Making Informed Decisions

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CHAPTER

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 globally[1]. 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 clear[3] and due to a shortage of tests the incidence of new COVID-19 cases was unknown[4]. 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 billion[8]. 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 Fleming[9], 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 antibiotics[10]. 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 annually[11] and AMR is expected to rise in the years to come[12]. 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 resort[15]. Various governments are looking to new funding models to incentivize the development of novel antibiotics, such as a subscription model in the United Kingdom[15]. 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 connected[16]. 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 infection[17]. 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 objectives[18]:

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 models[19]. 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 people[20]. 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 future[14]. 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 problems[20].

The value of tests to counter AMR is a clear focus of this thesis: although there is broad support from clinicians[22], researchers[11,14], companies[23], and policy makers[18] 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 gastroenterology ward. The aim is to find disease in a defined population, in people without, or unaware of, symptoms[24]. 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 tests[25]. 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 high[28]. 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 patient[29]. 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 management[30].

Currently, the majority of clinical tests are performed in hospitals and diagnostic laboratories, although the exact setting varies between countries[31]. 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 labs[32]. 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 pandemic[4]. 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 adherence[30]. 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 regulations[33]. 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 market[34]. As costs related to the delivery of care have been rising in the past decades[35], 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 patients[36]. 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 system[37]. 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 domains[38]. 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, pharmaceuticals[39]. 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 life[40]. 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 utility[41]. 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 simultaneously[42]. 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 isolation[44]. 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 *Enterococci*, 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 *Trombosedienst* 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 complex[14]. 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-generationally[20]. 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 implant[45]. 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 required[47]. Under the previous legislation, there was a focus on technical standards, for diagnostics this may concern the sensitivity and specificity of a test[48]. 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 evaluations[50]. 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