwd beslissingen te nemen. Voor vaccins betekent dit dat we moeten investeren in de ontwikkeling van platformtechnologieën die op nieuwe ziekten kunnen worden toegesneden; dat we bij de beoordeling rekening moeten houden met verschillende scenario's over de incidentie van de ziekte waartegen een vaccin bescherming biedt; en dat we bij de aanschaf rekening moeten houden met de beschikbaarheid van verschillende soorten vaccins tijdens uitbraken. Voor onze testinfrastructuur kan de ROA worden gebruikt om de waarde te beoordelen van een AMR-monitoringprogramma, een systeem voor vroegtijdige waarschuwing voor potentiële pandemische ziekten of de waarde van het kunnen screenen van de hele bevolking in geval van een pandemie.

In **hoofdstuk 9** heb ik de EF-methode bekeken aan de hand van een model voor een nieuw geneesmiddel voor de behandeling van hartfalen: sacubitril/valsartan. De EF-benadering is een methode om de kosteneffectiviteit van interventies te beoordelen die in Duitsland standaard is. De EF heeft het voordeel dat, naast QALY's, veel verschillende soorten uitkomsten kunnen worden gebruikt, en dat de bereidheid om te betalen voor een investering (willingness to pay) rechtstreeks van de frontier wordt afgeleid, zodat beleidmakers geen drempel hoeven vast te stellen. Een belangrijk nadeel van deze techniek werd ook in dit hoofdstuk geïllustreerd, namelijk de moeilijkheid om een nieuwe, innovatieve strategie (zoals sacubitril/valsartan) te vergelijken met gevestigde, veel minder dure, strategieën. In dit geval kon geen EF worden gecreëerd en kon de drempelwaarde voor de kosteneffectiviteit niet worden vastgesteld. Het belangrijkste voordeel van deze methode op het gebied van diagnostiek is dat verschillende diagnostische algoritmen kunnen worden vergeleken en gevisualiseerd, met verschillende uitkomsten die relevant zijn voor het beslissingsprobleem. Ik ben van mening dat deze benadering kan worden gebruikt als aanvulling op de standaardmethoden in de gezondheidseconomie, zoals de incrementele kosteneffectiviteitsratio (ICER) en kosteneffectiviteitsacceptatiecurven (CEAC's).

In **hoofdstuk 10** heb ik een tripartiet verzekeringsmodel (TIM) voorgesteld om prikkels te creëren ter voorkoming van uitbraken van resistente infecties in de ziekenhuissetting, door de ziekenhuizen, laboratoria en een schadeverzekeraar met elkaar te verbinden. Als het TIM wordt toegepast, onderhandelt het ziekenhuis met een laboratorium om voor een vast bedrag de microbiologische tests van de ziekenhuizen uit te voeren, met inbegrip van screening en diagnostiek. Dit neemt een drempel weg voor clinici om tests aan te vragen, aangezien zij niet voor elke afzonderlijke test hoeven te betalen. Tegelijkertijd sluit het ziekenhuis een verzekering af voor het risico van uitbraken, zodat een deel van de in hoofdstuk 3 besproken kosten, zoals de opportuniteitskosten van gesloten bedden, worden vergoed in geval van een uitbraak. Dit introduceert een prikkel voor de verzekeraar om dit risico te minimaliseren: de verzekeraar contracteert het laboratorium om het

ziekenhuis te controleren op de uitvoering van infectiepreventiemaatregelen. Onderdeel van TIM is dat het laboratorium niet alleen de testmonsters analyseert, maar ook expertise levert voor het interpreteren van de resultaten.

In dit proefschrift heb ik verschillende economische aspecten behandeld gerelateerd aan tests in de gezondheidszorg: van de organisatie van screenings tot het gebruik van diagnostica ter bestrijding van AMR. Het is belangrijk om na te denken over de testinfrastructuur: waar moeten de tests plaatsvinden; wie moet de test uitvoeren; en welke waarde hebben de testresultaten voor de volksgezondheid? Vanuit het oogpunt van kosteneffectiviteit moeten de onderliggende klinische gegevens toereikend zijn om de teststrategie met andere gezondheidstechnologieën te kunnen vergelijken, door gebruik te maken van generaliseerbare gezondheidsuitkomsten, zoals QALY's, en door de lange termijn mee te nemen in de analyse. In een kosteneffectiviteitsanalyse worden de kosten voor de samenleving gerelateerd aan de klinische voordelen voor de patiënt, maar voor microbiologische tests is de klinische waarde breder dan dat. De verzamelde gegevens kunnen worden gebruikt om beslissingen te nemen op het gebied van de publieke gezondheid, bijvoorbeeld door de behandelingsrichtlijnen voor infectieziekten te verbeteren en door te reageren op AMR of mogelijk pandemische ziekteverwekkers.

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Dankwoord

Aan al het moois komt een eind, en op het moment dat ik dit op papier zet, komt het einde van mijn tijd als promovendus wel erg dichtbij. Het is een periode geweest waar ik echt fantastisch mooie kansen heb gehad, zowel direct gerelateerd aan het onderzoek, als daarbuiten. Hoewel je nooit iedereen kan bedanken die daar een rol bij heeft gespeeld, ga ik hier toch een poging wagen.

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About the Author

Simon van der Pol was born in Groningen on December 22, 1991. After finishing grammar school at Gymnasium Celeanum in Zwolle in 2010, he moved to Groningen to study Pharmacy at the University of Groningen. During this time, he had various roles next to his core studies, including being employed at the department of Educational Support and Innovation of the Centre of Information Technology of the university, being appointed as president of the *Jongerenorganisatie Vrijheid en Democatie* (JOVD) Groningen, and being elected twice in the faculty council of the Faculty of Science and Engineering. While writing his Master thesis with Maarten Postma, his enthusiasm for health economics was raised, leading to the pursuit of a PhD in this field after obtaining a Master's in pharmacy in the Summer of 2017.

During Simon's PhD trajectory, he was involved with various organizational and political organizations next to his core work as a researcher. Directly related to health economics, he was secretary and later president of the ISPOR Student Chapter in Groningen; was involved with the fourth edition of the European Health Parliament, within the committee of Innovation & Value, and was an intern in the Dutch Tweede Kamer to write a memorandum of initiative. To represent PhD candidates and the broader academic community in Groningen, he was a member of the SHARE PhD Council, chair and secretary of the Groningen Graduate Interest Network (GRIN) and member of the University Council for the Personnel Faction. He also was involved with municipal politics in Groningen, as a spokesperson and, temporarily, as a member of the Municipality Council for the *Volkspartij voor Vrijheid en Democratie* (VVD).

Towards the end of his PhD studies, Simon launched his own company: Orbium Health B.V., where he collaborated with different partners such as the Netherlands Antibiotics Development Platform (NADP) on alliance management and with Health~Holland on a proposal for the Dutch growth fund on pandemic preparedness (APOLLONL). He also joined Health-Ecore, a start-up company looking to aid in the transition to more sustainable healthcare.

Publications and Presentations

Publications supporting this thesis

Scientific

Van der Pol, S., Jansen, D.E.M.C., van der Velden A.W., Butler C.C., Verheij T.J.M., Friedrich A.W., Postma, M.J., & van Asselt, A.D.I. (2022). The Opportunity of Point-of-Care Diagnostics in General Practice: Modelling the Effects on Antimicrobial Resistance. *PharmacoEconomics*

Van der Pol, S., Rojas García, P., Antoñanzas Villar, F., Postma, M.J., & van Asselt, A.D.I. (2021). Health-Economic Analyses of Diagnostics: Guidance on Design and Reporting. *Pharmacoeconomics*.

Van der Pol, S.* Rojas Garcia, P.* Postma, M.J., Antoñanzas Villar, F., & van Asselt, A.D.I. (2021). Economic Analyses of Respiratory Tract Infection Diagnostics: A Systematic Review. *Pharmacoeconomics*.

Van der Pol, S., Dik, J-W. H., Glasner, C., Postma, M.J., Sinha, B., & Friedrich, A.W. (2021). The tripartite insurance model (TIM): a financial incentive to prevent outbreaks of infections due to multidrug-resistant microorganisms in hospitals. *Clinical Microbiology and Infection*, 27(5), 665-667.

Van der Pol, S., Postma, M.J., & Jansen, D.E.M.C. (2020). School health in Europe: a review of workforce expenditure across five countries. *BMC Health Services Research*, 20(1), [206].

Van der Pol, S., de Jong, L.A., Vemer, P., Jansen, D.E.M.C., & Postma, M.J. (2019). Cost-Effectiveness of Sacubitril/Valsartan in Germany: An Application of the Efficiency Frontier. *Value in Health*, 22(10), 1119-1127.

Van der Pol, S., Jacobs, M.S., Meijer, K., Piersma-Wichers, M.G., Tielemans, R.G., Postma, M. J., & van Hulst, M. (2019). Perioperative Bridging of Vitamin K Antagonist Treatment in Patients with Atrial Fibrillation: Only a Very Small Group of Patients Benefits. *Europace*, 21(5), 716–723. [308].

Van der Pol, S., Degener, F., Postma, M.J., & Vemer, P. (2017). An Economic Evaluation of Sacubitril/Valsartan for Heart Failure Patients in the Netherlands. *Value in Health*, 20(3), 388-396.

Societal

Initiatiefnota van het lid Veldman over anticiperen op toekomstscenario's: beschikbaarheid van vaccins en antibiotica met behulp van reële optiewaarden – Kamerstukken II 2020/21, 35676, nr. 2

Other publications

Scientific

Rojas-Garcia, P., van der Pol, S., van Asselt, A. D. I., Postma, M. J., Rodriguez-Ibeas, R., Juarez-Castello, C. A., Gonzalez, M., & Antonanzas, F. (2022). Diagnostic Testing for Sepsis: A Systematic Review of Economic Evaluations. *Antibiotics* , 11(1), [27].

Van Dorst, P. W. M., van der Pol, S., Salami, O., Dittrich, S., Olliari, P., Postma, M., Boersma, C., & van Asselt, A. D. I. (2022). Evaluations of training and education interventions for improved infectious disease management in low-income and middle-income countries: a



systematic literature review. *BMJ Open*, 12(2)

Hagendijk, M.E., van der Schans, S., Boersma, C., Postma, M.J., & van der Pol, S. (2021). Economic evaluation of orphan drug Lutetium-Octreotide vs. Octreotide long-acting release for patients with an advanced midgut neuroendocrine tumour in the Netherlands. *European Journal of Health Economics*, 22(6), 991-999.

Rojas García, P., van der Pol, S., van Asselt, A.D.I., Postma, M.J., Rodríguez-Ibeas, R., Juárez-Castelló, C.A., González, M., & Antoñanzas Villar, F. (2021). Efficiency of Diagnostic Testing for Helicobacter pylori Infections: A Systematic Review. *Antibiotics*, 10(1), [55].

Van der Pol, S., Jong, de, L., Vemer, P., Jansen, D.E.M.C., & Postma, M.J. (2020). Author's Reply: Response to Defining comparators according to IQWIG's efficiency-frontier method. *Value in Health*, 23(5), 675-676.

Van der Schans, S., Vondeling, G.T., Cao, Q., van der Pol, S., Visser, S., Postma, M.J., & Rozenbaum, M.H. (2020). The impact of patent expiry on drug prices: insights from the Dutch market. *Journal of market access & health policy*, 9(1), [1849984].

Machlaurin, A., van der Pol, S., Setiawan, D., van der Werf, T.S., & Postma, M.J. (2019). Health economic evaluation of current vaccination strategies and new vaccines against tuberculosis: a systematic review. *Expert review of vaccines*, 18(9), 897-911.

Fens, T.* Van der Pol, S.* Kocks, J.W.H., Postma, M.J., & van Boven, J.F.M. (2019). Economic Impact of Reducing Inappropriate Inhaled Corticosteroids Use in Patients With Chronic Obstructive Pulmonary Disease: ISPOR's guidance on budget impact in practice . *Value in Health*, 22(10), 1092-1101.

Professional

van der Pol, S., Fens, T., Kocks, J.W.H., Postma, M.J., & van Boven, J.F.M. (2020). Goed volgen nieuwe COPD-richtlijn maakt kostenbesparing mogelijk. *Pharmaceutisch Weekblad*, 155(10), 26-27.

Reports

Van der Pol, S., Sandhu, A.K., Mierau, J.O., & Jansen, D.E.M.C. (2022). Strengthening Public Health in the Netherlands: Lessons from Global Public Health Systems. [report commissioned by the *Raad voor Volksgezondheid & Samenleving*]

Wolff, R., van Asselt, A.D.I., Emamipour, S., van der Pol, S., Postma, M.J., Chalker, A., Posadzki, P., Ahmadu, C., Armstrong, N., Harrison, S., de Kock, S., & Kleijnen, J. (2021). Sotorasib for previously treated KRAS G12C mutated, locally advanced or metastatic non-small-cell lung cancer [ID3780]: a Single Technology Assessment. [Evidence Review Group report commissioned by the NIHR Evidence Synthesis Programme]

Rojas García, P., C.A., González, M., Antoñanzas Villar, F., van der Pol, S., van Asselt, A.D.I., & Postma, M.J., (2020). Review of health-economic approaches for diagnostic-driven antibiotic use. [deliverable VALUE-Dx, Innovative Medicines Initiative]

Jansen, D.E.M.C., Visser, A., Vervoort, J.P.M., van der Pol, S., Kocken, P., Reijneveld, S.A., & Michaud, P.A. (2018). School and Adolescent Health Services in 30 European countries: A description of structure and functioning, and of health outcomes and costs. [deliverable MOCHA, Horizon 2020]

Conference presentations

Van der Pol, S., Postma, M.J., & van Asselt, A.D.I. (2022). Predicting Changes in Antimicrobial Resistance after Implementing Large-scale Point-of-care Diagnostics in the Netherlands. Oral presentation at EUHEA conference 2022, Oslo, Norway.

Leonard, C., Rojas García, P., van der Pol, S., & Feldhaus, I. (2020). Assessing the Value of Point-of-Care Diagnostics: Economic Analyses and Appraisals. Workshop presented at ISPOR Europe 2020, online.

Van der Pol, S., Rojas García, P., Juarez-Castello, C., van Asselt, A. D. I., Antonanzas, F., & Postma, M.J. (2019). Health-economic modelling of infectious disease diagnostics: current approaches and future opportunities. Poster session presented at ISPOR Europe 2019, Copenhagen, Denmark.

Van der Pol, S., Postma, M.J., Jansen, & D.E.M.C (2018). Costs and Cost Effectiveness of School Health Systems. Workshop presented at the 11th European Public Health Conference, Ljubljana, Slovenia.

Van der Pol, S. & Postma, M.J. (2018). Cost-effectiveness of sacubitril/valsartan in Germany: applying the efficiency threshold. Oral presentation at ISPOR Europe 2018, Barcelona, Spain.

Van der Pol, S. & Postma, M.J. (2018). Differences in health economic modelling guidelines in Germany and the Netherlands: a case study of one intervention. Oral presentation at EHMA annual conference 2018, Budapest, Hungary.

Van der Pol, S., Jacobs, M.S., Meijer, K., Piersma-Wichers, M. G., Tielemans, R.G., Postma, M.J., & van Hulst, M. (2018). To Bridge or Not to Bridge: Modelling Periprocedural Anticoagulation Management. E417. Poster session presented at 17th Biennial European Meeting of the Society for Medical Decision Making, Leiden, the Netherlands.

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