Costs of infectious diseases outbreaks and cost-effectiveness of interventions

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Costs of infectious diseases outbreaks and cost-effectiveness of interventions

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CHAPTER 1

General introduction

CHAPTER 1: GENERAL INTRODUCTION

Western economies rely on market forces that promote the health and wealth of their populations. Already in 1776, Adam Smith famously described in his book *The Wealth of Nations*, how such an economy is led by 'an invisible hand' towards economic success, wealth, and personal freedom. The economic growth, starting with the Industrial Revolution in the eighteenth century, has been responsible for millions of people escaping from material deprivation. The progress in wealth has been accompanied by a progress in health and a rise in life expectancy [1]. Around 1900 knowledge arose that microorganisms cause disease, and public health organisations and professionals put that knowledge into practice, leading to the provision of clean water and the development of vaccines and antibiotics to further reduce morbidity. In addition, Fogel found that a progress in peoples' nutrition and health further strengthens economy and welfare [2]. Paradoxically, health progress created gaps in health just as material progress created gaps in living standards. These 'health inequalities' come from a division between rich and poorer countries in which rich countries can benefit more from innovations in healthcare [1]. But also in developed countries health inequalities exist, expressed in differences in life expectancy between socio-economic groups in which less educated people have more chronic diseases [3]. Depending on how these inequalities are valued, public policies are needed to overcome these undesired outcomes of the market economy.

Currently, Western economies are far more complex than in the days of Adam Smith, which especially applies to the healthcare sector being a so-called 'imperfect' market in which the 'invisible hand' needs help of the government. First of all, prices of medicines, devices, and equipment are high due to the monopoly of manufacturers achieved through patents and marketing [4]. Second, the demand for most goods and services depends primarily on the willingness and ability of persons to pay. For most people, however, the need for (future) healthcare is unclear and utilization is highly concentrated in certain patient groups. Since most persons are risk-averse and diseases can lead to major and unaffordable expenditure, a person's uncertainty about demand for healthcare becomes a demand for health insurance. All Western countries, therefore, developed a sophisticated health care system in which risks are shared and the government subsidizes demand by paying for part or all of some patients' care. Finally, patients needing healthcare cannot always deliberately choose an intervention or treatment but they depend on the knowledge and information of the professional. As a result, suppliers have a certain level of influence to steer demand of patients, which is an important cause of increasing health expenditure.

Due to higher healthcare demands, the rise in people with chronic conditions, the availability of new medical technologies, and the increased specialization that accompanies it, health expenditures have been rapidly growing in the last decades. Therefore, the healthcare system faces governmental constraints and competing priorities [3]. With ongoing debates concerning the implementation and funding of preventive interventions, targeted at chronic diseases versus infectious diseases, cost-of-illness studies and economic evaluations are increasingly important to policy-makers [5, 6]. This thesis focusses on the prevention of infectious diseases.

Infectious diseases

Despite a global decrease in communicable diseases in the last decade, infectious diseases are still an important cause of worldwide morbidity and mortality [7]. For the Netherlands, the annual disease burden of 32 selected infectious diseases in the period 2007-2011 was estimated at approximately 58,000 Disability Adjusted Life Years (DALY) [8]. Disease burden studies use the DALY as a composite measure combining the number of life years lost and the number of years lived with morbidity. Invasive pneumococcal diseases and influenza generated the highest average annual disease burden at respectively 9444 DALYs/year and 8670 DALYs/year. The disease burden of infectious diseases is considerably higher since the above-mentioned study only includes 32 infectious diseases. For example, the average annual HPV disease burden, that was not included in the Dutch burden study, was estimated at 10,600 DALYs alone over the period 2011-2014 [9]. Enhanced hygienic measures and vaccination programs have reduced the burden of infectious diseases greatly in the past century [10]. However, an effective preventive intervention or treatment is not available for every infectious disease. In addition, vaccination refusal, climate change, globalization, increased mobilizations of populations, and aging populations being more susceptible for infection altogether contribute to disease transmission [11, 12]. Another concern is antibiotic resistance, which decreases the ability to cure many common acute infections [13]. Curing bacterial infections can be hampered by the absence of alternative treatments. Moreover, inappropriate use of antibiotics further stimulates antibiotic resistance.

Besides affecting mortality and morbidity, infectious diseases incur costs to society. It results in healthcare costs, productivity losses, patients' costs, and sometimes in costs in other domains of society such as (special) education costs. The enclosure of economic aspects in healthcare evaluation turns out to be a widely accepted part of health policy and planning [14, 15]. The assessment of the cost-of-illness of infectious diseases (outbreaks) is therefore also of interest in healthcare evaluation. Economic evaluations such as cost-effectiveness, cost-utility and social cost-benefit analyses

guide decision makers in choosing the most optimal intervention, given scarce resources, ultimately generating good value for money in the prevention of infectious diseases [16].

Costs of infectious diseases outbreaks

In 2015, World Health Organization considered eight pathogens as a top priority to cause severe outbreaks globally [17]. This list of pathogens included the following viruses: Crimean Congo haemorrhagic fever, Ebola virus, Lassa fever, Marburg virus, Middle East respiratory syndrome (MERS), Nipah, Rift Valley fever, and Severe acute respiratory syndrome (SARS) coronavirus diseases. The majority of worldwide emerging infectious diseases events comes from wildlife [18]. These outbreaks occur mostly in Africa and Asia and can become a disaster in the countries affected resulting in amongst others social disruptions, border control, restrictions on international trade, decline in travel and tourism income, and healthcare costs [19]. In the Western world, mostly other types of outbreaks are of importance such as foodborne and respiratory outbreaks. Although to a lesser extent, these outbreaks can have a large impact on society as well and induce financial costs, such as medical costs, productivity losses and a decline in consumption [20]. All these outbreaks have in common that they are poorly predictable, launching unforeseen control efforts to contain transmission. Therefore, healthcare organizations should be well prepared to address sudden increases in infectious diseases [21]. Evaluation of specific outbreak-related costs including preparedness and response activities of public health authorities is of importance. Such estimates of total costs of controlling outbreaks can help in planning activities around future outbreaks and optimizing the allocation of public resources.

Disease prevention

The US Center for Disease Control (CDC) has developed a framework to protect the general population from infectious diseases, and to reduce morbidity and save lives during outbreaks [22]. At first, a strong public health system is essential including infectious disease surveillance, laboratory detection, and epidemiologic investigation. The second component is the identification of instruments for preventive strategies for (amongst other diseases) vaccine preventable diseases, healthcare-associated infections, HIV/AIDS, foodborne infections, zoonotic diseases, and chronic viral hepatitis. These instruments can be vaccines, treatments, screening initiatives, but also health education programs. A couple of infections that are linked to chronic diseases can be prevented by vaccines such as hepatitis B and Human Papilloma Virus (HPV), others such as *Borrelia burgdorferi* (causing Lyme disease) can be prevented by education the population on inspection of the body and adequate removal of ticks.

Additionally, Lyme disease can be treated with antimicrobial drugs. A third element is the general development of evidence-based and cost-effective policies to prevent, detect, and control infectious diseases. These policies improve the health of vulnerable populations, promote collaboration with foreign partners to reduce cross-border disease spread, and contain outbreaks at their source. In the Netherlands, notification of 43 infectious diseases is legally anchored in the Public Health Act (Wet Publieke Gezondheid) [23, 24]. In this Act, 43 diseases are assigned into A, B, and C categories, depending on the necessary control measures. Many organisations are involved in infectious diseases prevention and control: municipal health services, hospitals, travel clinics, peripheral laboratories, general practitioners, and other professionals [25, 26]. In case of a nationwide outbreak the National Institute of Public Health and the Environment (RIVM) functions as a national coordinator, responsible for activation of control measures including communication to professionals and the public. Based on surveillance and epidemiological research, RIVM supports these organizations with specific advice and guidelines. Economic evaluations often contribute to the development of new national policies targeted at infectious diseases.

Economic evaluations

Health economic evaluations include a range of different approaches [27]. First, there are partial evaluations, which provide information on the cost implications of diseases, outbreaks, and interventions. These evaluations can be informative about how to reduce costs; however, they do not assess the value that is added with the money spent. Full economic evaluations compare the costs and effects of two (or more) competing possibilities, a new intervention versus current practice that is often no intervention but could as well be an already implemented alternative. In these evaluations efficiency is considered: what is the extra cost of one intervention compared to the other, and what gains would the funding body or society get in return for that extra cost? Three types of full economic evaluation exist: cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-benefit analysis (CBA).

These methods differ in how they assess health effects. Health outcomes in CEAs are expressed in terms of specific end points such as the number of persons vaccinated, infections averted or, more general, life years gained. In CUAs health effects are expressed in a generic measure of health, combining morbidity and mortality. The most common measures used are the quality adjusted life year (QALY) and the already described DALY. Findings of CEAs and CUAs are reported as an incremental cost-effectiveness ratio (ICER) representing the extra cost of gaining an additional health unit (CEA) or QALY (CUA). CBA is the broadest type of economic evaluation, expressing health effects of an intervention in monetary terms (for example in Euros or dollars). The cost categories included in these economic evaluations depend on

the perspective that is taken for the analysis. For example, if a healthcare payer perspective is adopted, only costs that are incurred by the payer are considered. In case a societal perspective is assumed, all costs borne by the whole society become important. A specific form of CBA is the social cost-benefit analysis (SCBA) [28]. This method assesses the distribution of the costs and benefits of new interventions over the different societal stakeholders involved. The valuation of the costs and benefits in an SCBA allows comparison and ranking of the results of the various interventions. The overall sum of benefits and costs is reported as a net value, being the sum of all the valued benefits minus the sum of all the valued costs. If the monetized balance of the total costs and total benefits is positive, this will guide implementation of preventive interventions having the largest impact on population level welfare. Depending on the specific type of information that is needed for answering the research question, one method will be more suitable than the others.

Aim of this thesis

The aim of this thesis is (1) to explore the costs of infectious diseases outbreaks in the Netherlands. Both the broad economic impact of infectious diseases outbreaks and possible room for improvement for reducing costs in future outbreaks are depicted. Furthermore (2), the cost-effectiveness of interventions in infectious disease control is evaluated for specific case studies.

Thesis outline

This thesis consists of two parts.

Part 1

In Part 1 the societal costs of various infectious diseases outbreaks are assessed. Here, research followed actual outbreaks that were observed in the Netherlands in recent years.

In **chapter 2,** the economic impact of a *Salmonella* Thompson outbreak, caused by smoked salmon is evaluated. In this study, total costs of the *S.* Thompson outbreak are assessed taking underestimated cases into account. In **chapter 3,** total costs of the 2013-2014 measles outbreak in orthodox Protestant communities with low measles-mumps-rubella vaccination coverage are estimated whereas in **chapter 4,** the costs of Ebola preparedness and response borne by the Dutch health system are described. Finally, costs related to a *Klebsiella pneumoniae* NDM-1 outbreak concerning 29 colonized patients in a Dutch hospital are assessed in **chapter 5**.

Part 2

Part 2 presents the results of several economic evaluations of infectious diseases interventions.

In **chapter 6,** the potential introduction of universal or targeted hepatitis A vaccination in the Netherlands is considered taking cost-of-illness, disease burden, hepatitis A epidemiology, and programme costs into account. **Chapter 7** systematically reviews economic evaluations of HPV vaccination including non-cervical HPV associated diseases. In **chapter 8,** the consequences of a restricted STI-testing policy for young heterosexuals in the Netherlands on test costs and QALY losses are evaluated. **Chapter 9** describes the design of a social cost-benefit analysis of preventive interventions for toxoplasmosis, of which the results are depicted in **chapter 10. Chapter 11** evaluates the cost-effectiveness of hepatitis B and C screening for foreign born migrants. Finally, in **Chapter 12** the results obtained in the presented studies are discussed and placed into broader perspective. This chapter concludes with implications of the findings for decision-making and recommendations for future research.

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CHAPTER 2

The economic burden of a *Salmonella* Thompson outbreak caused by smoked salmon in the Netherlands, 2012-2013.

Anita Suijkerbuijk, Martijn Bouwknegt, Marie-Josee Mangen, Ardine de Wit, Wilfrid van Pelt, Paul Bijkerk, Ingrid Friesema

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ABSTRACT

Background

In 2012, the Netherlands experienced the most extensive food-related outbreak of *Salmonella* ever recorded. It was caused by smoked salmon contaminated with *Salmonella* Thompson during processing. In total, 1,149 cases of salmonellosis were laboratory confirmed and reported to RIVM. Twenty percent of cases was hospitalised and four cases were reported to be fatal. The purpose of this study was to estimate total costs of the *S.* Thompson outbreak.

Methods

Data from a case-control study were used to estimate the cost-of-illness of reported cases (i.e. healthcare costs, patient costs, and production losses). Outbreak control costs were estimated based on interviews with staff from health authorities. Using the Dutch foodborne disease burden and cost-of-illness model we estimated the number of underestimated cases, and the associated cost-of-illness.

Results

The estimated number of cases, including reported and underestimated cases was 21,123. Adjusted for underestimation, the total cost-of-illness would be €6.8 million (95% CI €2.5 - €16.7 million) with productivity losses being the main cost driver. Adding outbreak control costs, the total outbreak costs are estimated at €7.5 million.

Conclusion

In the Netherlands, measures are taken to reduce salmonella concentrations in food, but detection of contamination during food processing remains difficult. As shown, *Salmonella* outbreaks have the potential for a relatively high disease and economic burden for society. Early warning and close cooperation between the industry, health authorities, and laboratories is essential for rapid detection, control of outbreaks, and to reduce disease and economic burden.

INTRODUCTION

From August to December 2012, the Netherlands experienced the largest foodborne outbreak of gastroenteritis due to salmonellosis in humans ever recorded [1]. The cause of the outbreak was smoked salmon processed at a single production site in Greece. In total, 1149 Salmonella cases due to *Salmonella* Thompson were identified, laboratory-confirmed and reported to the National Institute for Public Health and the Environment (RIVM) [1]. Most cases were female (65%); the median age was 45 years. A significant number of patients were hospitalised and four elderly were reported to have died due to the infection.

In addition to the burden of disease, acute gastroenteritis incurs considerable societal costs [2, 3]. Most cost studies include only healthcare costs and productivity losses due to work absence of persons that were ill themselves or had to take care of a sick child. Especially in the case of community-acquired foodborne outbreaks, however, costs are not limited to the cost-of-illness [3, 4]. Once an outbreak is identified public health authorities conduct investigations to determine the pathogen and the source, and if required, implement control measures to prevent further spread. Not considering these costs would result in an underestimation as they can be quite large [3].

The 1149 laboratory-confirmed and reported cases in the *S.* Thompson outbreak are expected to be an underestimation of the real number of cases. First, persons with symptoms might not see a physician, second, physicians might not perform diagnosis and, third, laboratories might not be reporting. For that reason, it is essential to correct for underestimation when estimating the total economic impact of an outbreak [5].

The evaluation of the economic impact of an outbreak is important input for public health policy with respect to prioritization of prevention and control efforts of Salmonellosis. This paper aims at estimating total costs of all cases corrected for underestimation of the *S.* Thompson outbreak, including cost-of-illness and outbreak control costs.

METHODS

General approach

We calculated total outbreak costs based on 1149 laboratory-confirmed and reported cases defined as persons in the Netherlands with *S.* Thompson cultured from any sample type, confirmed by the RIVM between August and December 2012, (and referred hereafter as reported cases) as well as on reported cases corrected for underestimation (referred hereafter as underestimated cases). Total outbreak costs estimates included cost-of-illness (i.e. healthcare costs, patient costs, and productivity losses), and outbreak control costs. All costs are expressed at the 2012-euro price level and were discounted at 4% according to the Dutch manual for health economic evaluations [6].

Surveillance system and outbreak responsibilities

Salmonellosis is not a notifiable disease in the Netherlands; clinicians are not legally obliged to report a single case with salmonellosis. The Dutch laboratory surveillance network consists of 16 regional public health laboratories covering 64% of the population, that voluntarily send *Salmonella* spp isolates to the RIVM for further typing. In the Netherlands, the RIVM, the Dutch Food and Consumer Product Safety Authority (NVWA) and Municipal Health Services (MHSs) are accountable for control of foodborne outbreaks. At the start of the outbreak the RIVM and NVWA collaborated in the outbreak investigation and the case-control study [1]. MHSs administered the questionnaires in cases, RIVM in controls. The NVWA was responsible for product tracing during the outbreaks. Where possible, supermarkets and patients were contacted and food samples were taken. Other outbreak response activities concerned the microbiological investigations both at the RIVM and at regional public health laboratories, advising the public, and activities regarding extensive media attention.

Cost-of-illness of reported cases

Healthcare costs

Information on healthcare use regarding the number of general practitioner (GP) visits due to gastroenteritis was not available. Since in all cases a laboratory test was performed, we assumed that all cases had to visit their GP at least once and typically would consult their GP by phone for the result of the diagnostic test. We assumed that

Table 1. Healthcare costs and patient costs of reported cases (N=1149)

	No. of patients	Unit cost (€)	Source unit cost	Utilized number of units per patient	Total cost (€)
Healthcare costs					
GP consultation non-hospitalised cases	919	29.73	[6]	1.5	40,983
GP consultation hospitalised cases	230	29.73	[6]	2	13,676
Subtotal GP consultation					**54,659**
Diagnostics: cases	1149	108	[11]	1	123,782
Diagnostics: additional samples	46	108	[11]	1	4,956
Subtotal diagnostics					**128,737**
Hospitalisation: general ward	230	485.28	[6]	4	446,458
Hospitalisation: nursing home	2	252.73	[6]	60	30,328
Subtotal Hospitalisation					**476,786**
Sequelae					
-ReA moderate cases visiting GP	20	29.73	[10]	1	595
-Cases needing medication	11	154[a]	[10]	-	1,756
-ReA severe cases	1	432.64[a]	[10]	-	433
IBS cases seeking healthcare[b]	70	406.67[a]	[10]	-	132,373
Subtotal sequelae					**135,156**
Total healthcare costs					**795,337**
Patient costs					
Over-the-counter-medication	1149	6.45	[10]	1	7,411
Travel cost moderate GE cases	919	1.59	[10]	1	1,461
Travel cost severe GE cases	230	6.25	[10]	1	1,438
Travel cost after hospital discharge	230	4.43	[10]	1	1,019
Total patient costs					**11,329**

[a] cost per case per year, [b] only 70% of IBS cases need medical care, discounted costs are calculated for 5 years, GP= general practitioner, ReA= Reactive Arthritis, IBS= Irritable Bowel Syndrome, GE=gastroenteritis

all regional laboratories performed a PCR and culture before sending the *Salmonella* isolates to the RIVM (personal communication D. Notermans, medical microbiologist RIVM). In addition, antibiotic susceptibility was assessed by the regional laboratories. Information on symptoms, onset of diseases and hospitalisation was gathered by a questionnaire (N=100 laboratory confirmed cases at the start of the outbreak) in the case-control study [1]. The average duration of hospitalisation in this sample was four days. We extrapolated this finding to all 1149 reported cases in the outbreak. The

estimated proportion of hospitalisation among reported cases was 20%, based on the number of hospital admissions due to salmonellosis as reported in the Dutch Hospital Data-database in 2012. For hospitalised cases, we assumed that they had visited their GP twice before hospitalisation. According to Friesema et al. one out of 17 hospitalised cases aged ≥65 stayed in a nursing home for 60 days after discharge [7]. According to Dutch guidelines, we assumed that reported cases would not require further treatment [8]. *Salmonella* infections occasionally result in sequelae as reactive arthritis (ReA), an acute aseptic arthritis caused by an infection elsewhere in the body and irritable bowel syndrome (IBS), a syndrome commonly causing cramping, diarrhea and/or obstipation or inflammatory bowel disease (IBD), a chronic intestinal disorder of unknown aetiology. We also assessed healthcare costs for these health outcomes. Incidence data, resource use, and illness duration were retrieved from two Dutch studies [9, 10] as no data was collected during the outbreak. In these studies ReA was further divided into three subcategories, so-called 'health states': mild (patient does not seek medical help, and recovers), moderate (patient visits a GP and recovers) and severe (patient is hospitalised and recovers). Healthcare resource utilization was multiplied by Dutch unit cost prices as published in national health economic evaluation guidelines [6] and list prices from the Dutch Healthcare Authority available online [11] (Table 1).

Patient costs

Patients cost are cost paid by patients themselves, so-called 'out-of-pocket-costs'. Estimates for travel cost and over-the-counter-medication (OCM) for gastroenteritis were based on Mangen et al. [10] and are summarized in Table 1.

Productivity losses

To calculate productivity losses for adults aged 18 to 64, sick leave length was multiplied by standard unit prices related to average wage by age and sex [6], adjusted for work participation and average working hours in all age groups [12]. Duration of sick leave of adult gastroenteritis patients was assumed to be similar to the duration of illness, i.e. on average 7 days [8]. Estimates for productivity losses for parents staying at home to take care for a sick child as well as for patients experiencing an episode of ReA and IBS were based on Mangen et al. [10] (Table 2). We considered no productivity losses for the four fatal cases, as they were all retired.

Outbreak control costs

Outbreak control costs included additional laboratory tests and staff time of the RIVM, NVWA, and MHSs. Regional laboratories sent positive isolates for further serotyping to the RIVM. In a subset of isolates the RIVM performed pulsed-field gel electrophoresis

(PFGE). For laboratory tests performed at the RIVM we used list prices online, which also include labour time [13]. Staff time of the RIVM was based on hours assigned to outbreak investigation and response. This was obtained from the RIVM time recording system and personal interviews with the staff in the relevant departments within the institute, the latter were held in January 2015. We calculated staff costs by multiplying a person's hourly tariff, by the time spent on the outbreak. The NVWA supplied the amount of personnel time associated with outbreak response activities of the organisation. An estimated time of 15 minutes was assumed for contacting a case; the telephone interview to complete the questionnaire by the MHS was assumed to last 30 minutes. We assumed that public health nurses spent most time (80%) on the outbreak while public health physicians spent 20% of the time.

Cost-of-illness for underestimated cases

To estimate the total impact of the *S*. Thompson outbreak, we corrected for underestimation, based on an incidence and pathogen based model that estimates the disease burden and cost-of-illness of *S*. Thompson cases amongst other *Salmonella* spp. infections in the Dutch community [9, 10]. Following the methodology described in Havelaar et al. [9], incidences for Salmonella infections and for sequelae were estimated. In short, the incidence estimate of *Salmonella* infections is based on data from a Dutch population-based cohort-study performed in 1998-1999 [14], and updated based on active surveillance data [15]. Moreover, estimates on GP visits, hospitalisations, and mortality were gathered from active surveillance, other registries and Dutch studies [12, 16]. Incidences for ReA, IBS, and IBD were estimated using probabilities of developing complications after an episode of gastroenteritis [9, 17, 18]. To estimate the total burden due to *S.* Thompson, two model runs were conducted: one based on the total number of reported salmonellosis cases, and one in which reported *S*. Thompson cases were excluded. The number of underestimated *S.* Thompson isolates could be estimated by comparing the proportion of reported incidence by the proportion of *S.* Thompson isolates in historical data of the population based study. The difference in estimates was attributed to the outbreak. These estimates were subsequently used to estimate the cost-of-illness consisting of healthcare costs, patient costs and productivity losses, for full detail see Mangen et al. [10]. Also productivity losses of fatal cases aged 18 to 64 years were calculated, following the friction-cost-method in which the amount of productivity losses due to death depends on the time-span needed by organisations to restore the initial production level, the so-called friction period which was assumed to be 160 days [6]. Costs were assessed until symptom recovery (i.e. <1 year for gastroenteritis and ReA; on average 5 year for IBS and lifelong for IBD) [10]. The model was built in Analytica Professional 4.4.1, Lumina Decision Systems, Los Gatos, CA, USA. Statistical

Table 2. Productivity losses of laboratory confirmed cases

Work absenteeism for adults[a]					
	Male	Female			All cases
Adult cases aged 18-64	209	377			586
Employment rate	74%	61%			
Working hours per week	39	28			
Productivity costs per hour (€)	34.50	27.54			
Subtotal productivity losses adult cases (€)	207,251	178,688			385,940
Work absenteeism for sick children[b]					
	Cases	Work absenteeism needed	No. of hours (work primary caregiver)	Cost per hour (€)	Productivity losses
Children aged 0-3	58	100%	16.4	27.54	26,196
Children aged 4-12	105	50%	16.4	27.54	23,712
Subtotal productivity losses due to sick children (€)					49,908
Productivity losses due to sequelae					
	cases	Work absenteeism needed	No. of hours	Cost per hour (€)	Productivity losses
ReA moderate	10	35%	7.67[c]	31.88	856
ReA severe	0.5	100%	196.04[c]	31.88	3,125
IBS adults	50	74.88%	18.43[c]	31.88	21,998
IBS children 0-3	5	100%	2.21[d]	27.54	307
IBS children 4-12	9	100%	1.11[d]	27.54	277
Subtotal productivity losses sequelae					26,562
Total productivity losses (€)					**462,410**

[a] mean duration of illness is 7 days,[b] we assumed that parents would not stay at home for sick children aged 12-18, [c] work absenteeism of patient, [d] work absenteeism of primary caregiver taking care of their children

uncertainty with respect to incidence estimates was considered using Monte Carlo simulation technique and running per simulation 10,000 iterations. All other variables were considered fixed by using average resource utilization and fixed unit cost prices. Results are presented as mean and the 95% confidence interval, representing the range between the 2.5 and the 97.5 percentile of the simulated results.

Total outbreak costs

Total outbreak costs were obtained by summing up cost-of-illness of underestimated cases and outbreak control costs. Cost-of-illness estimates of underestimated cases include uncertainty. Cost-of-illness of reported cases and outbreak control costs were regarded as fixed.

RESULTS

Cost-of-illness of reported cases

During the outbreak, 1149 cases were laboratory confirmed and reported; mostly adult cases aged 20 to 65 years. Of these cases, 230 patients were estimated to be hospitalised (Table 1). Twenty-one and 100 cases were expected to develop complications as ReA and IBS, respectively; no cases were expected to develop IBD. The main cost driver of healthcare costs was hospitalisation, followed by costs for laboratory tests. The average healthcare costs per hospitalised case were €1,941 (Table 1). Total patient costs were estimated at €11,329 (Table 1). An estimated €207,251 was attributed to productivity losses of men with confirmed diagnosis of *S.* Thompson (Table 2). Productivity losses for women due to infection were calculated at €178,688. Productivity losses due to complications of disease were assessed at €26,562 and for the care of sick children: €49,908.

Outbreak control costs

Three departments at the RIVM were involved in the outbreak: the Centers for Epidemiology and Surveillance of Infectious Diseases, Communicable Disease Control, and Infectious Diseases Research Diagnosis and Screening. During the outbreak, representatives of these departments participated in a weekly outbreak response meeting, in which the current outbreak and national containment strategies were discussed. Table 3 shows the total labour time and costs for all public health personnel involved as well as costs for serotyping and PFGE. Total outbreak investigations costs were estimated at €653,565. NVWA had with 61% the largest share within outbreak control costs. Adding up cost-of-illness of reported cases and outbreak control costs, total outbreak costs, without correction for underestimation, would have been € 1.9 million, whereof healthcare costs accounted for 41% of these total costs (with 1149 reported cases; € 1,673 per case). The outbreak control costs accounted for 34%, followed by the productivity losses with 24%. The patient costs comprised only 1% of total costs.

Table 3. Outbreak control costs (€)

	cases	labour time (hours)	Unit costs (€)	cost (€)
RIVM				
Serotyping				
Clinical samples	1149		62	71,238
Additional samples	46		62	2,852
Food samples	55		62	3,410
PFGE	60		113	6,780
Subtotal laboratory				84,280
Outbreak investigation, communication		1045	88.72	92,712
Total RIVM costs				176,992
NVWA				
Trace back, risk assessment		3333	119.62	398,733
MHSs				
Filling out questionnaires of cases, advice of local authorities and public		1228	63.40	77,839
Total costs				**653,565**

Correcting for underestimation

Comparing the number of *S.* Thompson infections with that of previous years, an estimated 22,123 persons in the general population would have had acute gastroenteritis with *S*. Thompson attributable to consumption of infected smoked salmon, of which 3473 cases would have consulted a GP, and around 25 persons may have died from this infection (Table 4). Adjustment for underestimation, yielded a total cost-of-illness of €6.8 million (95% CI €2.5 - €16.7 million). In these figure the costs of reported cases are included. Adding outbreak control costs, the total outbreak costs are estimated at €7.5 million. Productivity losses are the main cost driver, leading to two-third of total outbreak costs (€4.9 million). Healthcare costs were €1.7 million, outbreak control costs €0.7 million, and patient costs €0.1 million (Figure 1).

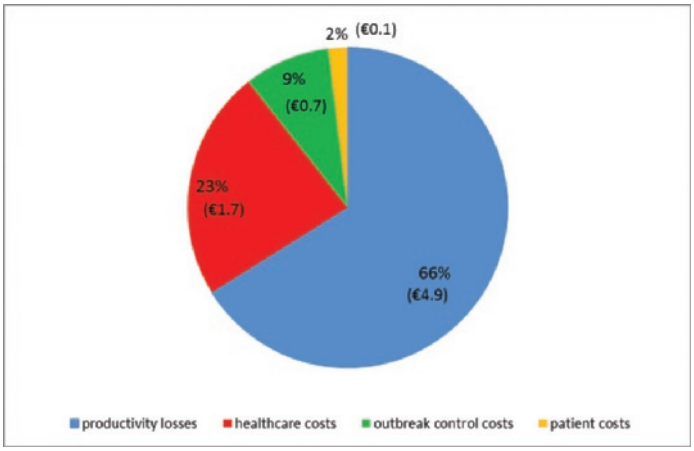

Figure 1. Distribution of main cost categories including laboratory confirmed and underestimated cases (costs*million)

Table 4. Incidence and costs of underestimated cases including reported cases

	Incidence		Costs * €1000							
			Healthcare		Productivity losses		Patient costs		Total	
Health state	**Mean**	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**
GE total	**22,123**	**3,340 - 65,800**	**1,117**	**1,024 - 1,360**	**4,373**	**1,170 - 11,700**	**89**	**35 - 207**	**5,580**	**2,300 - 13,000**
GE non consulting	18,651	0 - 62,600	-	-	3,134	0 - 10,500	50	0 - 167	3,184	0 - 10,700
GE at the General Practitioner	3,473	1,900 - 5,800	522	430 - 770	1,146	610 - 1,900	38	20 - 63	1,706	1,060 - 2,700
No stool sample submitted	2,187	690 - 3,900	106	34 - 191	719	230 - 1,300	24	7 - 42	848	270 - 1,500
Stool sample submitted	137	0 - 1,630	22	0 - 256	46	0 - 540	1.5	0 - 18	69	0 - 814
Reported to RIVM[a]	1,149	-	395	-	382	365 - 400	13	13 - 13	790	770 - 805
Hospitalized cases for GE[a]	230	-	595	590 - 600	62	60 - 65	1.9	1.9 - 1.9	659	653 - 663
Fatal GE cases[b]	25	21 - 29	-	-	31	27 - 36	-	-	31	27 - 36
Sequelae total	**2,229**	**544 - 6,150**	**624**	**125 - 1,800**	**577**	**90 - 1,740**	**54**	**9 - 160**	**1,255**	**225 - 3,700**
Reactive arthritis	285	110 - 570	20	4 - 55	3.6	0.9 - 9.6	0.2	0 - 0.5	24	5 - 66
Mild	225	80 - 450	-	-	-	-	-	-	-	-
Moderate	61	20 - 140	7.0	2.1 - 16	1.7	0.5 - 3.9	0.1	0 - 0.3	8.8	2.6 - 20
Severe	3	0 - 9	13	1.1 - 44	1.9	0.2 - 6.4	0.1	0 - 0.3	15	1.3 - 50
Inflammatory Bowel Disease	4	4 - 4	20	19 - 23	3.1	2.8 - 3.4	1.0	0.9 - 1.1	25	23 - 27
Irritable Bowel Syndrome	1,939	290 - 5,800	584	86 - 1,760	571	85 - 1,717	53	7.7 - 160	1,207	180 - 3,660
Total costs			**1,741**	**1,150 - 3,160**	**4,951**	**1,260 - 13,440**	**143**	**44 - 370**	**6,835**	**2,525 - 16,700**

[a] *known number / only additional costs that were not considered in previous health states are included*
[b] *only productivity losses considered, because healthcare and patient cost were already considered in previous health states*

DISCUSSION

The *S.* Thompson outbreak in the Netherlands was associated with substantial cost, accumulating to approximately €1.9 million if not correcting for underestimated cases and €7.5 million if underestimation is taken into account. The majority of the costs were incurred over a period of six months. Faster identification of the source was not possible given the setting of this outbreak (i.e. sale), with low number of cases in the beginning of the outbreak and as a result low number of completed questionnaires [1]. Moreover, the salmon was also part of other products, such as pre-sale ready-to-eat salads, hampering the detection of the source of infection.

In our study, the assessed total outbreak costs are an underestimation. Data restrictions did not allow the inclusion of the costs for the Dutch fish company and supermarket chains after setting the production on hold, recalling contaminated smoked salmon from supermarkets and potential economic losses due to loss of business. In the months after the outbreak, supermarket chains reported a decrease in salmon sale valued at €10 million (source: Nielsen Netherlands). Furthermore, costs of a nationwide evaluation of the *S.* Thompson outbreak performed by the Dutch Safety Board [19] were not included in this study, as well as continuing costs made by the NVWA after the acute outbreak phase. In addition, costs made outside the Netherlands were not taken into account, neither for foreign control authorities, nor for infected persons outside the Netherlands. Finally, we included productivity losses due to mortality using the friction approach rather than the human capital approach. The human capital approach would have led to considerable higher costs [20]. During this outbreak, large media activities targeted at the general public were set up to prevent the consumption of smoked salmon that was bought before the cause of the outbreak was detected. However, wide media attention might result in an increased demand for healthcare services (and consequently raise healthcare costs) for gastroenteritis not caused by *S.* Thompson [21].

In our study, the estimates of the underestimated cases are based on general *Salmonella* characteristics and may not fully represent healthcare resource use and productivity losses of *Salmonella* Thompson infection. For instance, the age distribution of cases in the model differs somewhat from that of the actual laboratory confirmed cases. In the model, the proportion of children is higher (37%) compared with the laboratory confirmed cases (26%). This could result in an overestimation of healthcare costs for small children. At the same time, productivity losses among adult cases may be underestimated. Healthcare costs per reported case are relatively

higher than healthcare costs per underestimated case, mainly due to the more severe illness of reported cases. In addition, the high number of productivity losses among the underestimated cases indicates that many persons experiencing gastroenteritis will not go to a physician but stay at home for a few days.

Cost studies on foodborne outbreaks in developed countries are scarce and show a large diversity for the cost categories considered [3, 22-26]. The costs of an outbreak depend on its size. If the source of infection was spread via large-scale sale-channels, the economic costs were considerable [22, 26, 27], for example in an Italian outbreak of Salmonellosis caused by contaminated chocolate economic costs were £0.5 million in 1982 [26]. Costs of foodborne outbreaks tended to be lower if the main source of contamination was food served in a closed setting such as a restaurant, party or catering [23-25, 28-31]. Moreover, the pathogen responsible for the outbreak is of importance such as the administration of e.g. immune globulin to contacts - as in the case of hepatitis-A virus - results in high control costs [29] ranging from 30,353 to 200,480 (US$ 2007) per affected person [32].

In this study, the findings highlight the considerable societal costs associated with foodborne outbreaks like the *Salmonella* Thompson outbreak. This information can be supportive in preparation for upcoming foodborne outbreaks and in optimizing allocation of public resources to preventive interventions and/or policy measures. In the Netherlands, various actions aimed at reducing risks for a *Salmonella* infection have been undertaken, such as measures taken in poultry farming, leading to a decreasing trend in human infections over the past few years [33]. Smoked salmon is an uncommon source of foodborne outbreaks of salmonellosis. According to the Dutch Safety Board, unpredictable contaminations in the food processing industry may take place that are difficult to prevent and thus cannot be ruled out. Therefore the food industry should be better prepared for such incidents [19]. Moreover, reinforcement of the incident management organisation of food manufacturers and retailers is needed for large-scale incidents. This outbreak showed that close collaboration between the industry, laboratories, national public health and food safety institutes, and MHSs is essential to contain outbreaks rapidly in order to reduce the burden of disease as well as societal costs.

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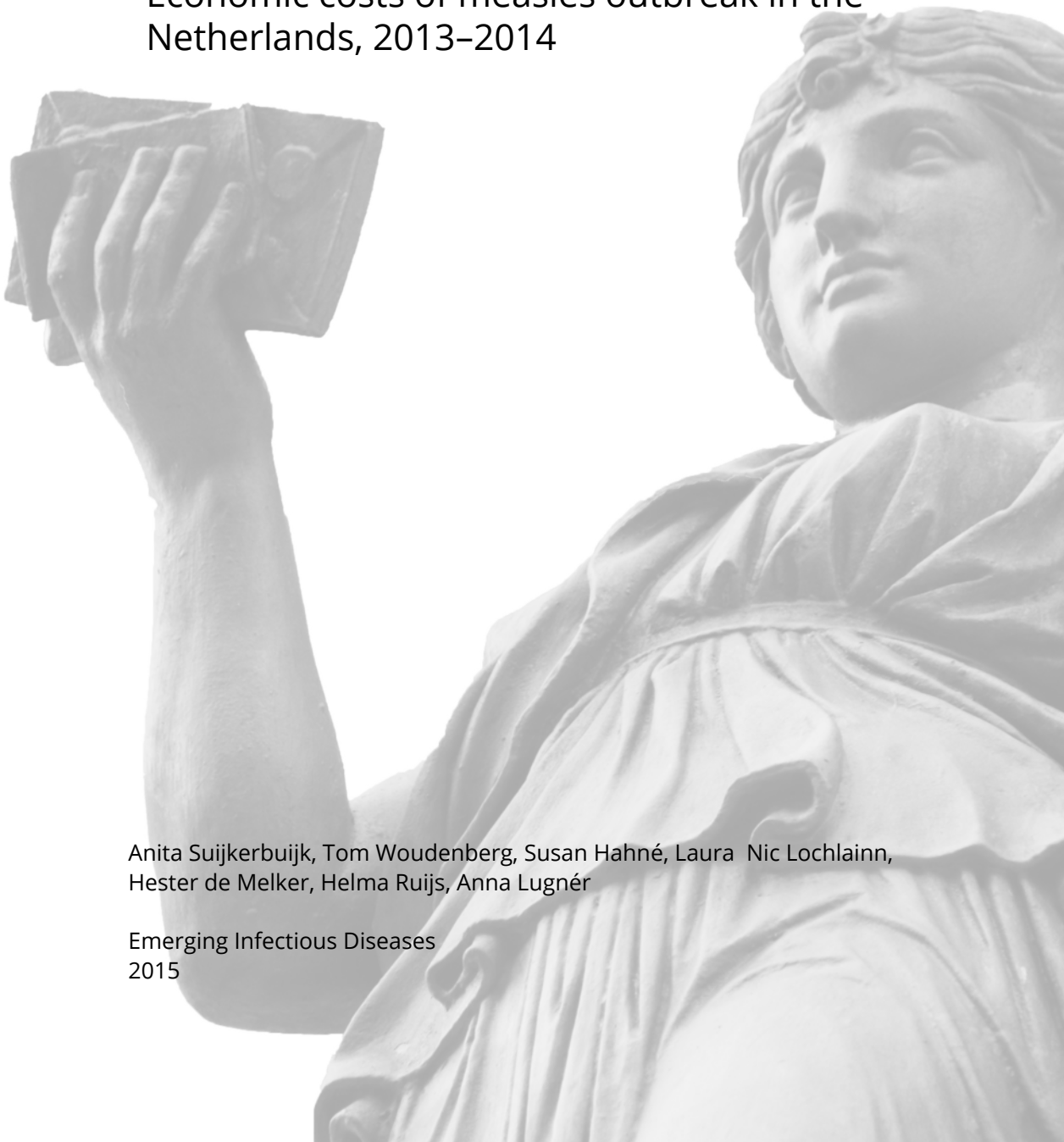
CHAPTER 3

Economic costs of measles outbreak in the Netherlands, 2013–2014



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ABSTRACT

In 2013 and 2014, the Netherlands experienced a measles outbreak in orthodox Protestant communities with low measles, mumps, and rubella vaccination coverage. Assessing total outbreak costs is needed for public health outbreak preparedness and control. Total costs of this outbreak were an estimated $4.7 million.

During May 2013–March 2014, the Netherlands was affected by a large measles outbreak [1]. The outbreak began in the center of the country in an orthodox Protestant community and spread mainly to regions with low vaccination coverage. Overall, the Netherlands has high measles–mumps–rubella (MMR) vaccination coverage, with >95% coverage for the first dose of MMR for children. However, some orthodox Protestant and anthroposophic communities opt out of childhood vaccination programs on religious grounds or personal beliefs [2]. In addition to the effects of disease on a society, measles outbreaks have economic consequences, including direct medical costs and productivity losses. Moreover, a measles outbreak demands a range of responses from the National Institute for Public Health and the Environment (RIVM) and municipal public health services (MHS). Assessing outbreak costs, including costs of response activities by public health authorities, can help in planning for future outbreaks and in optimizing allocation of public resources. Recent research on measles outbreak costs in industrialized countries is scarce and has addressed hospitalizations costs [3], costs of imported cases of measles [4-7] or small outbreaks [8, 9]. We assessed the economic costs of a large measles outbreak in the Netherlands.

THE STUDY

All physicians and laboratories are mandated to report measles to MHSs in the Netherlands. Each MHS records patient information in a national database, which includes information on age, postal code, date of symptoms, complications, hospitalization, and source of infection. Notifications of measles cases were used to assess medical costs and productivity losses (online Technical Appendix, http://wwwnc.cdc.gov/EID/article/21/11/15-0410-Techapp.pdf). Information on additional serologic tests and extra vaccinations among health care workers in hospitals were obtained from a study on the implementation of measles guidelines for hospitals (online Technical Appendix). Information about vaccinations of infants and older unvaccinated children in response to the outbreak was retrieved from the national immunization register. We interviewed staff at MHSs and the RIVM to assess the amount of personnel time related to outbreak response activities (online Technical Appendix).

Table 1. Estimated direct health care costs during measles outbreak, the Netherlands, 2013–2014*

Type of cost	Total no. patients	Unit cost, $	Average health care utilization	Total cost, $
Physician consultation				
Uncomplicated measles, no visits	2,320	37.35	0.2	17,330
Uncomplicated measles, no phone calls	2,320	18.07	0.1	4,192
Hospitalization, no. cases	181	37.35	1.0	6,760
Other complicated measles, no cases	199	37.35	2.0	14,865
Treatment for pneumonia in general practice, no. cases	75	16.02	.01	1,202
Length of hospitalizations, d				
General ward	174	600	4.6	480,240
Intensive care unit	7	2866	13.1	262,812
Rehabilitation	1	447	245	109,515
Serologic test results, no. cases†			.	
Positive tests	139	21.37	1.0	2,970
Negative tests	854	21.37	1.0	18,250
DNA/RNA amplification, no cases‡				
Positive tests	765	251.55	1.0	192,436
Negative tests	577	251.55	1.0	145,144
Total				**1,255,718**

**Costs are calculated in 2013 US dollars ($). Total number of measles cases = 2,700. Total cost differs from sum of category costs because of rounding. †IGM. ‡ PCR.*

During the epidemic, 2,700 measles cases were reported, mostly among children 5–14 years of age (Table 1). In 329 patients, complications such as otitis media, pneumonia, and encephalitis developed. One child died from measles complications, and 181 patients were hospitalized. One patient with encephalitis spent 8 months in a rehabilitation clinic. Of patients who consulted a physician but were not hospitalized, 199 experienced measles complications, mostly otitis media (104 patients) or pneumonia (75 patients). Total estimated cost for direct health care was $1,255,718 (mean $465/case). An additional $365,855 ($136/case) was attributed to productivity losses and informal child care losses (online Technical Appendix Table 1). In 2013, most (85%) of the responding hospitals in the Netherlands offered a serologic test to employees to ensure that they were sufficiently protected against measles (online Technical Appendix). Employees identified as being at risk for measles infection were offered an MMR vaccination. On average, 80 serologic tests led to 63 vaccinations per hospital for a total estimated cost of $222,203 (Online Technical Appendix Table 2).

At the start of the outbreak, the RIVM convened a national outbreak management team to discuss a strategy regarding targeted vaccination campaigns for infants living in communities with low vaccination coverage and for previously unvaccinated persons. A total of 6,652 infants received a complementary MMR vaccination. Among children 18 months–19 years of age, 6,948 received an MMR vaccination during July 2013–March 2014. Costs for these vaccinations were $299,840. During this outbreak, the RIVM also coordinated outbreak control, conducted enhanced surveillance, and responded to extensive media attention (online Technical Appendix). Total costs for outbreak response activities by the RIVM were an estimated $698,280 ($259/case). In addition, we collected information from 6 MHSs that together had recorded more than half of all notified measles cases nationally. Their response activities included registration and processing of cases, vaccination activities, and advising of local authorities, professionals, and the general population (Technical Appendix). Total estimated costs for all MHSs were $1,852,470 ($686/case).

The MHSs incurred most of the costs of the outbreak, followed by costs for hospitalizations (Table 2). Costs of outbreak response activities by the RIVM were also considerable. Costs classified as other medical costs (i.e., consultations with general practitioners), productivity losses, and costs for vaccination campaigns were among the lowest costs (Tables 2; online Technical Appendix Table 3).

Table 2. Distribution of costs of measles outbreak, the Netherlands, 2013–2014*

Category	Costs, $	% of total costs
MHS	1,858,470	39.5
Hospitalization	852,567	18.2
RIVM	698,280	14.9
Production losses	365,885	7.8
Laboratory tests	358,801	7.6
Vaccination of children	299,840	6.4
Vaccination of health care workers	222,203	4.7
General practitioner consultation	44,350	0.9
Total	**4,694,395**	**100**

**Costs are calculated in 2013 US dollars ($). Total costs and % does not equal because of rounding. MHS, municipal public health services; RIVM, National Institute for Public Health and the Environment, the Netherlands.*

CONCLUSIONS

The measles outbreak occurring in the Netherlands during 2013–2014 is associated with substantial costs of ≈$4.7 million (€3.9 million) or 0.0042% of overall health care costs ($113 billion in 2013) in the Netherlands. The 2,700 reported measles cases during this outbreak resulted in an estimated $1,739 per case. Outbreak management costs were the primary cost, probably because of demands for expert advice, response to extensive media attention, registration of notified cases, and more surveillance activities than usual.

Despite being substantial, the outbreak costs in our study are underestimated. Because of data limitations, we were unable to estimate normal human immunoglobulin costs, patients' traveling costs, or costs of vaccinations of adults or of long-term complications of disease. Also, cases in other countries have been linked to this outbreak, including Canada, United States, and Belgium; associated costs for cases imported to other countries are not included in our calculations. Furthermore, surveillance systems are affected by a degree of underreporting; therefore, uncertainty exists about the "true" economic costs of disease [10]. In a previous measles outbreak in the Netherlands, the estimated true number of measles cases was ≈10 times the number of cases reported in the surveillance system [11]. Moreover, only 47% of hospitalized cases in the previous outbreak were reported [12]. Applying these data to our results, the estimated total outbreak costs would be ≈$0.9 million higher. Further research into the extent of underreporting in this outbreak is planned.

In Australia, the public health unit cost for responding to a single case of measles was $1,701 [7], a similar amount to our results. In the United States, costs of containing an outbreak were estimated at $6,180 per case. Additional U.S. studies report that containment of a single imported measles case resulted in even higher costs per case [5, 6]. Explanations for the higher costs in the United States include more extensive contact tracing and higher medical care expenses.

The 2013–2014 measles outbreak posed considerable logistical challenges for MHS staff. Registration of reported cases contributed especially to the increased workload and costs created by this measles outbreak. To reduce this workload during a large outbreak, information considered to be critical for review could be collected for most patients, who usually recover within a few days or weeks, while more detailed information should continue to be collected for patients with complications or serious illness.

Measles substantially affects patients' quality of life [13] and their ability to perform their usual daily activities. Complications resulting from measles, such as pneumonia, encephalitis, and subacute sclerosing panencephalitis, sometimes occur a few years after the illness [14]. Complications from measles also affect quality of life and incur high financial costs, as shown in the extensive rehabilitation care needed by a patient with encephalitis that resulted from this outbreak. In the Netherlands, because religious arguments affect vaccination rates [15], elimination of measles will be challenging. For the foreseeable future, measles outbreaks are expected to continue to cause substantial effects from disease and economic costs. To prepare for new outbreaks, medical costs, productivity losses, and containment costs should be considered.

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TECHNICAL APPENDIX
ADDITIONAL METHODS AND RESULTS

Case Definition

The measles case definition used is based on the presence of clinical symptoms and laboratory confirmation of diagnosis. An epidemiologically linked case is defined as someone with a matching clinical presentation who had contact with a laboratory-confirmed case. The measles case definition used is consistent with that of the European Centre for Disease Control and Prevention [16].

Assessment of Outbreak Costs

Direct Medical Costs

Information on health care use regarding the number of general practitioner (GP) visits due to measles infection has been reported [11]. In a previous Dutch outbreak, van Isterdael et al. (2004) estimated that 30% of the measles patients consulted their GP. We used this average number of consultations for patients without complications and assumed that 1 third of the patients contacted their GP by phone and the remainder by a GP visit (unpub. data, Tom Woudenberg, RIVM, Bilthoven, the Netherlands). In line with the Dutch health care system, we assumed that all hospitalized patients had consulted a GP once. Patients for whom complications developed (but who were not hospitalized) were assumed to have visited their GP twice. According to Dutch guidelines, apart from pneumonia, most measles complications reported by GPs (i.e., otitis media, dehydration, and upper respiratory infection) do not require further treatment [17]. Medical costs were gathered from standard unit cost lists [18] and list prices available online [19]. The unit cost per hospitalized day comprises treatment in hospital, treatment in an intensive care unit, and clinician consultation fees. Since the database of notified cases did not include negative diagnostic tests, we estimated the total number of diagnostic tests by applying the ratio of positive and negative diagnostic tests of the RIVM laboratory to all positive tests recorded in the national database. All costs are expressed as U.S. dollars as of 2013. Euros were converted to US$ by using data on purchasing power parity of the Organization for Economic Co-operation and Development: 1 US$ = 0.83 euro.

Productivity Losses

Almost all notified measles cases were unvaccinated orthodox Protestants. Orthodox Protestants constitute a Calvinistic religious minority in the Netherlands who believe in predestination and divine providence. Their lifestyle is based on the scripture and religion, which play an important role in daily life. Many of them reject vaccination for religious reasons. Since most orthodox Protestant women do not have a paid job to take care of their children, productivity losses of women with measles were calculated as loss of informal care [18, 20].To calculate productivity losses for men, we used standard tariffs (mean, all ages) [18], adjusted for work participation in all age groups [21]. We did not calculate productivity losses for parents taking care of sick children. The duration of productivity losses was calculated for the average duration of illness (i.e., 14 days).

Costs of Targeted Vaccination Campaigns

In the beginning of the outbreak, health care workers born after 1965 were encouraged to check their vaccination and measles infection status and complete their MMR vaccination if necessary [22]. Data about serologic tests and extra vaccinations among health care workers in hospitals were obtained from a study on the implementation of measles guidelines for hospitals (unpub. data, Lydia Fievez, RIVM). In this study 85% (69) of responding hospitals (81 of 88 hospitals in the Netherlands) offered a serologic test to employees.

In July 2013, parents of children 6–14 months of age who lived in communities with vaccination coverage <90% or who belonged to orthodox Protestant communities received a personal invitation for an early MMR vaccination. The normal schedule for MMR in the Netherlands is to receive the MMR-1 at 14 months and the MMR-2 at 9 years of age. Children 6–12 months of age received an MMR-0 vaccination, and those 12–14 months of age received an early MMR-1 vaccination. In addition, the MHSs offered an MMR vaccination to children and adolescents within the vaccination program up to 19 years of age if they had not yet received an MMR vaccination. To avoid including routine MMR-1 vaccinations at 14 months in the outbreak costs, we selected children who received their MMR-1 during the outbreak period who were >18 months–19 years of age. All vaccinations used in this study were recorded in the national immunization register (unpub. data; Praeventis database for registering vaccinations in the Netherlands). Vaccine price and administration costs were gathered from the Dutch Healthcare Authority [19].

Costs of Outbreak Response Coordination at the National Level (RIVM)

Personnel time spent on outbreak control and on investigating and processing the outbreak was also estimated. Given the limited resources, this reallocation of personnel time represents the loss of other production (i.e., opportunity costs). Personnel time of the RIVM was determined by hours allocated to surveillance, response, laboratory, and vaccination activities at the national level. This time estimate was obtained from personal interviews with the personnel in the relevant departments within the Institute. We calculated personnel costs by multiplying a person's salary tariff by the time spent on the measles outbreak.

Costs of Outbreak Response Coordination at the Regional Level (MHS)

To estimate the amount of personnel time associated with local outbreak response activities, we developed a questionnaire for semistructured interviews of MHS staff (i.e., doctors, nurses, and managers) in some of the regions with the highest number of notified measles cases. The interviews explored all MHS activities and the associated time investment of the personnel involved. All possible local reports and registries were collected for additional information. The estimated time investment of physicians, nurses, nursing assistants, managers, and communication employees involved in the outbreak were converted to costs by using an average salary tariff per hour of MHS staff. We calculated time and costs per each notified case in these regions and extrapolated these estimates to all notified cases in the Netherlands.

ADDITIONAL TABLES

Technical Appendix Table 1. Estimated indirect costs and productivity losses for men and women during measles outbreak, the Netherlands, 2013–2014*

	Sex	
Category	**M**	**F**
Adult cases, no.	100	109
Employment or provision of informal child care, %*	72.3%	100%
Employment or provision of informal child care, h/wk*	36.1	40.0
Productivity costs/h, $†	42.67	16.42
Total productivity losses, $†	222,740	143,145

**Productivity losses were calculated for 2 weeks (10 working days) as average duration of illness. Because orthodox Protestant women tend to stay at home taking care of their children, we calculated production losses of work absenteeism for men and production losses of informal child care provided by women.*
†Production costs and losses are calculated in 2013 US dollars ($).

Technical Appendix Table 2. Costs of targeted vaccination campaigns during measles outbreak, the Netherlands, 2013–2014*

	Costs and factors affecting costs			
Population/category of cost	**Unit costs, $**	**Hospitals, no.**	**Average no.**	**Total costs, $**
Health care workers				
Serologic test	21.37	69	80	117,962
Vaccination	8.33	69	63	36,211
Administration costs	15.65	69	63	68,031
Total				222,203
Children 6–14 mo		MMR-0, no.	Early MMR-1, no.	
Vaccination	8.33	5,238	1,414	55,380
Administration costs	14.76	5,238	1,414	98,177
Total				153,557
Children 18 mo–19 y			MMR-1, no.	
Vaccination	8.33		6,948	57,877
Administration costs 0–5 y	14.76		2,764	40,797
Administration costs 5–19 y	11.37		4,184	47,572
Total				146,246

**Costs are calculated in 2013 US dollars ($).Total cost differs from sum of category costs because of rounding. MMR, measles–mumps–rubella; MMR-0, extra MMR vaccination given to children 6–12 months of age; Early MMR-1,MMR vaccination given to children 12–14 months of age; MMR-1, MMR vaccination given to children 18 months to 19 years of age.*

Technical Appendix Table 3. Main cost categories of measles outbreak, the Netherlands, 2013–2014*

Category	Costs,$	% of total costs
Outbreak management	2,556,750	54.3
Medical costs	1,255,718	26.8
Prevention (vaccination)	522,044	11.1
Production losses	365,885	7.8
Total	4,694,395	100

**Costs are calculated in 2013 US dollars ($). Outbreak management and medical costs differ slightly from itemized costs in Table 4 due to rounding.*

Additional Results of Costs of Outbreak Response Coordination

Costs of Outbreak Response Coordination at the National Level (RIVM)

Four departments at the RIVM were involved with the measles outbreak: the Centres for Epidemiology and Surveillance; Communicable Disease Control; Infectious Diseases Research Diagnosis and Screening; and Policy and Regional Support. During the outbreak, representatives of these departments participated in a weekly response meeting at which the current outbreak and national containment strategies were discussed. Online Technical Appendix Table 4 shows the total labor time and costs for all personnel involved. Total costs were estimated at $698,280.

The interviewed MHS staff confirmed that measles response activities were time consuming, especially registration and processing of new measles cases in their region. On average, these activities required 2–3.5 hours per case. At the beginning of the outbreak, numerous internal staff meetings were held to organize regional response activities adequately. Vaccination activities were limited because the targeted group of orthodox Protestants is generally unwilling to accept measles vaccination. Of the different personnel categories, public health nurses spent most of their time performing outbreak response activities (online Technical Appendix Table 5). Based on these data, the total cost for all MHSs was estimated to be $1,858,470 ($686.1 for each of 2,700 notified cases).

Technical Appendix Table 4. Labor time and costs for personnel involved in outbreak management at the national level (RIVM) during the outbreak of measles, the Netherlands, 2013–2014*

Department	Task	Labor time, h	Costs, $
Disease control	Coordination of outbreak control and communication	2,730	300,723
Support	Organization of MMR-0 and MMR-1 vaccination campaigns	1,754	177,372
Surveillance	Analysis and reporting of outbreak data	996	118,257
Diagnostics	Advice and Interpretation of laboratory results†	846	101,928
Total			698,280

**Costs are calculated on the basis of 2013 US dollars ($). RIVM, Ministry of Health, Welfare and Sport, the Netherlands; MMR, Measles–Mumps–Rubella. MMR-0, extra MMR vaccination given to children 6–12 months of age; Early MMR-1,MMR vaccination given to children 12–14 months of age; MMR-1, MMR vaccination given to children 18 months to 19 years of age. †Costs of laboratory tests are presented in Table1 of article.*

Technical Appendix Table 5. Labor time and costs for personnel involved in outbreak management at regional level MHSs in measles outbreak, the Netherlands, 2013–2014*

Employee	Tariff, $	Labor time per notified case, h	Costs per notified case, $
Nurse	69	5.2	359
Physician	107	1.9	203
Manager	103	0.6	62
Communication employee	88	0.4	35
Nursing assistant	54	0.5	27
Total		8.6	686

**Costs are calculated in 2013 US dollars ($).Total cost differs slightly from sum of category costs because of rounding.*

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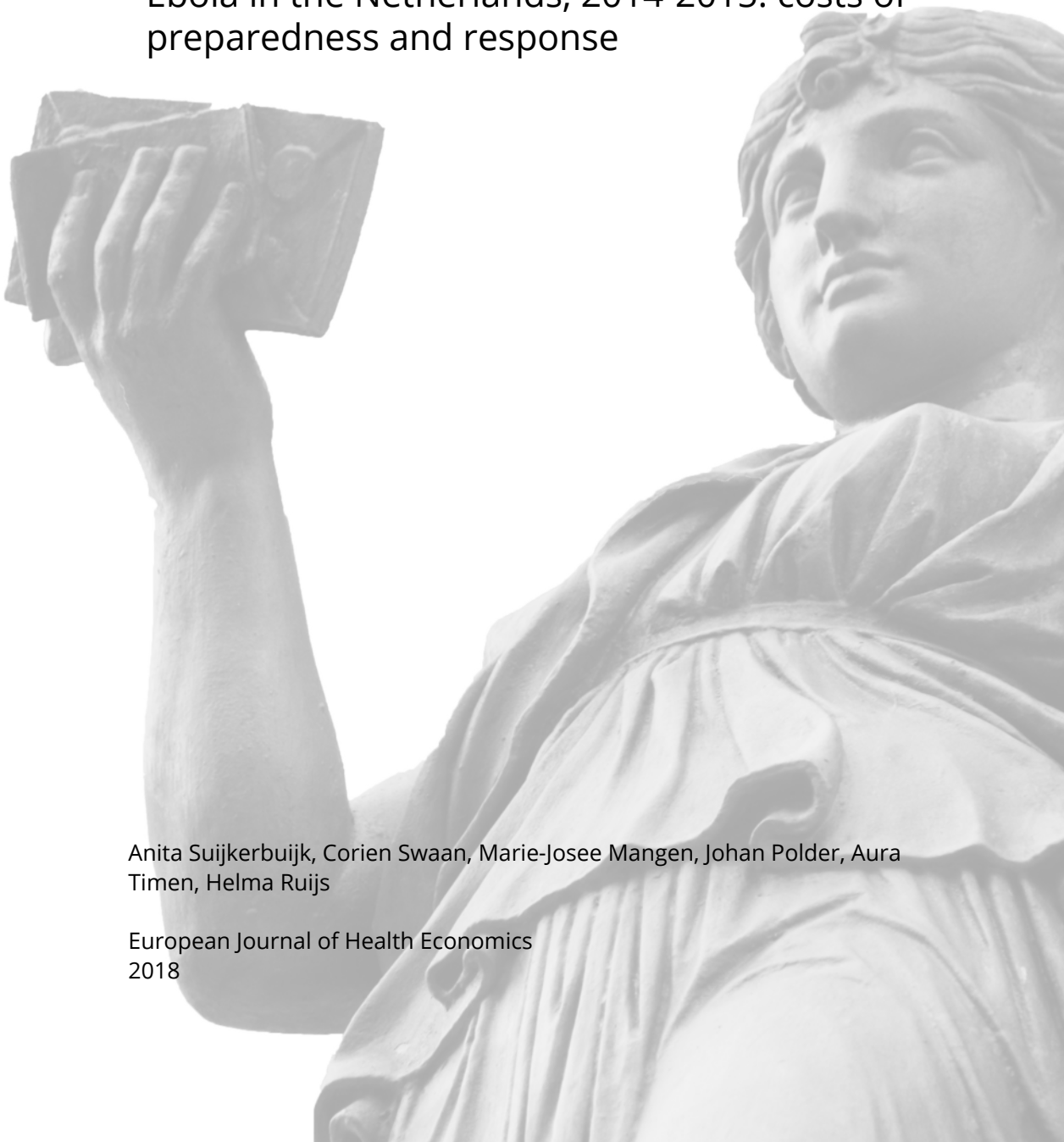
CHAPTER 4

Ebola in the Netherlands, 2014-2015: costs of preparedness and response



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ABSTRACT

The recent epidemic of Ebola virus disease (EVD) resulted in countries worldwide to prepare for the possibility of having an EVD patient. In this study, we estimate the costs of Ebola preparedness and response borne by the Dutch health system. An activity-based costing method was used, in which the cost of staff time spent in preparedness and response activities was calculated based on a time-recording system and interviews with key professionals at the healthcare organisations involved. In addition, the organisations provided cost information on patient days of hospitalisation, laboratory tests, personal protective equipment (PPE), as well as the additional cleaning and disinfection required. The estimated total costs averaged €12.6 million, ranging from €6.7 to €22.5 million. The main cost drivers were PPE expenditures and preparedness activities of personnel, especially those associated with the ambulance services and hospitals. There were 13 possible cases clinically evaluated and one confirmed case admitted to hospital. The estimated total cost of EVD preparedness and response in the Netherlands was substantial. Future costs might be reduced and efficiency increased by designating one ambulance service for transportation and fewer hospitals for the assessment of possible patients with a highly infectious disease of high consequences.

INTRODUCTION

Between December 2013 and April 2016, the largest epidemic of Ebola virus disease (EVD) ever recorded took place. It included at least 28,616 suspected, probable, and confirmed cases and 11,310 documented deaths, but the real numbers were probably much higher [1]. Most cases occurred in the West-African countries of Guinea, Liberia, Sierra Leone and, to a lesser extent, in Mali, Nigeria, and Senegal. The rise in EVD cases in July 2014 prompted World Health Organization (WHO) to declare the outbreak a public health event of international concern [2]. On September 28, 2014, the United States encountered its first patient with symptoms of EVD, who originated from Liberia [3]. Fear of local outbreaks arose in non-African countries because of this patient and cases among healthcare workers (HCWs) returning from Africa [4]. Internationally, health systems were urged to prepare for the possibility of an EVD patient presenting to hospitals [5-8]. In western countries, EVD care was required for 27 patients, of whom 22 were healthcare personnel. Of the total, 24 were medically evacuated from West Africa or were infected with Ebola virus in West Africa and had onset of disease in Europe or the United States. The remaining 3 were secondary patients infected in the United States or Europe [9, 10]. The Netherlands received an infected United Nations (UN) worker in December 2015 [11].

Although technical guidance was provided by WHO [12], European Centre for Disease Prevention and Control [13], and US Centers for Disease Control and Prevention [14], this had to be adjusted to the specific circumstances of each country by its own infectious disease control organisations. Country-specific guidelines were developed and included flowcharts and algorithms for identification of patients, isolation precautions, laboratory testing, patient transportation, waste disposal, quarantine procedures, and management of widespread anxiety about EVD [15].

An outbreak of such a highly virulent disease not only results in a disease burden to society, but the containment efforts also have economic consequences. These economic costs include social disruptions in the countries affected, border control, restrictions on international trade, a downturn in travel and tourism income, and additional healthcare costs [16-18]. To date, a few studies have measured the costs of EVD preparedness and treatment of patients in hospitals [17, 19-21]. In public health and primary care institutions, such preparedness costs in not affected countries have not been studied, but their evaluation is important for future preparedness of similar

outbreaks of highly virulent infectious diseases. The aim of this paper is to present the total costs associated with EVD preparedness and response in healthcare in the Netherlands.

METHODS

Infectious diseases preparedness and response in the Netherlands

In the Netherlands, notification of 43 infectious diseases is legally anchored in the Public Health Act (Wet Publieke Gezondheid) [22, 23]. In this act, 43 diseases are assigned into A, B, and C categories, depending on the necessary control measures. In case of an A-notifiable disease such as EVD, national outbreak management is centralized to effectively implement uniform control measures, in line with International Health Regulations [24]. The Dutch Minister of Health, Welfare and Sports appointed the National Institute for Public Health and the Environment (RIVM) as a national coordinator, responsible for guidelines and advice, communication to professionals and the public, and the activation of control measures in the event of a possible EVD case.

Within the healthcare sector in the Netherlands, general practitioners (GPs) are first responders [25]. Except for emergencies, patients must consult their GP for referral to a hospital. During the EVD epidemic, GPs were responsible for referral of suspected cases to one of the eight academic hospitals in the Netherlands. In addition, eighty peripheral hospitals facing suspected cases at the emergency department had to refer such cases to an academic hospital. Twenty-five regional ambulance services were accountable for transportation of suspected and confirmed EVD cases to an academic hospital. All eight academic hospitals were responsible for management of EVD patients admitted for diagnostics, whereas four of them were appointed for long-term care of patients diagnosed with EVD [26, 27]. One virological laboratory, the Department of Virology of the Erasmus Medical Center, was designated for EVD diagnostics for the whole country. This laboratory is a reference centre for WHO on viral infections. Twenty-five Municipal Health Services (MHSs) were accountable for regional public health activities including control, monitoring, and contact-tracing of suspected cases. Figure 1 depicts all healthcare and public health organizations involved in EVD response and preparedness, showing on the left side the routing of a suspected EVD case through GPs and emergency departments to academic hospitals and, on the right side, the public health organizations: MHSs and RIVM.

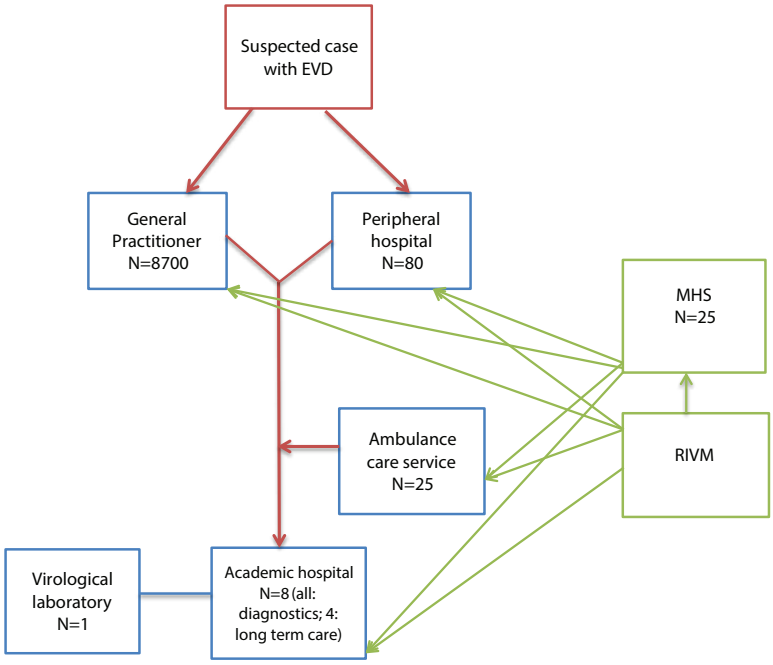

Figure 1: Organizations involved in EVD preparedness and response in the Netherlands
(~17 million inhabitants, blue=healthcare, green=public health, MHS=Municipal Health Service, RIVM=National Institute for Public Health and the Environment).

Costs of preparedness and response

We used an activity-based costing method. Total costs of preparedness and response were based on interviews with key professionals in EVD preparedness and response in the organisations involved. Time spent on EVD by a wide range of professionals within the organisations was investigated during these interviews. Information on GP efforts was obtained through semi-structured phone interviews with five GPs. A face-to-face interview with the coordinator of the association of ambulance care services (AZN) was followed by phone interviews with medical managers of the five regional ambulance services that transported suspected EVD cases during the epidemic. Information on the operational deployment of personnel was retrieved from three peripheral hospitals, five academic hospitals (both selected for diagnostics only and for additional long-term care), and the Erasmus Medical Center virological laboratory. This information was gathered through face-to-face interviews with professionals such as infection prevention experts, microbiologists, and virologists. One MHS consultant on infectious diseases control was interviewed face-to-face to obtain the time spent on activities for EVD preparedness and response, and five other MHS consultants were interviewed by phone. For RIVM, staff hours assigned to EVD preparedness and

response were retrieved from a time-recording system. The number of ambulance transportations of suspected EVD cases was retrieved from the RIVM database of suspected EVD cases, along with the number of hospitalisations. Data on length of hospital stays, costs of laboratory tests, personal protective equipment (PPE) and other equipment, additional cleaning and disinfection were acquired from the individual organisations. The Erasmus Medical Center performed diagnostics not only for EVD but also for alternative diagnoses such as other hemorrhagic diseases and malaria.

Personnel costs were calculated by multiplying a person's hourly wages (according to the middle step plus 1 of the relevant salary scale per discipline) by 1.39 for social obligations, vacation bonus etc., and by the hours expended on EVD [28]. Besides these base case costs we present costs including overhead, depreciation and housing costs by using higher rates for staff time. Tariffs were already available for RIVM and MHSs. For hospitals, and GPs, we added 44% to the wages, following the Dutch manual for economic evaluations [28]. For ambulance services, wages were added-up by 20%, based on real data from NZA (with lower costs for overhead and housing). The costs for admission to a high-level isolation unit were based on the list-price online of admission to an intensive care unit from which the costs of labour hours were subtracted, since these were calculated separately [28].

We present mean cost per type of healthcare institution, as well as a range of minimum and maximum costs. Furthermore we extrapolated these estimates to all healthcare institutions in the Netherlands by multiplying mean, minimum and maximum costs with the number of total organisations involved. Mean costs related to transportation and hospital care of suspected EBV cases (i.e. cost of response) were multiplied with the total number of transportations and hospital admissions of suspected EBV cases. Costs related to the single EVD-diagnosed UN worker (hospitalisation, diagnostics, transportation by ambulance, and MHS activities) were subtracted from the costs of the separate organisations to avoid double-counting. For ambulance care services and academic hospitals, costs were further split into a) costs for preparedness (i.e. developing specific EVD guidelines, purchase of PPE, and training employees) and b) response to a suspected case (transportation and admission to hospital). All costs are expressed at the 2015-euro price level.

RESULTS

EVD in the Netherlands

During the epidemic period, Dutch healthcare professionals consulted the RIVM 89 times about a possible EVD case [29]. Based on a protocol for triage and care, thirteen cases were referred to an academic hospital in strict isolation, pending results of laboratory diagnostics. In all cases, results proved to be negative for EVD. However, at the request of the UN and the Dutch Government, an Ebola virus-infected UN employee was brought from a hospital in Africa to the Dutch Major Incidence Hospital (MIH) at one of the eight academic medical centres [11]. He was discharged in good health 14 days later.

General practitioners

The total 8,700 GPs in the Netherlands spent each an estimated 1-2 hours (at €62 per hour) to be informed of EVD relevant guidelines. The 50 cooperative GP services (providing care beyond normal working hours) each spent 70 to 90 hours for EVD preparedness. According to the Dutch guidelines, no PPE was used except for masks and gloves, so no additional costs were incurred for PPE storage. Overall costs averaged €1.06 million (uncertainty interval (UI) €0.76 million-€1.36 million).

Ambulance care services

For ambulance care services, the highest costs were incurred in acquisition of materials such as PPE (€0.53 million), followed by costs for coordination of preparedness activities (€0.41 million) (Table 1 and Table A1 and A2 Appendix File). The latter included the development of EVD-related protocols within each of the services. Twelve suspected EVD cases were transported by ambulance to a hospital. Two services adapted an ambulance for the transportation of a suspected case at the cost of €18,000 and €30,000, respectively (costs not included in table 1.) The AZN performed activities regarding development of protocols, policy advice, and gatherings with other organisations, resulting in costs estimated at €0.09 million. Mean overall costs were €1.48 million (UI: €0.89 million-€2.41 million).

Table 1 EVD-related costs to ambulance care facilities in Euros (* 1000) N=25

	Base case			Costs including overhead[a]	
Activity	**Mean costs/ organisation (range)**	**Mean total costs[b] (range)**	**Percentage %**	**Mean costs/ organisation (range)**	**Mean total costs[b] (range)**
Preparedness					
Coordination	16.4 (9.1-26.7)	409.2 (226.8-666.4)	27.7	19.6 (10.9-32.0)	491.1 (272.2-799.7)
meetings	4.5 (4.1-6.1)	112.6 (102.5-153.0)	7.6	5.4 (4.9-7.3)	135.2 (123.0-183.6)
training	12.4 (3.0-29.9)	310.7 (74.7-747.3)	21.0	14.9 (3.6-35.9)	372.9 (89.6-896.8)
materials	21.3 (15.0-29,0)	531.5 (374.4-725.5)	36.0	21.3 (15.0-29.0)	531.5 (374.4-725.5)
AZN	98.7	98.7	6.7	118.4	118.4
Subtotal		1,462.7 (877.1-2,390.8)	99.1		1,649.0 (977.6-2,723,9)
Response					
transport of suspected case	1.2 (1.0-1.4)	14.0 (11.5-17.3)	0.9	1.2 (1.0-1.4)	14.0 (11.5-17.3)
Total costs		**1,476.7 (888.5-2,408.1)**	**100**		**1,663.0 (989.0-2,741.1)**

AZN=Ambulance Zorg Nederland (association of ambulance care services).
[a] Wages are increased by 20% to account for overhead costs, depreciation, and housing costs
[b] Extrapolated to all 25 ambulance care services (for preparedness), and to 12 transportations of suspected cases (for response).

Hospitals

Total costs for hospital EVD preparations averaged €4.77 million (UI: €2.39 million-€7.97 million) for all peripheral hospitals and €3.62 million (UI: €1.76 million-€7.14 million) for all academic hospitals (table 2 and Table A3/A4/A5 Appendix File). At one of the three peripheral hospitals where we conducted interviews, a portable clinical instrument was purchased to perform point-of-care laboratory tests for suspected cases that might be admitted, at a cost of €20,000 (not included in table 2). The costs associated with the infected UN patient were estimated at €0.24 million (see Appendix File table A6).

Table 2 EVD-related costs to peripheral and academic hospitals in Euros (*1000)

	Base case			Costs including overhead[a]	
Activity	**Mean costs/ organisation (range)**	**Mean total costs[b] (range)**	**Percentage %**	**Mean costs/ organisation (range)**	**Mean total costs[b] (range)**
Peripheral hospitals (N=80)					
Preparedness					
coordination	21.6 (9.0-35.5)	1,728.0 (719.4-2,837.9)	36.3	31.1 (13.0-51.1)	2,488.3 (1,036.0-4,086.6)
meetings	5.7 (1.9-12.0)	452.3 (150.4-956.8)	9.5	8.1 (2.7-17.2)	651.3 (216.6-1,377.8)
protocol	12.0 (8.2-17.8)	958.3 (652.8-1,419.0)	20.1	17.3 (11.8-25.5)	1,380.0 (940.0-2,043.3)
training	18.3 (10.6-29.9)	1,466.5 (845.0-2,394.4)	30.8	26.4 (15.2-43.1)	2,111.7 (1,216.9-3,448.0)
materials	2.0 (0.3-4.5)	158.3 (21.1-360.0)	3.3	2.0 (0.3-4.5)	158.4 (21.1-360.0)
Total costs	59.5 (29.9-99.6)	4,763.4 (2,388.8-7,968.1)	100	84.9 (42.9-141.4)	6,789.6 (3,430.6-11,315.6)
Academic hospitals (N=8)					
Preparedness					
coordination	102.9 (68.3-176.8)	822.9 (546.6-1,414.7)	22.7	148.1 (98.4-254.6)	1,185.0 (787.1-2,037.2)
meetings	56.2 (3.2-138.9)	449.3 (25.8-1,111.3)	12.4	80.9 (4.6-200.0)	647.0 (37.1-1,600.2)
protocol	24.7 (1.9-76.2)	197.9 (15.0-609.2)	5.5	35.6 (2.7-109.7)	285.0 (21.7-877.2)
training	61.9 (23.8-119.5)	495.2 (190.6-955.6)	13.7	89.1 (34.3-172.0)	713.1 (274.5-1,376.0)
materials	92.5 (24.9-250.0)	739.7 (199.2-2,000.0)	20.4	92.5 (24.9-250.0)	739.7 (199.2-2,000.0)
Subtotal	338.1 (122.2-761.3)	2,705.0 (977.2-6,090.7)	74.7	446.2 (164.9-986.3)	3,569.8 (1,319.5-7,890.7)
Response					
Costs/admitted patient[c]	52.5 (42.3-62.7)	682.1 (550.0-815.5)	18.8	52.5 (42.3-62.7)	682.1 (550.0-815.5)
Costs/EVD patient	236.2	236.2	6.5	236.2	236.2
Total costs		**3,623.3 (1,763.4-7,142.5)**	**100**		**4,488.1 (2,105.8-8,942.4)**

[a] Wages are increased by 44% to account for overhead costs, depreciation, and housing costs.
[b] Extrapolated to all organisations, i.e., 80 peripheral hospitals and 8 academic hospitals, and 14 admissions of suspected cases.
[c] None of the admitted suspected patients was diagnosed with EVD; hospital admittance averaged 3 days.

Virological laboratory

Department of Virology staff at Erasmus Medical Center advised on the EVD preparations for admission of a suspected EVD case at Erasmus; guided other laboratories through the diagnostics of suspected cases, and assisted with the EVD patient brought from Africa to MIH. Since the Erasmus laboratory staff was already thoroughly trained in handling extremely hazardous infectious agents, they needed only regular updates on EVD developments worldwide and more specifically in the Netherlands. Mean total costs for deployment of personnel and diagnostics were estimated at €0.25 million (UI: €0.23 million-€0.27 million) (Appendix File Table A7).

MHS

The mean number of hours spent on EVD preparedness and response at one MHS was estimated at 1,131 hours, or €0.49 million (Appendix File Table A8). Extrapolated to all 25 MHSs, this finding would lead to total average costs of €1.23 million (UI: €0.45 million-€3.11 million).

RIVM

At the RIVM, 28 persons spent 4,385 hours on EVD preparedness and response, resulting in total costs of €0.23 million (Appendix File Table A8). Activities included advice to the Ministry of Health, Welfare and Sport, organisation of expert meetings, development of guidelines, media activities, consultations regarding possible EVD cases, information on the website, e-mail communications, and a telephone line especially set up for questions regarding EVD.

Total costs

The mean total costs for the Dutch health system were €12.6 million (UI: €6.7 million-22.5 million), see Table 3. Taking overhead costs into account, total costs averaged €17.9 million (UI: €9.4 million-€32.6 million). For ambulance services and academic hospitals, we distinguished costs for preparedness and response. Costs for preparedness were highest. The costs of response activities of ambulance services (transportations of suspected EVD cases) were 0.94% (range 1.29-0.72%) of total EVD-related ambulance care costs. The costs of response activities of academic hospitals (admissions of suspected cases) were 18.82% (range 11.42-31.19 %) of total costs of all academic hospitals. The costs related to the admission of the infected UN patient comprised 44.8% of all EVD-related costs of the academic hospital that cared for him.

Table 3 Total costs of EVD preparedness and response in Euros (* million)

Organisations	Mean total costs base case	Percentage %	Range	Mean total costs including overhead[a]	Range
peripheral hospitals	4.8	38	2.4-8.0	6.8	3.4-11.3
academic hospitals	3.6	29	1.8-7.1	4.5	2.1-8.9
ambulance services	1.5	12	0.9-2.4	1.7	1.0-2.7
MHSs	1.2	10	0.5-3.1	2.6	1.0-6.7
GPs	1.1	8	0.8-1.4	1.5	1.1-2.0
virological laboratory	0.3	2	0.2-0.3	0.3	0.3-0.4
RIVM	0.2	2	0.2	0.5	0.5
Total	**12.6**	**100**	**6.7-22.5**	**17.9**	**9.4-32.6**

[a] *Wages are increased to account for overhead costs, depreciation, and housing costs*

DISCUSSION AND CONCLUSIONS

The estimated total costs of EVD preparedness and response in the Netherlands were substantial: on average €12.6 million (UI: €6.7 million-€22.5 million), although that figure is (only) 0.6% of the country's routine annual expenditures on prevention and treatment of infectious diseases (€2.2 billion in 2011 [30]). Taking into account the overhead costs of the various organisations would raise total costs by 42%. Thirteen possible and a single confirmed EVD case were evaluated, respectively treated, in a hospital.

Costs for healthcare organisations were higher than for public health organisations. Hospital EVD preparations required unusually high resources, which were diverted from routine infection prevention activities. Costs incurred by an academic hospital were much higher than those incurred by a peripheral hospital, since more divisions were involved in preparation for a possible EVD admission. At each academic hospital, several management and medical professionals were occupied full-time with EVD preparedness for about half a year.

In this study, we included a range of organisations and factors, but certain cost items could not be included. Costs of adjusting isolation units to be prepared for a suspected EVD patient were not included, as only minor adjustments were required. In addition, two unforeseen cases came up at emergency departments of peripheral hospitals, leading to extra time investments and costs for these hospitals. Air transportation of the EVD patient from Africa to Amsterdam also led to substantial costs, up to $200,000 (€162,000) according to a newspaper report (https://www.

washingtonpost.com/news/federal-eye/wp/2014/10/28/the-world-relies-on-this-one-company-to-fly-ebola-patients/?utm_term=.82a41fcd4088). EVD-related costs were also incurred by institutions outside the scope of our study, such as the Ministry of Health, Welfare and Sport, the Inspectorate of Health, international aid organisations working in the Netherlands, and umbrella organisations of hospitals, GPs, MHSs, and GHOR organisations (Geneeskundige Hulpverleningsorganisatie in de Regio). GHOR organisations, which are targeted at local safety issues and collaborate with MHSs, police, fire service, etc., spent variable time on EVD, according to key professionals of four GHOR organisations. To be prepared for EBV, one organisation spent only 10 hours on EVD whereas another spent 500 hours, leading to substantial costs. Erasmus Medical Center virological laboratory was involved with the deployment of a mobile laboratory in Sierra Leone [31]. This was a support offered by the Dutch government to Sierra Leone that was independent from the Dutch preparedness and response, and therefore outside of the scope of the current cost analysis. Furthermore, EVD costs beyond the healthcare domain were experienced by public transportation, waste management, and undertaker's businesses. Finally, our interviews were conducted more than a year after the threat of EVD, leading perhaps to recall bias and to underestimation of costs, as seen in other publications [32, 33]. Therefore, our reported total costs of EVD preparedness and response in the Netherlands should be regarded as the best possible estimate, with a broad uncertainty interval.

We found a large variation in hospital costs and ambulance care service costs independent of the size of the hospitals and ambulance care services. The costs of material and training in these organisations depended highly on the number of staff involved with the management of a possible EVD case. Such personnel was trained extensively in donning and doffing PPE in anticipation of transportation and admission of EVD cases. In addition, costs varied for management of admission of possible cases in an academic hospital, depending on the necessity to close beds in the same ward or to allocate an isolation unit especially for EVD. Also, a large variation was observed in the activities and hours spent by professionals from several MHSs: 3 of the 6 we interviewed developed their own regional EVD guidelines, whereas the others relied on the national guidelines. Two of the MHSs participated in a regional training program, while the others did not. Most MHS variation could be explained by communication and collaboration with other professionals in the region, informing general population, and events linked to possible cases in the region.

Up to now only a few publications have provided estimates of costs of preparedness and treatment of suspected EVD cases in the western world. Herstein et al. assessed the costs incurred to establish an Ebola treatment center in 55 US hospitals [20]

and found the mean total hospital costs to create such a facility were $1,197,993. Zacharowski described the treatment and costs of a Ugandan medical doctor with EVD at a German Hospital [21, 34]. Total costs of the transfer, treatment, and management of that patient exceeded €1 million. Given the severe illness and need for lengthy intensive care, the costs exceeded those associated with the EVD patient in the Netherlands (€236,209), even if we add transfer costs of €162,000.

The Ebola outbreak urged organisations in both clinical care and public health sectors to be prepared for the introduction of a highly contagious infectious disease. Close collaboration between but also within these organisations has led each to a better understanding of the others' operating procedures. In addition, organisations have learned important practical lessons. For example, the location of a high-level isolation unit in the hospital proved to be important and is more favourable near the ambulance entrance [35]. Additionally, the possible presence of an EVD case led to anxiety and uneasiness among HCWs and their families, which had to be addressed in information meetings [4].
A critical appraisal of this costing study also raises suggestions for improvements. At the start of the epidemic neither ambulance services nor hospitals had extensive operating procedures for preparedness and management of a suspected EVD case. All the hospitals in which we conducted interviews experienced internal debates regarding the proper materials, shortage of PPE supplies and, as a result, higher costs when extra materials had to be purchased. National standard guidelines would have been helpful and efficient, for example, regarding the donning and doffing procedures and the appropriate PPE [25]. In order to alleviate potential shortages of materials, it may be useful to build a temporary nationwide supply chain when an epidemic threatens [36].

This study demonstrated that ambulance care services and hospitals experienced far more costs for preparedness activities than for response activities. Given the small size of the Netherlands and the few cases evaluated for EVD in this epidemic, it is important to discuss whether it is necessary that every ambulance care service and hospital nationwide ought to be prepared for a threat of this magnitude. Dividing ambulance costs by the number of transportations (12) and hospital costs by the number of admissions (14) would result in about €123,000 per transportation and €599,000 per admission of a suspected or diagnosed case. Instead, a few selected organisations might fulfil these tasks for the whole country, while the rest could rely on more general preparedness [25]. Major expansion of capacity and resources is thus required only within these select organisations. In the UK, for example, suspected EVD patients could only be admitted for treatment to high-level isolation units at just

two hospitals [37, 38]. In Israel, the Ministry of Health designated a single hospital to serve as the national Ebola treatment centre, whereas the other hospital emergency departments were instructed to offer only life-saving interim care for suspected cases while following strict isolation and personal protection practices [39].

In conclusion, the large unforeseen and unbudgeted expenses for EVD preparedness and response posed a substantial financial burden on the Dutch health system, especially ambulance care, peripheral and academic hospitals. The nationwide experience and collaboration of healthcare organisations that managed patients with suspected EVD can serve as a valuable resource for future outbreaks of other highly infectious diseases [40]. Ongoing updating of guidelines and training will be needed to sustain the preparations for upcoming outbreaks. Designating one ambulance service and just a few hospitals for the transportation and admission of patients with suspected viral haemorrhagic fever or other highly infectious disease might improve efficiency and reduce future costs.

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APPENDIX FILE

Additional results in tables.

Table A1 Time and costs expended by ambulance care services (N=25)

Professional	Unit costs / hour	No of hours	Base case costs/ service	Cost sensitivity analysis/service*
Coordination				
medical manager	€ 49	0-544	0-€26,656	0-€31,987
specialist nurse	€ 42	0-306	0-€12,852	0-€15,422
Subtotal			€9,072-€26,656	€10,886-€31,987
Meeting				
medical manager	€ 49	0-20	0-€980	0-€1,176
nurse	€ 32	0-70	0-€2,240	0-€2,688
chauffeur	€ 25	0-70	0-€1,750	0-€2,100
team manager	€ 39	15-80	€585-€3,120	€702-€3,744
Subtotal			€3,030-€5,952	€3,636-€7,142
Training				
trainer	€ 32	0-48	0-€1,536	0-€1,843
medical manager	€ 49	0-3	0-€147	0-€176
specialist nurse	€ 42	0-12	0-€504	0-€605
nurse	€ 32	36-398	€1152-€12,736	€1,382-€15,283
chauffeur	€ 25	36-398	€900-€9,950	€1,080-€11,940
team manager	€ 39	12-181	€468-€7,059	€562-€8,472
Subtotal			€2988-€29,892	€3,586-€35,870

* Wages are increased by 20%.

Training and instructing staff at ambulance services

Informing and instructing staff for EBV took mainly place during work meetings. Besides these meetings special training sessions, especially for donning and doffing were organized. From 4 ambulance care services we collected detailed information.

Table A2 Number of training sessions at ambulance services

Ambulance care services	No of ambulances / 100,000 inhabitants	No of inhabitants	No of meetings	No of persons	No of hours
1	3.4-4.1	484,986	4	17	3
2	4.1-4.8	531,591	12	4	2
3	3.4-4.1	774,476	1	220 (and 20)	3 (8)
4	3.4-4.1	670,924	1	80	1

Source: AZN Nederland, names could not be disclosed

Table A3 Time and costs expended by peripheral hospitals (N=80)

Professional	Unit costs	No of hours	Base case cost	Costs sensitivity analysis*
Coordination				
physician	€ 81	0-139	0-€11,259	0-€16,213
infection prevention expert	€ 37	173-519	€6,401-€19,203	€19,394-€27,652
manager	€ 66	17-104	€1,122-€6,864	€1,616-€9,884
communication employee	€ 28	0-139	0-€3,892	0-€5,604
Subtotal			€8,993-€35,476	€12,950-€51,085
Meeting				
physician	€ 81	10-100	€810-€8,100	€1,166-€11,614
manager	€ 66	10-50	€660-€3,300	€950-€4,752
communication employee	€ 28	0-20	0-€560	0-€806
quality officer	€ 42	0-10	0-€420	0-€605
Subtotal			€1,880-€11,960	€2,707-€17,222
Protocol				
physician	€ 81	0-80	0-€6,480	0-€9,331
infection prevention expert	€ 37	0-260	0-€9,620	0-€13,853
quality officer	€ 42	0-40	0-€1,680	0-€2,419
Subtotal			€8,160-€17,735	€11,750-€25,538
Training				
physician	€ 81	50-115	€4,050-€9,315	€5,832-€13,414
nurse	€ 32	60-265	€1,920-€8,480	€2,765-€12,211
physician assistant	€ 33	83-185	€2,739-€6,105	€3,944-€8,791
quality officer	€ 42	0-8	0-€336	0-€484
manager	€ 66	23-55	€1,518-€3,630	€2,186-€5,227
other employee	€ 30	0-10	0-€300	0-€432
Subtotal			€10,563-€29,930	€15,211-€43,099

**Wages are increased by 44% to account for overhead costs, depreciation, and housing costs*

Table A4 Time and costs expended by academic hospitals (N=8)

Professional	Unit costs	No of hours	Base case costs	Costs sensitivity analysis*
Coordination				
physician	€79	500-624	€39,500-€49,296	€56,880-€70,986
infection prevention expert	€37	779	€28,823	€41,505
assistant infection prevention specialist	€28	0-779	0-€21,812	0-€31,409
manager	€66	0-500	0-€33,000	0-€47,520
head of group	€66	0-500	0-€33,000	0-€47,520
policy maker	€42	0-779	0-€32,718	0-€47,114
Subtotal			€68,323-€176,837	€98,385-€254,645
Meeting				
physician	€79	20-958	€1,580-€75,682	€2,275-€108,982
manager	€66	0-400	0-€26,400	0-€38,016
other employee	€30	0-400	0-€12,000	0-€17,280
representative board	€82	0-20	0-€1,640	0-€2,362
Subtotal			€3,220-€138,910	€4,637-€200,030
Protocol				
physician	€79	20-40	€1,580-€3,160	€2,275-€4,550
manager	€66	0-30	0-€1,980	0-€2,851
nurse	€32	0-60	0-€1,920	0-€2,765
other employee	€30	10-300	€300-€9,000	€432-€12,960
policy maker	€42	0-20	0-€840	0-€1,210
Subtotal			€1,880-€15,270	€2,707-€21,989
Training				
physician	€79	109-486	€8,611-€38,394	€12,400-€55,287
nurse	€32	191-1000	€6,112-32,000	€8,801-€46,080
physician assistant	€33	183-380	€6,039-€12,540	€8,696-€18,058
communication employee	€28	6-120	€168-€3,360	€242-€4,838
other employee	€30	20-240	€600-€7,200	€864-€10,368
manager	€66	20-120	€1,320-€7,920	€1,901-€11,405
security personnel	€28	0-100	0-€2,800	0-€4,032
Subtotal			€23,828-€75,024	€34,312-€108,035

**Wages are increased by 44% to account for overhead costs, depreciation, and housing costs*

Training and instructing staff at hospitals

In several ways personnel was trained and instructed for EBV, for example during EBV information meetings organized for a large group of personnel or on a small scale with a few persons during work time.

Table A5 Number of employees trained for Ebola in hospitals

Type of hospital	No of beds	No of hospital admissions	No persons participating in large training (4-8 hours)	No of persons involved in general instructions (1-2 hours)	No of persons instructed for donning and doffing (0.5-1 hour)
Academic	1320	41773	46	200	420
Academic	953	31137	300	-	624
Academic	882	23033	125	-	840
Academic	733	27058	18	100	150
Academic	1042	34902	30	150	279
Peripheral	818	37702	7	36	150
Peripheral	809	34144	-	50	280
Peripheral	1116	44698	50	-	600

Source for no of beds and hospital admissions: academic hospitals: Rathenau Instituut, De Nederlandse universitaire ziekenhuizen, feiten en cijfers, 2014. No of beds and hospital admissions for the peripheral hospitals were retrieved from facts and figures from individual hospital websites (names could not be disclosed).

Table A6 Estimated costs of the admitted EVD patient[a]

Cost category	Costs / hour or unit costs (€)	No of employees	No of hours	Patient days	Total (€)
Transportation ambulance					5,278
Intake					
nurses	32	4	8	1	1,024
infectious diseases specialist	113	1	8	1	904
guard	28	1	24	1	672
Daily meeting					
manager	66	2	1	14	1,848
nurses	32	3	1	14	1,344
communication employee	42	1	1	14	588
infectious diseases specialist	113	1	1	14	1,582
other physicians	113	2	1	14	3,164
Admission					
infectious diseases specialist	113	1	4	14	6,328
medical microbiologist	113	1	1	14	1,582
nurses	32	9	8	14	32,256
manager	66	1	4	14	3,696
communication employee	42	1	1	14	588
guard	28	3	8	14	9,408
admission costs per day	1313			14	18,382
closure 3 other isolation units	1313			14	55,146
closure isolation unit for another 14 days	1313			14	18,382
Diagnostics:					
I-STAT portable clinical analyzer	2,000				2,000
PCR: 2*121,50					729
transportation costs to Bernard Nocht Institut 2*1200					2,400
other diagnostics at Erasmus Virology laboratory 7*500					3,500
Cleaning costs					35,000
Costs PPE	50	25		14	17,500
Labour time MHS					
nurses	33	55			1,815
physicians	49	165			8,085
policymaker	42	40			1,680
communication employee	36	16			576
manager	49	4			196
vice-director	63	4			252
director	76	4			304
Total					236,209

[a] *Based on information and resource use from interviews PPE=personal protective equipment*

Table A7 Costs expended by virological laboratory (N=1)

Professional	**Costs / hour (€)**	**Mean no hours (range)**	**Base case mean total costs * €1000 (range)**	**Sensitivity analysis[b] mean total costs * €1000 (range)**
medical staff	79	2100 (1900-2300)	165.9 (150.1-181.7	238.9 (216.1-261.7)
medical microbiological analyst	30	1550 (1440-1700)	46.5 (42.0-51.0)	67.0 (60.5-73.4)
Subtotal			**212.4 (192.1-232.7)**	**305.9 (276.6-335.1)**
Diagnostics[a]	**No**	**Costs (€)**	**Total (€)**	
PCR Ebola	42	122	5,103	
PCR Lassa	23	122	2,795	
PCR Marburg	22	122	2,673	
Malaria quick test	7	30	210	
PCR Malaria	3	122	365	
PCR Crimean Congo	18	122	2,187	
If IgG Ebola	1	32	32	
PCR Leptospirosis	14	122	1,701	
clinical chemical tests	14	500	7,000	
transportation to Germany[c]	11	1,200	13,200	
Subtotal			35,265	
Total base case			**247,665 (277,365-267,965)**	
Total sensitivity analysis			**341,121 (311,889-370,353)**	

[a] In addition, costs for diagnostics for the EVD patient (€6629, table 3) were performed at the virological laboratory.
[b] Wages are increased by 44%.
[c] For confirmation of diagnosis at Bernard Nocht Institut.

Table A8 Time and costs expended by public health institutes

Professionals	Mean no of hours (range)	Costs per hour (€) (base case)	Base case mean total costs (€) (range)	Costs per hour (€) (sensitivity analysis)	Sensitivity analysis mean total costs (€) (range)
MHSs (N=25)					
public health nurse	201 (102-484)	33	6,599 (3,351-15,903)	68	13,697 (6,956-33,009)
communication employee	76 (6-294)	36	2,738 (217-10,614)	84	6,370 (504-24,696)
policy maker	268 (0-1504)	42	11,317 (0-63,474)	92	24,761 (0-138,869)
public health physician	506 (288-484)	49	24,751 (14,079-23,660)	104	52,406 (29,808-50,094)
manager	80 (6-220)	49	3,886 (293-10,754)	104	8,228 (621-22,770)
Total	1131 (402-2986)		49,292 (17,940-124,404)		105,461 (37,889-269-438)
All MHSs			**1,232,290 (448,496-3,110,102)**		**2,636,533 (947,235-6,735,953)**
RIVM (N=1)					
assistants	145	22	3190	76	11,020
policy makers[a], epidemiologists	912	31	28,272	88	80,256
policy makers[b],	1770	42	74,340	104	184,080
managers, medical doctors	1558	56	87,248	124	193,192
Subtotal	**4385**		**193,050**		**468,548**
Costs for materials			**37,867**		**37,867**
Total			**230,959**		**506,415**

[a] *junior,* [b] *senior*

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CHAPTER 5

Cost of nosocomial outbreak caused by NDM-1–containing *Klebsiella pneumoniae* in the Netherlands, October 2015–January 2016

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Emerging Infectious Diseases
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ABSTRACT

During October–December 2015, 29 patients in a hospital in the Netherlands acquired nosocomial infection with a multidrug-resistant, New Delhi-metallo-β-lactamase–positive *Klebsiella pneumoniae* strain. Extensive infection control measures were needed to stop this outbreak. The estimated economic impact of the outbreak was $804,263; highest costs were associated with hospital bed closures.

In 2008, New Delhi-metallo-β-lactamase (NDM), an enzyme that confers bacteria with resistance to a range of antimicrobial drugs, was detected for the first time in a patient from Sweden during a trip to India [1]. Subsequently, NDM-producing isolates rapidly spread and have been found dispersed throughout the world. However, in western and northern Europe, identification of patients with NDM-producing *Enterobacteriaceae* is uncommon [2]. Infections with multidrug-resistant, gram-negative bacteria are a concern worldwide, given restricted treatment options and excess costs of care [3, 4]. During October 1–December 30, 2015, an outbreak of *Klebsiella pneumoniae* containing a NDM-1 plasmid affected 29 patients residing in Jeroen Bosch Hospital ('s-Hertogenbosch, the Netherlands), a 683-bed tertiary teaching hospital. This hospital outbreak started in a surgical ward. On November 23, 2015, NDM-producing extended-spectrum β-lactamase (ESBL)–positive *K. pneumoniae* bacteria were cultured and isolated from surgical drain fluid. At the time of identification, the patient was already discharged. Shortly thereafter, screening cultures of long-term admitted surgical patients revealed 2 additional patients with NDM-producing *K. pneumoniae*. Contact tracing and weekly screening rounds of all in-hospital patients were performed, identifying additional NDM carriers. Weekly screening rounds revealed 7 wards with uncontrolled NDM transmission (i.e., ≥2 NDM carriers). On the basis of an epidemiologic curve of the NDM carriers detected, all patients admitted to 1 of these wards beginning October 1 were defined as at risk of carrying NDM. Because the policy that was chosen was search and destroy (detect patients as quickly as possible and isolate them to protect the others), all patients residing at high-risk wards were tested.

Six months after the start of the outbreak, 2,964 patients had been flagged as at-risk patients; >95% of these patients had been screened, and a total of 29 NDM carriers were identified. No risk factors, such as recent travel abroad or a common source of transmission, were identified among the cases of this outbreak. In 2016, weekly screening rounds were continued in wards with populations at-risk to confirm the outbreak was successfully controlled.

Apart from the physical burden to patients and hospitals caused by multidrug-resistant microorganisms, nosocomial outbreaks also entail an economic burden. Estimates of the cost of outbreaks of multidrug-resistant bacteria in healthcare institutions are scarce. Insight on outbreak costs can help to justify the necessary investments in infection prevention and control measures, facilitating the decision making process on prevention and control policy. In this study, we assessed the total costs of this outbreak on the basis of interviews and data from the affected hospital.

THE STUDY

The outbreak occurred in a hospital with 683 registered beds, including a separate rehabilitation center. We assessed outbreak-related costs by using an activity-based costing model and performed interviews with staff working in the hospital to gather additional information about outbreak control activities performed and costs (online Technical Appendix, https://wwwnc.cdc.gov/EID/article/23/9/16-1710-Techapp1.pdf). We calculated hospital costs from October 1, 2015, the beginning of the outbreak, through January 31, 2016, one month after the end of the outbreak, when the greater part of costs had been made. We divided outbreak costs into diagnostics costs, ward-related costs, and other outbreak-related control measure costs. All costs are expressed as 2015 US dollars and Euros. Euros were converted to US dollars by using the data on the purchasing power parity of the Organization for Economic Co-operation and Development (https://data.oecd.org/conversion/purchasing-power-parities-ppp.htm): €1 = US $1.23.

The laboratory of the hospital performed diagnostic tests (bacteria cultures and PCR tests) and antimicrobial drug susceptibility testing for patients. All PCR tests were performed in batches. Items that were included in the determination of the costs of diagnostics were testing materials, procedures, and laboratory personnel. Personnel time of the microbiologists was valued by multiplying the time spent on laboratory and outbreak management activities, as quoted during the interviews, by unit costs per hour, taken from Dutch guidelines for economic evaluations [5].

We retrieved loss of revenues caused by closed beds after the outbreak from the hospital database and list prices online [5] and adjusted this number for the occupancy rate of the hospital, which was 85% on average. The extra expenses for personal protective equipment (disposable aprons, gloves, and masks) and cleaning the wards affected by the outbreak were gathered by the department of technical and facility services.

We also included costs associated with the additional time spent by healthcare workers on patient isolation. Following Wassenberg et al., we assumed 30 min/d for nurses and 10 min/d for physicians as the time required for adhering to control

measures [6]. The infection prevention expert provided the number of staff meetings in which outbreak interventions were discussed and the number of employees participating in these meetings. Both the executive manager and the communication manager provided data on the amount of time associated with outbreak response activities. Finally, other costs included costs for sending test kits to persons who had been hospitalized in the outbreak period.

We estimated total outbreak costs at $804,263 or €653,801 (Table), corresponding to a cost of $27,700 per patient. The loss of revenues on behalf of closure of beds contributed the most to the total costs. Other cost drivers were diagnostic tests and personnel time spent by laboratory employees and infection prevention experts.

CONCLUSIONS

The NDM-1 outbreak at Jeroen Bosch Hospital in the Netherlands in 2015 was associated with substantial costs incurred by the hospital, estimated at $804,263 or €653,801, which was 12% of the total budget allocated that year for medical microbiology and infection prevention, and $27,700 per patient. Blocked beds had the highest effect on the total costs, followed by staff time targeted at infection prevention activities.

A few studies have evaluated outbreak costs in hospitals; however, none of these were targeted at NDM outbreaks. Compared with other studies on the costs of hospital outbreaks with other pathogens, such as *Acinetobacter baumanni* [7, 8], norovirus [9], ESBL-producing *K. pneumoniae* [9], and *Enterococcus faecium* [9], our estimates are higher. One major factor explaining this difference was the testing of a relatively high number of patients; the closure of beds was the main cost driver in all applicable studies.

Despite being substantial, the cost we calculated for the outbreak is an underestimate. At least 9 NDM-1–positive patients and 28 other patients were discharged to a long-term care facility resulting in additional infection control measures and costs that were not taken into account for this report. In addition, a medical doctor, infection prevention expert, and infectious diseases nurse of the Municipal Health Service spent 95 h, 65 h, and 30 h, respectively, on the outbreak, accounting for $9,551 additional costs. Furthermore, phylogenetic molecular methods were performed at the National Institute of Public Health to confirm the outbreak. Finally, we only calculated the outbreak costs through January 31, 2016, but additional costs probably were incurred after this date.

As shown in this study, the expansion of multidrug-resistant, gram-negative bacteria is of great concern; these bacteria both threaten patient safety and increase healthcare costs. The intensive outbreak control measures of the hospital were

costly and inconvenient for patients and staff. In countries where NDM-1–positive *K. pneumoniae* is not endemic, early detection of colonized patients and adequate infection prevention control strategies will be key factors in minimizing the spread of multidrug-resistant bacteria.

Table 1. Total outbreak costs stratified by type of cost, Jeroen Bosch hospital, the Netherlands, Oct 2015–Jan 2016*

Type of cost	Explanation	Total cost, US $	Total cost, €
Diagnostics			
Other laboratory personnel	Estimated 2,517 h†	93,789	76,251
Microbiological tests	Material costs to perform cultures in batches	60,070	48,837
Microbiologists	Estimated 376 h†	46,017	37,412
Molecular diagnostics	Material costs to perform PCRs in batches	24,523	19,937
Subtotal diagnostics		**224,399**	**182,437**
Ward-related costs			
No. blocked beds	582 beds, occupancy rate 0.85 at $550/d or €447/d (5)	272,085	221,131
Personal protective equipment	Expenditures for extra disposable aprons, gloves, and masks	55,121	44,814
Cleaning wards	Purchase of 2 fogging devices and personnel time for extra cleaning	46,881	38,115
Subtotal ward-related costs		**374,087**	**304,060**
Other outbreak control costs			
Infection prevention experts	Estimated 2,336 h for internal advice and guidance†	105,356	85,655
Patients in isolation	280 patients, averaged at 5.2 d of hospitalization, at $31.40/d or €25.53/d (6)	45,718	37,172
Staff meetings	23 staff meetings with on average 21 participants × 0.75 h × $1,525/h†	26,306	21,390
Communication	320 h for internal and patient-related communication spent by several communication employees†	17,696	14,387
Costs for mailings		10,701	8,700
Subtotal outbreak control costs		**205,777**	**167,304**
Total costs		**804,263**	**653,801**

**Resource use related to this outbreak was provided by the hospital.*
†Labor costs/h were determined by using the Dutch manual for economic evaluations [5].

TECHNICAL APPENDIX

Description of interviews conducted with hospital personnel.

At first, we contacted the microbiologist of the hospital and asked for the right persons involved with the outbreak who could give us additional information about outbreak control activities performed and costs. Second, we emailed the relevant employees for their willingness to participate in this cost evaluation and invited them for an interview. In preparation of the interview, we sent them the questionnaire and asked for available data on costs.

Face-to-face interviews were held with the general business manager of the hospital, a medical microbiologist, the manager of technical and facility services, a person accountable for planning of hospitalizations, the head nurse of the hospital ward mostly affected by the outbreak, an infection prevention expert, and the executive manager responsible for the laboratory personnel and infection prevention. In addition, the communication manager and the Municipal Health Service physician were interviewed by phone and through email.

The interviews were conducted in February and March 2016. At that time, all outbreak activities were over.

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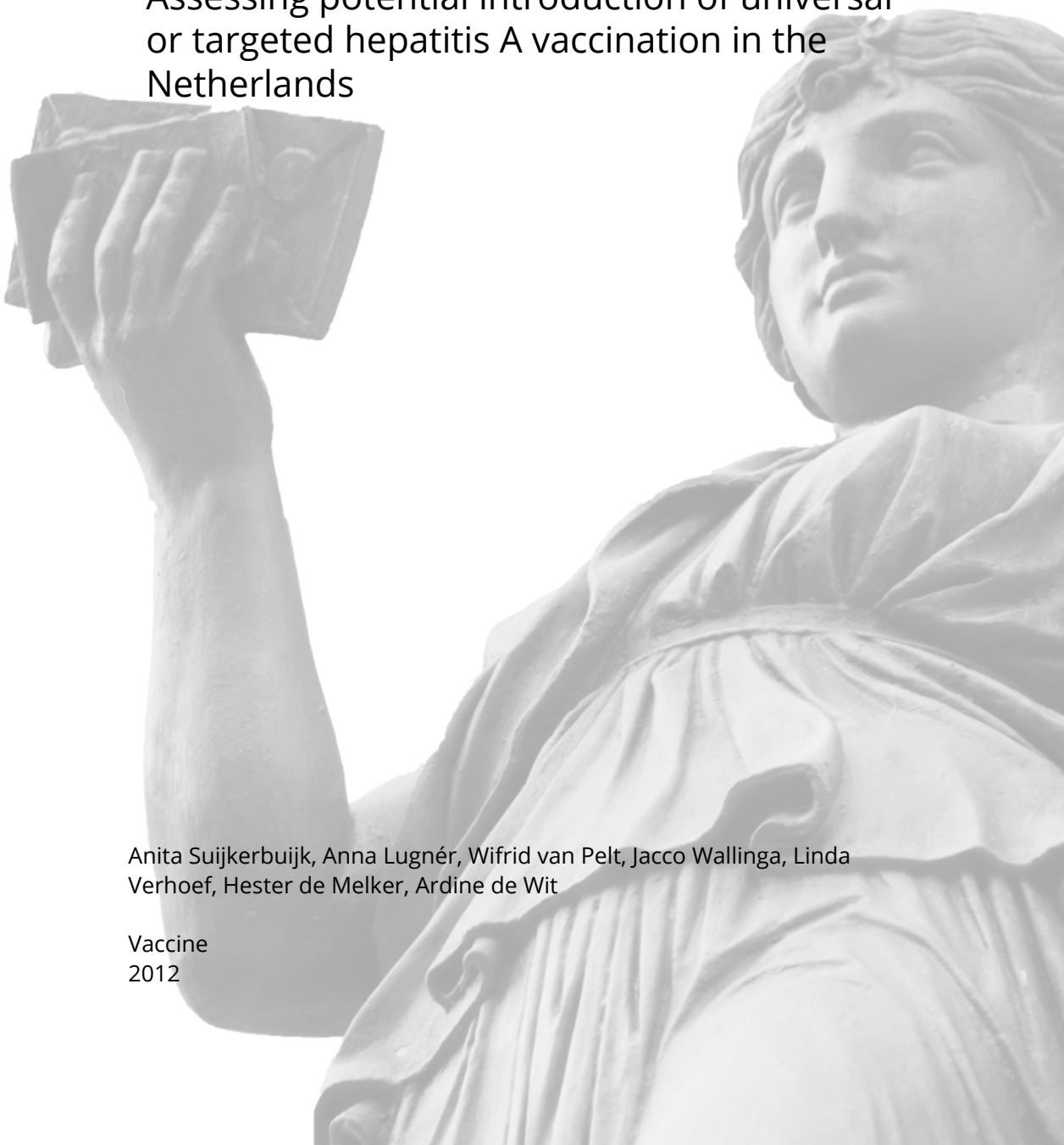
CHAPTER 6

Assessing potential introduction of universal or targeted hepatitis A vaccination in the Netherlands



Anita Suijkerbuijk, Anna Lugnér, Wifrid van Pelt, Jacco Wallinga, Linda Verhoef, Hester de Melker, Ardine de Wit

Vaccine
2012

ABSTRACT

In many industrialized countries, hepatitis A incidence rates have declined steadily in the past decades. Since future cohorts of non-vaccinated elderly will lack protection against disease and the burden of hepatitis A is higher with increasing age, this could be an argument in favour of taking preventive measures such as including hepatitis A vaccine into the national immunisation program, or offering hepatitis A vaccine to the elderly only. Using a vaccination evaluation scheme, we assessed the potential benefits and drawbacks of introducing hepatitis A vaccine in the national immunisation program in the Netherlands. The average number of annual hepatitis A notifications is declining, from 957 in the period 1991 to 1995 to 211 over the period 2006 to 2010. The direct health care costs and costs due to productivity losses per patient are rising, because the age at infection increases and older patients require a relatively higher number of hospitalizations. Initiating a vaccination program would most likely not be cost-effective yet. The annual costs of mass-vaccination are large: about €10 million for infants and €13 million for older people (and only in the first year €210 million), based on current retail prices. The annual effects of mass-vaccination are small: the cost-of-illness in recent years attributed to hepatitis A infection is estimated to be €650,000 per year, and the disease burden is on average 17 DALYs. Given the current low hepatitis A incidence, and the continuing decline in incidence, targeted preventive measures such as vaccinating travellers and other high-risk groups and timely vaccination of close contacts of hepatitis A patients are adequate. However, because susceptibility to hepatitis A is increasing in the group with the highest risk of developing severe complications upon infections, careful monitoring of the epidemiology of hepatitis A remains important.

INTRODUCTION

In many industrialized countries, hepatitis A (HAV) incidence rates have declined steadily, resulting in a low endemicity in a large part of the world [1, 2]. Recent serological studies indicate that future cohorts of elderly will lack protection against disease, due to less exposure to HAV at younger ages [3, 4]. Therefore, there could be reasons for taking preventive measures against future outbreaks and growing disease burden in elderly people. The existence of a safe and effective vaccine against HAV, has started a debate on adding this vaccine to national vaccination programs, or targeted to older persons only [4]. Currently, there is no universal HAV-vaccination program in the Netherlands.

Introducing a new vaccination scheme into the National Immunisation Program (NIP) entails careful considerations about numerous factors. Kimman et al developed an evaluation model to structure significant information to support decision making on a NIP, which has been used for several vaccinations [5-8].

In this study we present the epidemiology of HAV in the Netherlands, estimates of the cost-of-illness of HAV, the disease burden, and costs of possible vaccination schemes, in order to assessing the evidence for implementing HAV into the NIP in a country of low-endemicity, the Netherlands [5].

METHODS

The assessment tool of Kimman collects relevant information on the topics 'vaccine', 'pathogen', 'disease burden' and 'cost-effectiveness' [5]. We describe the vaccine and disease characteristics, based on the literature. Thereafter, we present cost and disease burden estimates using existing notification data. In the Netherlands, all physicians are obliged to report a hepatitis A infection to the Municipal Health Service who record patient characteristics in a national database. We extracted information from the national database on HAV-patients in the years 1991 to 2010. Data on mortality were obtained from the website of Statistics Netherlands [9]. We acquired hospitalization data acquired from the National Medical Registry. Data on liver transplantations due to HAV were obtained from the Dutch Transplant Foundation. Most likely, not all infected (and symptomatic) persons will visit the general practitioner (GP), and not all cases will be notified by the GP. We therefore also describe estimates of expected underreporting and underascertainment.

Costs were gathered from standard unit cost lists [10, 11], list prices available online [11], and from the literature [12]. Information on health care consumption regarding average number of GP visits among HAV patients, and average number of contacts to

be vaccinated were taken from a Belgian survey [3]. Productivity losses were valued using standard tariffs for the Dutch population (mean, all ages) [10], adjusted for work participation in all age groups [9]. The length of the productivity loss was calculated for the same duration as of illness, 14 days for patients visiting their GP and 30 days for hospitalized patients [13]. The percentage of patients for whom someone stayed at home as care giver were obtained from the survey [3]. In concordance with the Dutch guidelines for pharmaco-economic studies the estimate of productivity loss in case of deaths is based on the friction cost methods. We included cost estimates for HAV from a societal perspective; all costs were expressed in Euros price level of 2009 (Table 1).

In order to explore the number and extent of HAV outbreaks in the Netherlands in the past ten years we searched for those outbreaks in the archives of the Dutch Infectious Diseases Journal and in the weekly reports of the early warning committee [14, 15]. Furthermore, we searched for evidence on the cost-effectiveness of HAV vaccination in other countries for children or adults in studies that have been published during January 2000 and May 2011 using PubMed database.

Table 1 Unit costs and average health care utilization and productivity losses (€2009)

	< 15 years		**≥ 15 years**	
	Unit cost (€)	**Average 1999-2010**	**Unit cost (€)**	**Average 1999-2010**
Healthcare costs				
GP	28	2.3 visits	28	3.7 visits
Vaccination contacts[1]	80.60	81%, 3.2 contacts	101.40	76%, 5.6 contacts
Serological test	34.10	80% (GP pat) 100% (hosp pat)	34.10	80% (GP pat) 100% (hosp pat)
Hospitalization	456	4,55 (< 10 yrs) 5,56 (10 – 15 yrs)	456	5,27 (15 – 65 yrs) 11,83 (≥ 65 yrs)
Ultrasonography	86.20	100% hosp pat	86.20	100% hosp pat
Liver transplantation			119,404	0.8 per year
Productivity losses				
Pat. visiting GP	NA	-	1,897	75.6% working 14 days
Hospitalized pat.	NA	-	4,066	75.6% working 30 days
Death	NA	-	13,565	
Care givers		40% of pat		14% of pat
Pat visiting GP	759	14 days	190	10 days
Hosp pat	759	14 days	379	20 days

Notes: yrs=years, GP=general practitioner, pat=patient, hosp=hospitalized, NA=not applicable 1 including GP visit

RESULTS

The vaccines

Available vaccines and indications

Havrix®, the first commercially produced monovalent formaldehyde inactivated hepatitis A vaccine was launched in 1992, shortly followed by Avaxim®, Vaqta® and Epaxal® [16-18]. In addition, inactivated combination vaccines are available. The WHO recommends HAV-vaccination for defined risk groups such as travellers to HAV endemic countries, men having sex with men (MSM), injecting drug users, patients with chronic liver disease, food handlers, health care workers and day-care centre staff [19]. Finally, vaccination is indicated as post-exposure prophylaxis after contact with a patient diagnosed with hepatitis A and during outbreaks [19].

Effectiveness

The vaccine against HAV is highly effective in preventing infection; a protective efficacy up to 100% in healthy individuals has been shown [18, 20, 21] and it provides high effectiveness when used as post-exposure prophylaxis, given that vaccination is started in time [22, 23]. Two doses of the vaccine generate at least 25 years protection and possibly lifelong in immune competent recipients. A prospective study in the elderly showed a seroprotection of approximately 65% after a primary dose in subjects over the age of 50 years compared to 100% in the younger control group. However, seroprotection was 98% in the older age group after receiving a booster dose [24].

Safety

The overall safety profile of inactivated vaccines, administered to children and adults has proven to be good [25, 26]. Most adverse reactions are mild and include fever, myalgia, headache, pruritus, and nausea. Reports of serious adverse events include anaphylaxis, multiple sclerosis, and encephalopathy [27]. However, a causal relationship has not been proven so far.

Factors affecting successful implementation in the National Immunisation Program

In general, vaccination uptake of regular childhood vaccines is very high in the Netherlands. The potential uptake of universal vaccinations in the NIP depends on the willingness of the population to accept vaccination [28]. Factors such as risk perception (susceptibility to and severity of disease), and outcome expectations (the perceived safety and reliability of the vaccines) are related to a positive attitude to

vaccination [28, 29]. Since hepatitis A is mostly asymptomatic in young children and disease severity is highest in older people specific health education messages would be necessary when starting a new vaccination program.

Pathogen

Pathogenicity

Verhoef and colleagues assessed the prevalence of antibodies to HAV in a sample representative of the Dutch population in 2006–2007, and compared these results to the seroprevalence data from a similar study in 1995–1996 [4]. The overall seroprevalence increased from 34% to 39% (Figure 1). In the second study, 12.6% of the participants was vaccinated, whereas only 0.8% was vaccinated in 1995-1996. Furthermore, a trend of increasing age of the susceptible population is seen as result of a cohort effect of those born after World War II. Figure 1 suggests that in the next 10 years 60% of the population of 60 years or over might be susceptible in absence of vaccination or other exposure to HAV.

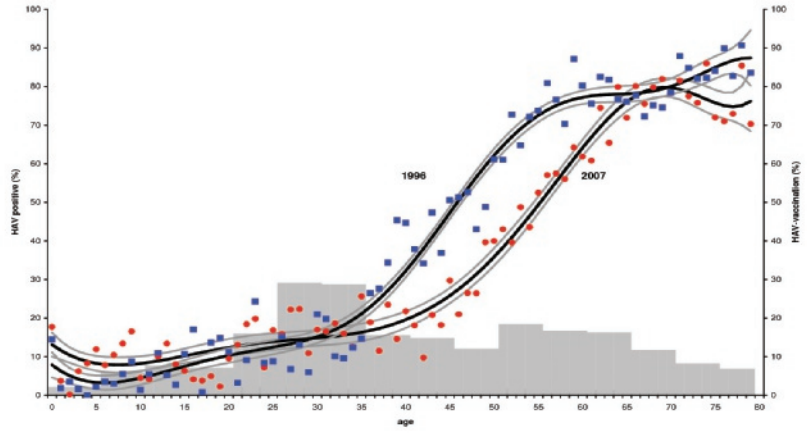


Figure 1. Age prevalence of hepatitis A antibodies presented per year in age including 90% confidence intervals in non-HAV vaccinated persons in two nationwide samples of the Dutch population in 1995–1996 (n=7287, excluding 59 vaccinated participants) and 2006–2007 (n=5442, including 786 vaccinated participants, grey bars) [4].

Infectiveness and transmissibility

HAV has only one known serotype. The incubation period for the virus is on average 28 days and infection is generally acquired by the faecal-oral transmission route [30]. Symptoms include variable combinations of jaundice, fever, malaise, anorexia, nausea

and vomiting, arthralgia, myalgia and flu-like symptoms. Fulminant hepatitis is a rare complication of HAV and in some cases, a liver transplantation may be necessary. HAV is not linked to chronic liver disease.

Burden of disease in the Netherlands

Notifications

Between 2006 and 2010, the average annual number of notifications was 211 compared to 957 in the years 1991 to 1995. The mean age at infection increased from 17 in 1991 to 30 in 2010. During the whole period, more men than women were infected. Between 1999 and 2010, the mean annual number of hospitalizations was 35. The proportion of hospitalized hepatitis A cases increased from 4% of the total number of notifications in 1999 to 20% in 2010. Since 1999 nine fatal hepatitis A infections have been registered [9].

Risk factors for infection in the Netherlands

Since 2005, the notification data include the most likely source of infection and country where the infection was contracted suggesting that almost half of the infections is travel-related. A small number of infections relates to homosexual contact, occupational activities, and ingestion of contaminated food. Yearly, Turkish and Moroccan families who have spent their summer holidays in the country of origin import HAV into the Netherlands. Notification data revealed that infections contracted in Turkey and Morocco peaked in 1997 and has decreased ever since [31], supporting the recent shift from high to intermediate HAV endemicity observed in these countries, associated with the improvement of economic and sanitary conditions [32-34].

Burden of disease expressed in DALYs

Based on notification data the annual average disease burden between 2005 and 2010 due to HAV infection is estimated to be 2.75 DALYs for deaths and 14.2 DALYs lost due to disease (Table 2). These estimates are based on published disability weights for the different disease stages as found in the literature [13, 35].

Table 2 Annual disability losses due to HAV (life years lost discounted at 1.5%)

	Disability weight	Disability loss (DALYs, averages)			
		1999-2004		2005-2010	
		No. patients	DALY loss	No. patients	DALY loss
Visiting GP	0.058[a]	510	29.58	179	10.38
Hospitalization	0.106[a]	38	4.01	33	3.46
Liver transplantation 1st year	0.43[b]	0.8	0.34	0.8	0.34
		LYL		LYL	
Death	1	13.51	13.51	2.75	2.75
Total			**47.44**		**16.93**

Note: DALY=disability adjusted life years, LYL=life-years lost, GP=general practitioner, [a] [13] [b] Weighted average based on [13, 35]

Costs of the vaccination program

When introducing a new vaccination scheme there will be campaign (once-only) costs surrounding implementation of the vaccine, including costs for education of health care workers and developing information materials. Costs associated with distribution, invitation, and administration of the vaccines also need to be considered. Monitoring adverse events and safety would be included in the already existing surveillance system. The retail prices of several HAV vaccines available in the Netherlands are similar (€31.20 per adult dose and €20.80 per paediatric dose). If the vaccination against HAV would be included into the NIP for children in their first year of life, costs would be €10 million per year, (Table 3). If GPs would implement the vaccination of all people of 60 years and above, analogous to the influenza vaccination program, the total vaccination costs will be more than €210 million in the first year, due to the need for a catch-up campaign for all persons older than 60. Annual costs of the vaccination of every new cohort reaching the age of 60 would be approximately €13 million. However, in case of introduction in the NIP the actual price of a vaccine can be expected to be lower than the retail price due to centralized purchasing. Moreover it is difficult to estimate the future participation rate in the HAV vaccination program, influencing the total costs.

Table 3 Costs of potential vaccination programs, € 2009

	Target group	
	Children at age 1	**All people > 60 years**
Population size	184,900	3,512,400
Uptake	95%	70%
Vaccine price	2 doses á €20.80	2 doses á €31,20
Administration cost	€3[a] + 2*€6[b]	€3[a]+2*€10[b]
Campaign cost, once only	€200,000	€200,000
Total cost, 1st year	€ 10.1 million	€ 210.1 million
Annual vaccination cost	€10.1 million	€13.4 million (cohort 221,550)

[a] distribution costs, [b] application costs

Cost-of-illness

The overall costs associated with HAV are declining, due to the declining number of hepatitis A diagnoses (Figure 2 and Table 4). However, the health care costs per patient between 2005 and 2010 were 63% higher than in the period 1999 to 2004. The older mean age of patients, the relatively higher number of hospitalizations in these older age groups, and a longer duration of hospitalization stay explain this rise. A large part of the economic burden is attributed to productivity losses when patients with symptomatic infection and caregivers of symptomatic patients may be unable to work. Between 1999 and 2004, the productivity losses were considerable higher than the direct costs of treatment. In the period 2005-2010, the productivity losses were lower than the direct health care costs. The productivity loss per case was slightly higher in the second period.

By using notification data to calculate the cost-of-illness, we left underreported and underascertained cases of HAV out of account. Havelaar et al estimated that in 2009 the number of new infections would be 862 (range 557-1,390) (compared to 163 cases in our study) based on notified cases which were adjusted for underestimation using a capture recapture study [13]. Assuming the same cost and age distribution as in our calculation, the costs of HAV infections would be €345,741 (direct costs, range €317,549 – €394,500) and €922,201 (productivity loss, range €613,606 - €1,455,918) if including the estimates of the underestimation. The direct costs are in line with our averages for 2006-2010, because 20% of clinical cases were assumed not to consult their GP, and the number of hospitalizations was taken directly from the National Medical Registry and would not be affected by the underestimation. Assuming that the underestimated cases give rise to the same amount of productivity losses as the notified cases, the costs would be 2.7 times higher.

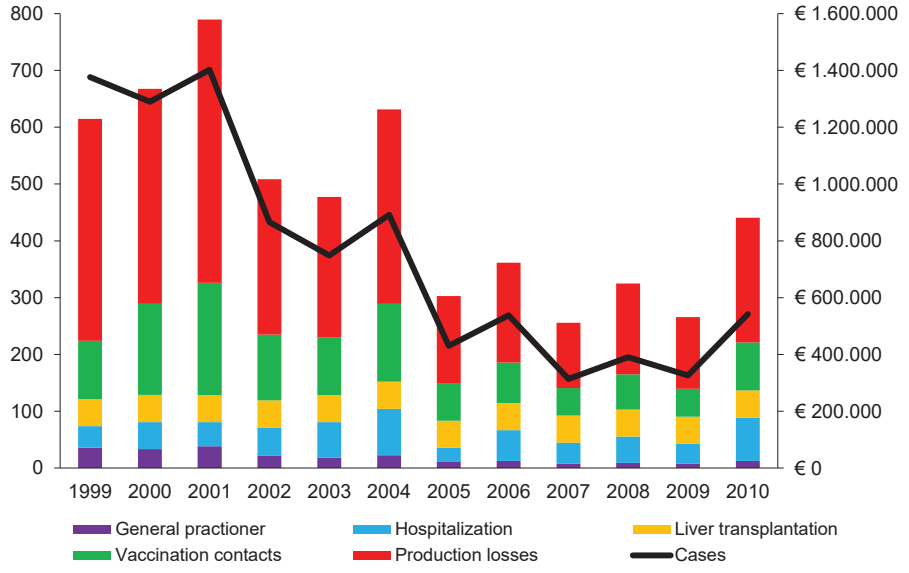


Figure 2. Number of notifications and costs of HAV, the Netherlands 1999-2010.

Table 4 Costs of hepatitis A in the Netherlands (€ 2009)

	Annual costs (averages)			
	1999-2004		2005-2010	
	Average no. of cases	Costs (€)	Average no. of cases	Costs (€)
Direct healthcare costs				
Patients visiting GP	510	57,060	179	20,782
Hospitalizations	38	106,932	33	90,767
Costs for vaccinating contacts	2934	271,670	1375	127,122
Costs for liver transplantation	0.8	95,523	0.8	95,523
Total	**548**	**531,185**	**212**	**334,194**
Cost per case		970		1,579
Productivity losses				
Hepatitis A diagnosed patients	211	440,989	99	229,698
Death	1.7	2,261	0.3	0
Care givers	414	255,024	160	86,484
Total		**698,273**		**316,182**
Cost per case		1,275		1,494

Hepatitis A outbreaks

Between 2001 and 2010 the Dutch Infectious Diseases Journal (Infectieziekten Bulletin) and the weekly early warning record reported 20 outbreaks with HAV [14]. Close contacts within schools and day care centres played an important role in the transmission of the infections. The majority of outbreaks was confined to 2 - 10 detected cases. Still, a few outbreaks were considerably more extensive. In 2004, 15 homeless persons who visited different shelters in Rotterdam contracted HAV. In the region Kennemerland 30 clustered cases were detected at four primary schools between September 2005 and April 2006. Another outbreak at the end of 2009 consisted of 14 patients in which the probable source of infection was semi-dried tomatoes [36]. Finally, there were increases in HAV infections among MSM in 2001, 2004 and 2010.

Cost-effectiveness studies

Searching the literature for cost-effectiveness studies on vaccination against HAV revealed that since the introduction of the vaccine in the early nineties, several countries have implemented universal and selective vaccination programs. No economic evaluations were found regarding vaccinating older people. Three studies evaluated cost-effectiveness of adult vaccination programs [3, 37, 38]. These studies assessed that vaccination would not be cost-effective; cost-effectiveness ratios (converted to euros and indexed to 2009), were all above accepted thresholds: vaccinating 50-year-old US residents would cost €559,153 per life year saved [37]; universal vaccination in Ireland among individuals 10-29 years of age generated an incremental cost-effectiveness ratio (ICER) of €169,290 per case prevented [38]; vaccination in adults in Belgium resulted in an ICER of €211,483 per QALY gained [3]. Jacobs assessed that universal vaccination of 1 or 2-year-old children in all US regions would cost €1414 per QALY gained, according to Rein this would be €26,583 per QALY gained [39, 40]. Herd-immunity effects would be expected to produce substantial additional benefits, lowering the cost of the immunisation program to €949 per QALY gained for the first 10 birth cohorts, starting in 2005 [41]. Other studies in countries with a high incidence (Chile, Argentina, Brazil, Israel and China) estimated that a universal vaccination program would be cost saving [42-46]. In the Belgian study, however, universal infant vaccination at 95% uptake produced an ICER of €277,340 (direct costs per QALY gained) [3].

DISCUSSION

In this study, we assessed the disease burden, costs of a vaccination program and cost-of-illness to advise on potential introduction of universal HAV-vaccination in the Dutch NIP. Based on the observations and estimations presented here, such a program would most likely not be cost-effective. The annual costs for vaccination would be about €10 million for infants and €13 million for elderly (and €210 million in the first year only). The possible savings would be the cost-of-illness attributed to HAV (on average €650,000 per year) and the average number of DALYs averted would be 17. Even if all costs-of-illness would be saved and all DALYs would be averted, the costs of achieving those gains by vaccination would not be justified.

Our study revealed that in the Netherlands, incidence of HAV-infections is low and declining in the past decade [47]. The mean age at infection is rising, as well as the proportion of infections resulting in hospitalization. Taken together, this indicates an increased morbidity due to HAV-infection. However, the mortality caused by a HAV infection did not increase, and the annual burden of disease, expressed in DALYs, is decreasing.

Incidence of HAV-infection turns out to be one of the major determining factors for the cost-effectiveness of hepatitis A vaccination. In Belgium, a neighbouring country with comparable HAV epidemiology, an extensive study, including transmission effects, demonstrated that both universal and adult vaccination would not be economically attractive [3]. As many factors affecting cost-effectiveness of vaccination are comparable between Belgium and the Netherlands, this could imply that vaccination would have similar unfavourable cost-effectiveness ratios in the Netherlands.

With a relatively long incubation period of HAV, timely vaccination of household and other contacts can be an adequate alternative in order to effectively mitigate HAV-outbreaks. Such an approach was proven to be cost saving when the primary case was located in a day care centre or school, and to have acceptable costs per symptomatic case prevented when vaccinating household contacts of cases [48].

It remains important to continue HAV vaccination for high-risk target groups such as patients with chronic liver disease. Furthermore, the special attention of Municipal Health Services to Turkish and Moroccan children to propagate a HAV vaccination before they travel to their country of origin is important. Travellers to endemic areas, as well as MSM, often choose to be vaccinated (at their own cost). In the future, the risk of exposure to and infection with HAV for travellers will gradually decrease by improvement of hygienic standards at popular travel destinations [49]. However, the

potential of common source outbreaks in endemic countries continues to expose unprotected travellers to hepatitis A and therefore vaccinating travellers to endemic countries remains necessary.

Results from clinical trials in the USA, and interventions during HAV outbreaks in other countries, suggest that a single HAV vaccination per person may be sufficient to interrupt the transmission of HAV in the population at risk [18, 23]. In 2005, public-health authorities in Argentina began a universal vaccination program, using a single-dose vaccine schedule at relatively low costs. With a vaccination coverage of 95% in 2006 incidence of symptomatic HAV dropped sharply in all age groups [50]. However, before introducing this policy in other countries, it remains to be investigated if a single-dose immunisation will provide long-term protection.

CONCLUSION

We aimed at presenting data and estimates of aspects needed to be considered for introduction of HAV vaccination in a NIP following an evaluation model [5]. Considering all elements of this model, universal or targeted HAV vaccination is not expected to be cost-effective in the Netherlands and probably will not be in other West-European countries with a low incidence of HAV. Bearing in mind that due to less exposure to HAV at younger ages, the susceptibility of older age groups could increase, and together with further changes in the epidemiology of HAV, it may be vital to reassess the evidence for introduction of universal or targeted HAV vaccination. For that reason, careful monitoring the HAV epidemiology remains important.

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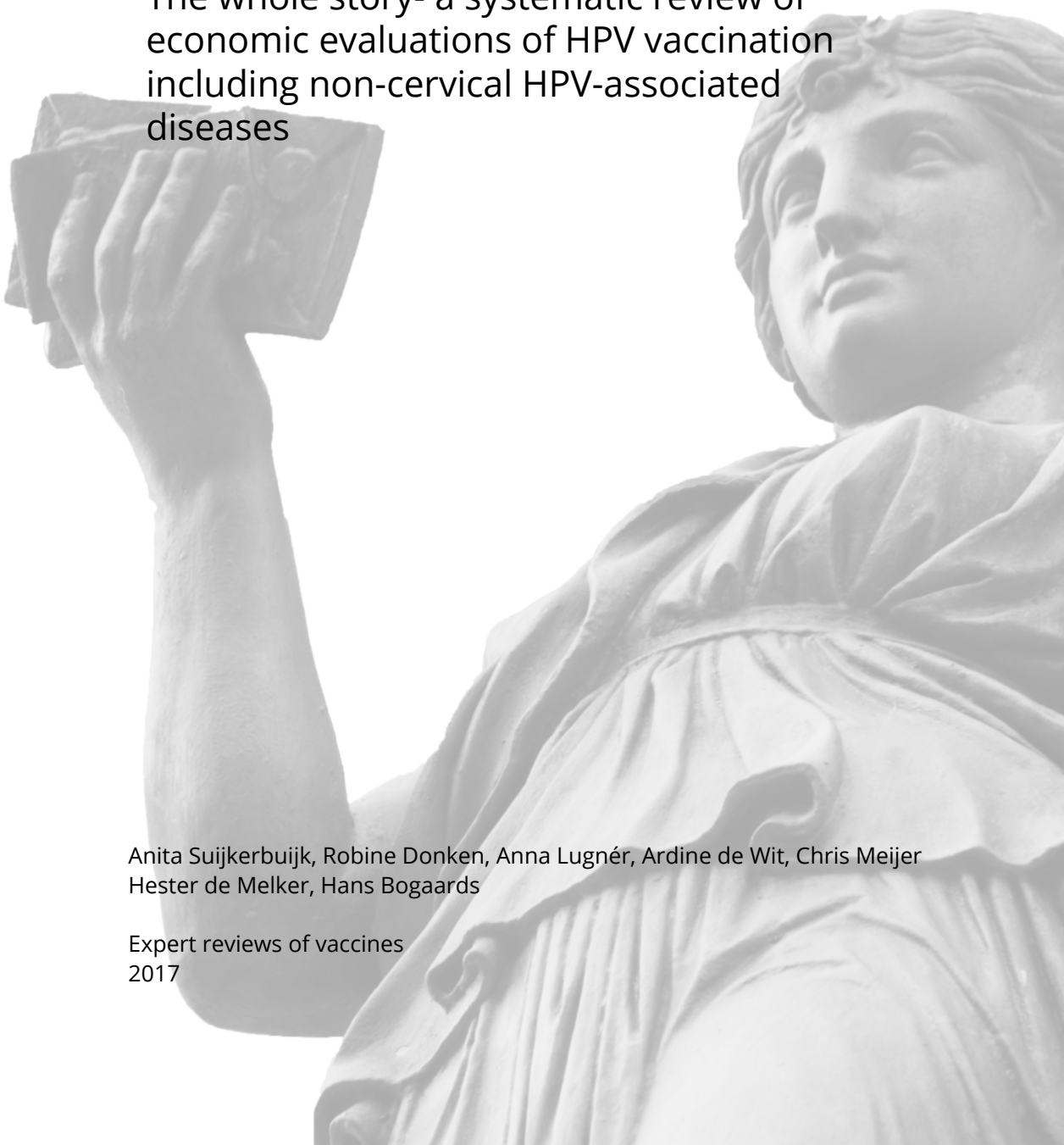
CHAPTER 7

The whole story- a systematic review of economic evaluations of HPV vaccination including non-cervical HPV-associated diseases



Anita Suijkerbuijk, Robine Donken, Anna Lugnér, Ardine de Wit, Chris Meijer
Hester de Melker, Hans Bogaards

Expert reviews of vaccines
2017

ABSTRACT

Introduction: Many economic evaluations of HPV vaccination have been published, but most have focused on the prevention of cervical disease as a primary health outcome. The cost-effectiveness of vaccination is likely to be underestimated if not all HPV-associated diseases are taken into account. In this review, we assess the influence of non-cervical HPV-associated diseases on the incremental cost-effectiveness ratio (ICER) of preadolescent HPV vaccination.

Areas covered: We systematically searched the literature and identified 18 studies that included non-cervical diseases in the estimates of cost-effectiveness of HPV-vaccination. The ICERs became substantially more favorable when HPV-related diseases other than cervix carcinoma were taken into account: compared to not including such other diseases, the mean ICERs were 2.85 times more favorable (95%CI 1.35-4.36) for girls only vs. no vaccination, and 3.89 times (95% CI -0.10-7.85) for gender neutral vs. girl only vaccination.

Expert commentary: Including non-cervical diseases in economic evaluations of HPV vaccination programs makes it more likely that the ICER falls beneath accepted cost-effectiveness thresholds and therefore increases the scope for gender neutral vaccination.

1. BACKGROUND

The human papillomavirus (HPV) is a non-enveloped DNA virus of which more than 175 types exist [1, 2]. These types are divided into high-risk (hr) and low-risk (lr) HPV types [3]. A persistent infection with an hr HPV type is a necessary cause in the development of cervical cancer [4]. Moreover, HPV is associated with the development of a proportion of vaginal, vulvar, penile, anal and oropharyngeal cancers [5, 6]. Lr types of HPV are the causative agents in the development of (genital) warts and recurrent respiratory papillomatosis (RRP) [7, 8]. RRP is a rare syndrome of recurring proliferations of multiple papillomas in the respiratory tract [9].

In 2006/2007, two prophylactic L1 vaccines (a bivalent, Cervarix® and a quadrivalent, Gardasil®) became available, both protecting against infections with hr-types HPV16 and HPV18 [10]. These types account for approximately 70% of cervical cancer cases. For both vaccines, over 95% efficacy against HPV16- and HPV18-associated cervical lesions has been shown. Additionally, the quadrivalent HPV vaccine targets lr types HPV6 and HPV11, which are accountable for approximately 90% of genital warts [11]. Both vaccines induce cross-protection against hr types other than HPV16 and HPV18 [12]. Since 2015, a third, nonavalent, prophylactic L1 vaccine has become licensed (Gardasil9®), additionally targeting hr types HPV31, 33, 45, 52 and 58 [13]. Following licensure of the prophylactic vaccines, many countries have introduced vaccination programs with the primary aim to prevent cervical cancer [14]. These programs are expected to also prevent non-cervical HPV-associated cancers, i.e. vaginal, anal, vulvar, oropharyngeal and penile cancer [15, 16]. In fact, the quadrivalent and nonavalent vaccines are also registered against (precursors of) anal, vaginal and vulvar cancer, and have shown an efficacy over 75% against precursor lesions [11, 17, 18].

Studies evaluating the costs of vaccination in relation to the expected health gain of the intervention are a tool to support policy making and reimbursement decisions [19]. Despite the high pricing of HPV vaccines at market introduction, most economic evaluations of girls only vaccination programs showed favorable cost-effectiveness ratios [20]. Since most estimates were just below country specific thresholds for cost-effective strategies, HPV vaccination generally was observed as a costly intervention. Economic evaluations of vaccinating boys in addition to girls have been less conclusive in supporting the cost-effectiveness of gender neutral HPV vaccination [21]. Systematic reviews that analyzed the cost-effectiveness of gender neutral vaccination also include economic evaluations targeted at the effects on cervical cancer in women and genital warts [20, 22, 23]. By not considering other HPV-associated diseases, these economic

evaluations might have underestimated the cost-effectiveness of HPV vaccination, both for vaccination programs restricted to females, and for gender neutral vaccination [24]. The aim of this study was to systematically review published literature on the cost-effectiveness of HPV vaccination, not only considering (precursors of) cervical cancer, but taking all diseases into account with strong evidence for a causal link with HPV [25]. Specifically, we aimed to study the influence of inclusion of non-cervical HPV-associated diseases on the incremental cost-effectiveness ratio (ICER) of vaccination programs targeted both at girls only and at both girls and boys.

2. METHODS

A systematic literature search was performed for publications up to January 18th 2016 in PubMed, SciSearch, EMBASE, International Pharmaceutical Abstracts (IPA), BIOSISPreviews, and the Centre of Reviews and Dissemination (CRD) database of the University of York to identify economic evaluations regarding HPV vaccination. The following key-words were used: Human Papillomavirus, HPV, vaccine, immunization, vaccination, cost-effectiveness, cost-utility, cost-benefit, economic evaluation, economic study, cost-effectiveness analysis (CEA) and cost-utility analysis (CUA). The detailed search strategy is added in an appendix file (Table A1).

Selection criteria were original full economic evaluations of all prophylactic HPV vaccines of girls and/or boys at preadolescent age. A full economic evaluation implies that two or more vaccination strategies are compared with each other or with usual care with regard to both costs and outcomes. In the case of studying the cost-effectiveness of HPV vaccination, comparisons with usual care include, at least in industrialized countries, organized screening programs for cervical cancer. In order to be selected, studies had to include an ICER estimating the cost-effectiveness of vaccination including at least one other HPV-associated cancer besides cervical cancer and be written in English. Papers should have included at least one non-cervical HPV-associated cancer; however, effects on all HPV-related diseases mentioned in these papers were taken into account. Abstracts of congress meetings, editorials, letters, and reviews were excluded from analysis. Nonetheless, the latter were used to detect additional possible relevant studies from reference lists.

We extracted information from the publications following the 24- items checklist of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [26]. Besides additional items specifically for HPV vaccination, such as efficacy, uptake and cervical cancer screening program were included. The principal items considered in this review were: the description of the objectives, vaccination strategies, the type

of model used, health state values and costs of HPV-associated diseases, vaccine characteristics, results expressed in ICERs of the base case, and the use and results of sensitivity analyses. When available from the original publication, we extracted cost-effectiveness ratios for several vaccination scenarios: vaccination of girls versus no vaccination and gender neutral vaccination versus vaccination of girls only. In countries where vaccination of girls is already implemented, only the second scenario would be of interest. In addition, when included in the reviewed papers, we extracted the ICER when only cervical cancer was included, and the ICER(s) when other HPV-associated cancers were incorporated in the estimations of cost-effectiveness. To compare the ICERs including only cervical cancer or more HPV-associated diseases, we calculated the mean ICERs over all studies reporting an ICER for cervical cancer and for all studies reporting an ICER including also other HPV-associated diseases. We estimated the mean reduction in ICERs that resulted from the inclusion of non-cervical diseases from studies reporting both an ICER for cervical cancer alone and an ICER for cervical cancer plus other diseases, that is, from within-study comparisons.

To be able to compare costs and cost-effectiveness ratios of the economic evaluations with different base years and different currency units, all local currencies were first transferred to the Euro currency values of that time, using data on purchasing power parity (PPP) of the Organization for Economic Co-operation and Development (OECD). Next, they were recalculated to 2014 € values, using the consumer price index of Statistics Netherlands. The average conversion rate of US dollars to Euros in 2014 was 0.83.

3. RESULTS

The literature search resulted in 403 articles (Figure 1). After reading the abstracts 26 published economic evaluations targeted at HPV vaccination were selected. After reading full texts, 18 economic evaluations were included in this review. Of the studies that were excluded, four studies concerned no full economic evaluation, one study only considered vulvar cancer and the remaining studies only considered the effects in men. As the latter studies by definition did not include cervical cancer, answering our research question was not possible.

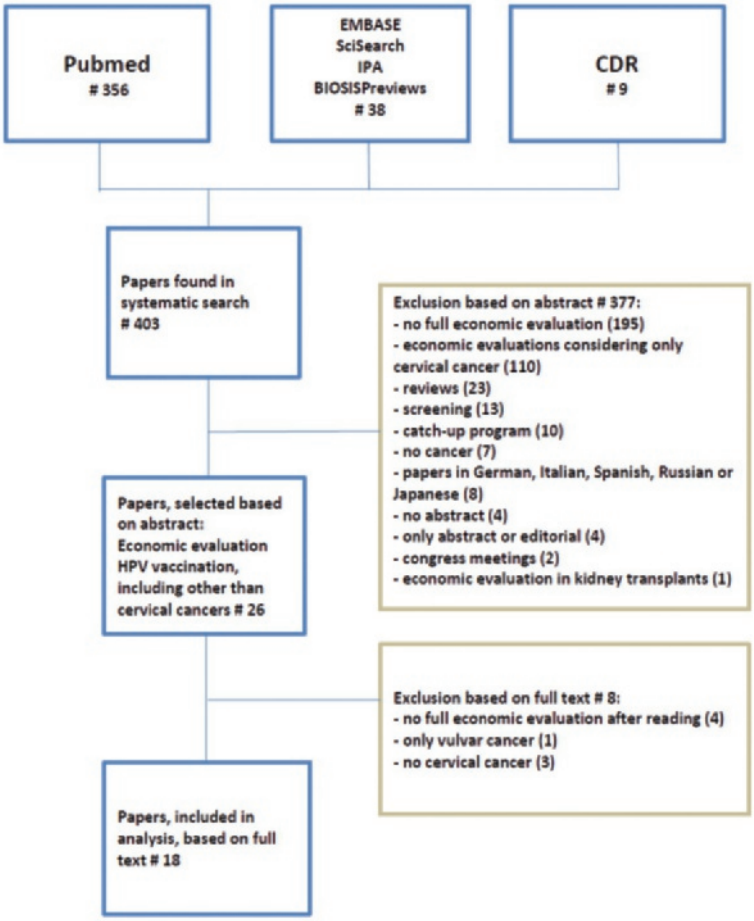


Figure 1. Flowchart HPV economic evaluations

General features

The included articles originate from the US (5), Canada (3), New Zealand (2), UK (3), Austria (1), Norway (1), Italy (1), Denmark (1), and the Netherlands (1). A summary of the general features is given in Table 1. One study used a Markov model without consideration of herd effects [27] and three other studies used a hybrid model, i.e. a Markov model including indirect effects of vaccination through a reduced force of infection over time [28-30]. The remaining studies used a dynamic transmission model. Fifteen studies used a time horizon longer than 70 years and two studies a horizon of respectively 55 and 62 years. Additionally in one paper, the time horizon was not described [29]. Thirteen studies choose a healthcare perspective to assess costs and benefits of the intervention. Five studies were conducted from a societal perspective [31-35]. However, in these studies the included range of additional cost categories was relatively small, considering additional transportation costs and patient time but ignoring other relevant societal costs, such as productivity losses. Only six economic evaluations included all currently recognized HPV-associated health outcomes (Table 1). Most frequently RRP was not taken into account (eleven times), followed by penile cancer (four times), vaginal cancer (twice), and genital warts (once).

To arrive at an expected health gain by preventing disease, health states need to be assigned a value reflecting severity of the state. Different methods were used to obtain these quality of life metrics (Table A2, appendix file). Blakely et al. and Pearson et al. both followed a disability adjusted life year (DALY) approach and used the same disability weights [28, 29]. In all other studies utility was defined as the quality adjusted life year (QALY) gain, with weights based on several sources resulting in small variability in values, especially with respect to penile, anal, and oropharyngeal cancer. In addition, QALY gains are determined by assumptions on survival rates of HPV-associated diseases. In case these were reported, mortality or survival rates varied widely between the studies (Table A3, Appendix file).

Table 1. General features and HPV-associated diseases of the studies included

Author	year of publication	Country	time horizon	Discount rate	RRP	Genital warts	Cervix cancer	Vulvar cancer	Vaginal cancer	Anal cancer	Penile cancer	Oropharynx cancer
Blakely [28]	2014	New Zealand	110 years	3%	-	+	+	+	-	+	-	+
Bresse [36]	2014	Austria	100 years	3%	-	+	+	+	+	+	+	+
Brisson [37]	2013	Canada	70 years	3%	-	+	+	+	+	+	+	+
Brisson [35]	2016	US	70 years	3%	-	+	+	+	+	+	+	+
Burger [31]	2014	Norway	lifetime	4%	+	+	+	+	+	+	+	+
Chesson [32]	2011	US	100 years	3%	+	+	+	+	+	+	+	+
Drolet [38]	2014	Canada	70 years	3%	-	+	+	+	+	+	+	+
Elbasha [39][b]	2010	US	100 years	3%	+	+	+	+	+	+	+	+
Haeussler[30][b]	2015	Italy	55 years	3%	-	+	+	+	+	+	+	+
Jit [40]	2008	UK	lifetime	3.5%	-	+	+	+	+	+	+	+
Jit [41]	2011	UK	100 years	3.5%	+	+	+	+	+	+	+	+
Jit [42]	2015	UK	100 years	3.5%	+	+	+	+	+	+	+	+
Kim [33][c]	2008	US	lifetime	3%	+	+	+	+	+	+	-	+
Kim [34][c]	2009	US	lifetime	3%	+	+	+	+	+	+	+	+
Laprise [43]	2014	Canada	70 years	3%	-	+	+	+	+	+	+	+
Luttjeboer [27]	2013	Netherlands	lifetime	4%; 1.5%[a]	-	-	+	+	+	+	-	+
Olsen [44][b]	2015	Denmark	62 years	3%	-	+	+	+	+	+	+	+
Pearson[29]	2014	New Zealand	not described	3%	-	+	+	+	-	+	-	+

*[a] 4% costs and 1.5% health gains, + =included, - =not included *RRP=Recurrent respiratory Papillomatosis, [b] Head/neck cancer instead of oropharyngeal cancer, [c] Also oral cancer*

Vaccination strategies

The vaccination strategies varied in the included economic evaluations (Table 2). In fifteen studies introduction of vaccination in girls was compared to no vaccination [27-29, 31-34, 37-44]. All countries had implemented a cervical cancer screening program, and this was incorporated in the comparator strategy, that is vaccination of girls was considered in addition to the existing screening program. In eight of these studies, a scenario of gender neutral vaccination was also compared with vaccination in girls alone [28, 29, 31, 34, 39, 40, 43, 44]. Bresse et al. assessed the cost-effectiveness of gender neutral vaccination compared to no vaccination only [36], whereas Pearson performed an economic evaluation of three strategies: girls versus no vaccination, gender neutral versus no vaccination, and gender neutral vaccination versus vaccination of girls only [29]. The 2016 paper by Brisson et al. assessed whether the nonavalent vaccine among girls only or boys and girls was more cost-effective than gender neutral vaccination with the quadrivalent vaccine or with vaccination of girls only [35]. Not all studies reported the setting, but this appeared to be community based vaccination in three studies [27, 36, 43], school based vaccination in four studies [31, 37, 40, 41] and a combination of school based and primary care vaccination program in two other studies [28, 29]. All studies used a three-dose schedule, except the studies by Laprise et al. and by Jit et al. that used a two-dose schedule [42, 43].

Table 2. Vaccination scenarios and setting

Author	Scenario		Setting
	Intervention	Comparator	
Blakely [28]	Girls (3D)	No vaccination	Mix between school based and primary care vaccination program
Bresse [36]	Gender neutral (3D)	No vaccination	Population-based
Brisson [37]	Girls (3D)	No vaccination	School based
Brisson [35]	1. Gender neutral (4HPV; 3D)	1 vs no vaccination	
	2. Girls only (9HPV; 3D)	2 vs 1, 3 vs 2 3 vs 1	
	3. Gender neutral (9HPV; 3D)		
Burger [31]	Gender neutral (3D)	No vaccination or	School based (7th grade)
		girls only (3D)	
Chessson [32]	1. Girls only	1. No vaccination	
	2. Gender neutral	2. Girls only	
	3. Gender neutral	3. Increased coverage among girls	
Drolet [38]	Girls (3D)	No vaccination	
Elbasha [39]	Gender neutral (3D)	Girls only (3D)	
Haeussler [30]	Gender neutral (3D)	No vaccination or	
		girls only (3D)	
Jit [40]	1. Girls only (3D)	No vaccination	School based
	2. Gender neutral (3D)		
Jit [41]	Girls only (3D)	No vaccination	School based
Jit [42]	1. Girls only (2D)	1. No vaccination	
	2. Girls only (3D)	2. Girls only (2D)	
Kim [33]	Girls only (3D)	No vaccination	
Kim [34]	1. Girls only (3D)	No vaccination	
	2. Gender neutral (3D)		
Laprise [43]	1. Girls only (2D)	1. No vaccination	Population based
	2. Girls only (3D)	2. Girls only (2D)	
	3. Gender neutral (2D)	3. Girls only (2D)	
	4. Gender neutral (3D)	4. Girls only (3D) or	
		gender neutral (2D)	
Luttjeboer [27]	Girls only (3D)	No vaccination	Population based
Olsen [44]	1. Girls only (3D)	1. No vaccination	
	2. Gender neutral (3D)	2. Girls only (3D)	
Pearson [29]	1. Girls only (3D)	All interventions compared to no vaccination. Further 2 vs 1, 3 vs 1, 4 vs 2 and 4 vs 3	Mix between school based and primary care vaccination program
	2. Girls only (school based) (3D)		
	3. Gender neutral (3D)		
	4. Gender neutral (school based) (3D)		

HPV-associated diseases incidence

In fourteen studies, cancer incidences were based on cancer/statistical registries or previous publications [27-34, 36, 39-42, 44] (Table A4, appendix). Six of these studies reported that the estimates were based on these sources, although the exact estimates were not shown in the publication [27-30, 40, 41]. Five out of six papers in which incidences were mentioned used different incidences for HPV-associated cancers occurring both in females and males. Assumed incidences varied widely, for example for cervical cancer between 4.2 and 62.8 per 100.000 women and for genital warts between 7 and 620 cases per 100.000 individuals. Finally, five studies used the HPV-ADVISE model for determining cancer incidence, which uses several sources to obtain parameter sets [35, 37, 38, 42, 43] (Table A4, appendix).The HPV-ADVISE is a transmission dynamic model based on Canadian data.

Vaccine characteristics

As shown in table 3, seventeen of the included studies [28-44] investigated the quadrivalent vaccine (of which six studies compared the quadrivalent with the bivalent vaccine [33, 34, 36, 40-42] and two studies compared the quadrivalent vaccine with the nonavalent vaccine [35, 38]), whereas only one study focused on the bivalent vaccine alone [27]. The studies varied largely with regard to assumed vaccine uptake (ranging from 20% up to 100%) and in the assumed duration of protection (ranging from 10 years until lifelong). All but one study assumed a prophylactic efficacy against HPV infection in females above 95%, whereas the efficacy in men was assumed to be lower (range 41%-90%). Nine studies assumed cross-protection in their model, and one additional study explored the influence of cross-protection in a scenario analysis. Vaccine prices varied between €63 and €146 per dose.

Table 3. Vaccine characteristics in the base case

Author	Vaccine type	Uptake in regular program	Duration of protection[b]	Vaccine efficacy	Cross-protection	Vaccine price per dose
Blakely [28]	Quadrivalent	Maori: 56%, Non-Maori: 45%	20 years	99%	Not described	€67, Adm. €75-€84
Bresse [36]	Quadrivalent	65%	Lifelong	♀ CIN: 97.9% - 100%, GW: 98.9% - 100% ♂ GW: 84.3% - 90.9%	No	€124,- incl. adm. costs
Brisson [37]	Bivalent & Quadrivalent	80%	20 years	95%	Yes	€72,- incl. adm. fees
Brisson [35]	Quadrivalent & Nonavalent	Males 62% Females 38%	Lifelong	85%	Yes	qHPV € 134,-
Burger [31]	Quadrivalent	71%	Lifelong	♀ 100%, ♂ 90%	No	€69, adm. costs € 13
Chesson [32]	Quadrivalent	20%, 30%, and 75%	Lifelong	♀ 95%, ♂ 90%	Not described	€467, fully vaccinated
Drolet [38]	Quadrivalent & Nonavalent	20%	20 years	95%	Yes	€72,- (incl. adm. fees)
Elbasha [34]	Quadrivalent	Females: 80%, Males 48%	32 years	♀ 76-96%, ♂ 41-62%	No	€124 (€374 for all doses)
Haessler [30]	Quadrivalent	90,48%	Lifelong	cervix, 78% anal 70% head/neck 50%	No	mean €63,- adm. costs €8,-
Jit [40]	Bivalent & Quadrivalent	80%	20 years	100%	Yes	€91- €122
Jit [41]	Bivalent & Quadrivalent	100%	20 years – lifelong	100%	Yes	qHPV €125, bHPV €114, adm. costs €13
Jit [42]	Bivalent & Quadrivalent	80%	3D lifelong 2D 10/20/30 years	100%	Yes	bHPV €100, qHPV €107 adm. fee €12
Kim [33]	Bivalent & Quadrivalent	75%	Lifelong	100%	Yes	€121
Kim [34]	Bivalent & Quadrivalent	75%	Lifelong ♂ 90%	♀ 100%	Yes	€121

Laprise [43]	Quadrivalent [a]	80%	10 years – lifelong	95%	Yes	€64
Lutjeboer [27]	Bivalent	80%	Lifelong	100%	In scenario analysis	€131
Olsen [44]	Quadrivalent	85%	Lifelong	100%	No	€137,- per dose, total €463,-
Pearson [29]	Quadrivalent	Maori: 56%, Non-Maori: 45%	20 years	99%	No	€67, adm. €75-€84

[a] Not described, since anogenital warts are included we assumed quadrivalent vaccine [b] Vaccine types (no cross-protection), adm. = administration

Incremental cost-effectiveness ratios

As hypothesized, the ICERs of analyses including more recognized HPV-associated diseases were substantially lower compared to analyses that only included cervix carcinoma. In the study by Bresse et al. comparing gender neutral vaccination to no vaccination, the ICER decreased a factor 2.7 from €27,493 to €10,331 per QALY gained when taking only cervical cancer, respectively, all HPV-associated diseases into account [36]. While including all HPV-associated diseases Brisson et al. found that a gender neutral vaccination strategy with the nonavalent vaccine compared to the quadrivalent vaccine was cost-saving [35]. A gender neutral nonavalent vaccination program compared to the nonavalent vaccine for girls and the quadrivalent vaccine for boys resulted in an ICER of €129,814 per QALY gained.

In studies examining cost-effectiveness of girls only vaccination compared to no vaccination, the ICER varied between €10,406 and €40,570 per QALY gained (or DALY averted) if only cervical carcinoma was taken into account with a mean of €24,080 (Table 4). The ICERs reported in the studies that included all currently recognized HPV-associated diseases varied between €3,006 and €35,277 per QALY gained (or DALY averted) with a mean of €15,216 (Figure 2). Seven studies reported both an ICER for cervix carcinoma alone and an ICER for cervix carcinoma with other HPV-associated diseases. The ICERs including also other diseases were a mean factor 2.85 (95%CI 1.35-4.36) lower than ICERs including only cervix carcinoma (Figure 3). Comparing the cost-effectiveness of gender neutral versus girls only vaccination resulted in a mean ICER of €180,823 studying only cervix carcinoma, with the ICERs ranging between €113,778 and €292,159 per QALY gained (or DALY averted) (Figure 2). For studies that also had included other HPV-associated diseases, the ICERs varied between €13,700 and €261,866, with a mean of €95,444 per QALY gained (or DALY averted). Four studies reported both an ICER for cervix carcinoma alone and an ICER for cervix carcinoma with other HPV-associated diseases when studying gender neutral vaccination in contrast to girls only vaccination. The ICERs of scenario's including also other diseases besides cervix carcinoma were a mean factor 3.89 times lower (95%CI -0.10-7.85), than in scenarios where only cervix carcinoma was included (Figure 3).

In sensitivity and scenario analyses presented in the papers it was explored that variation in duration of protection, discount rate and vaccine cost had the highest impact on the ICER (Table 4).

Table 4. HPV-associated diseases included, ICERs and uncertainty

Author	ICER in €/QALY per vaccination strategy						Most influential variables on results (ICERs) based on uncertainty and scenario analysis
	Girls vs. no vaccination			Gender neutral vs. girls vaccination			
	Only cervix carcinoma	All HPV-associated diseases	Factor	Only cervix carcinoma	All HPV-associated diseases	Factor	
Blakely [28]		€11,135-€18,361[a]					Vaccine costs, future cervical cancer incidence, disability weights, assumptions on herd immunity
Brisson [37]	€25,258 qHPV €22,831 bHPV	€11,778 qHPV €15,308 bHPV	2.26 qHPV 1.49 bHPV				Excluding warts, discount rate, time-horizon, burden of cancer, duration of protection and the disease endpoint considered.
Burger [31]	€19,074	€4,630	4.12	€134,721	€55,648	2.42	Vaccine costs and discount rate
Chesson [32]	€19,915	€6,732	2.96	€113,788	€38,708	2.93	Vaccine costs, vaccination coverage, health outcomes included, QALYs lost per health outcome, male vaccine efficacy, incidence rates of health outcomes
Drolet [38]		qHPV €11,778 nHPV €9,256					Vaccine costs, duration of protection, and effectiveness
Elbasha [39]	€ 20,675	€3,069	6.74	€182,623	€23,995	7.61	Vaccine costs, vaccination coverage, HPV disease included, duration of protection, treatment costs, efficacy of two doses.
Haeussler [30]					€13,700		Vaccine costs, duration of protection, discount rate, time horizon, HPV-diseases, vaccine efficacy, cross-protection, sexual activity, frequency of cervical screening
Jit [40]		€34,040			€261,866		Vaccine costs, duration of protection, discount rate and natural immunity
Jit [41]		€16,933-€26,811 qHPV €22,577-€35,277 bHPV					Vaccine costs, duration of protection, discount rate and natural immunity
Jit [42]		€3006 qHPV[dp20b] €6372 bHPV[dp20b]					Discount rate, duration of protection

Kim [33]	€ 33,917	€21,135	1.64				Duration of protection, HPV associated diseases included, booster vaccination, cross-protection.
Kim [34]	€ 40,570	€21,125	1.92	€292,159	€115,247	2.54	Vaccine costs, vaccination coverage, duration of protection, HPV-associated diseases, vaccine efficacy, combination with screening
Laprise [43]		€5,992[dp30]-€7,888[dp20b]			€65,392[dp30]-€102,737[dp20b]		Vaccine costs and duration of protection
Luttjeboer [27]	€ 10,406	€6,338	1.64				Vaccine costs, discount rate, cost of cancer, cross-protection.
Olsen [44]		€3975 Dominance[b]			€46,216 €31,114[b]		Vaccine costs, discount rate, costs of cancer, HPV-associated diseases, horizon, vaccination rate, and application of a 2-dose regime
Pearson[29]		€11,135			€69,890		Vaccine costs and vaccination coverage
Mean	**€ 24,080**	**€ 15,216**		€ 180,823	€ 95,444		

[a] Depending on the intensity of the program, [b] for two doses, qHPV=quadrivalent vaccine, bHPV=bivalent vaccine, nHPV=nonavalent vaccine, CS= cost-saving, dp20=assuming duration of protection is 20 years for two doses, dp30= assuming duration of protection is 30 years for two doses

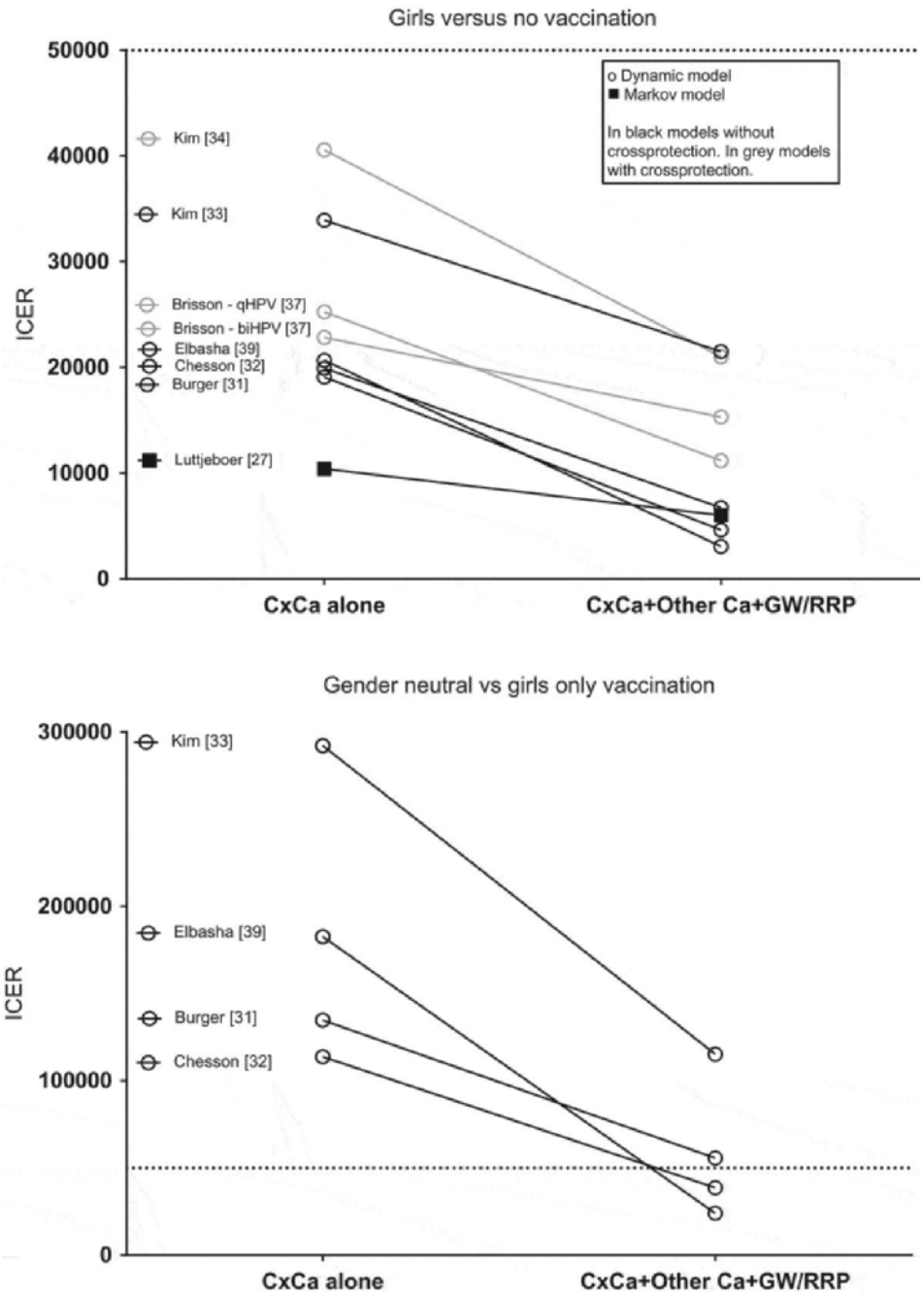


Figure 2. ICER in €/QALY when only cervical cancer or additional HPV-associated diseases are taken into account comparing different strategies.

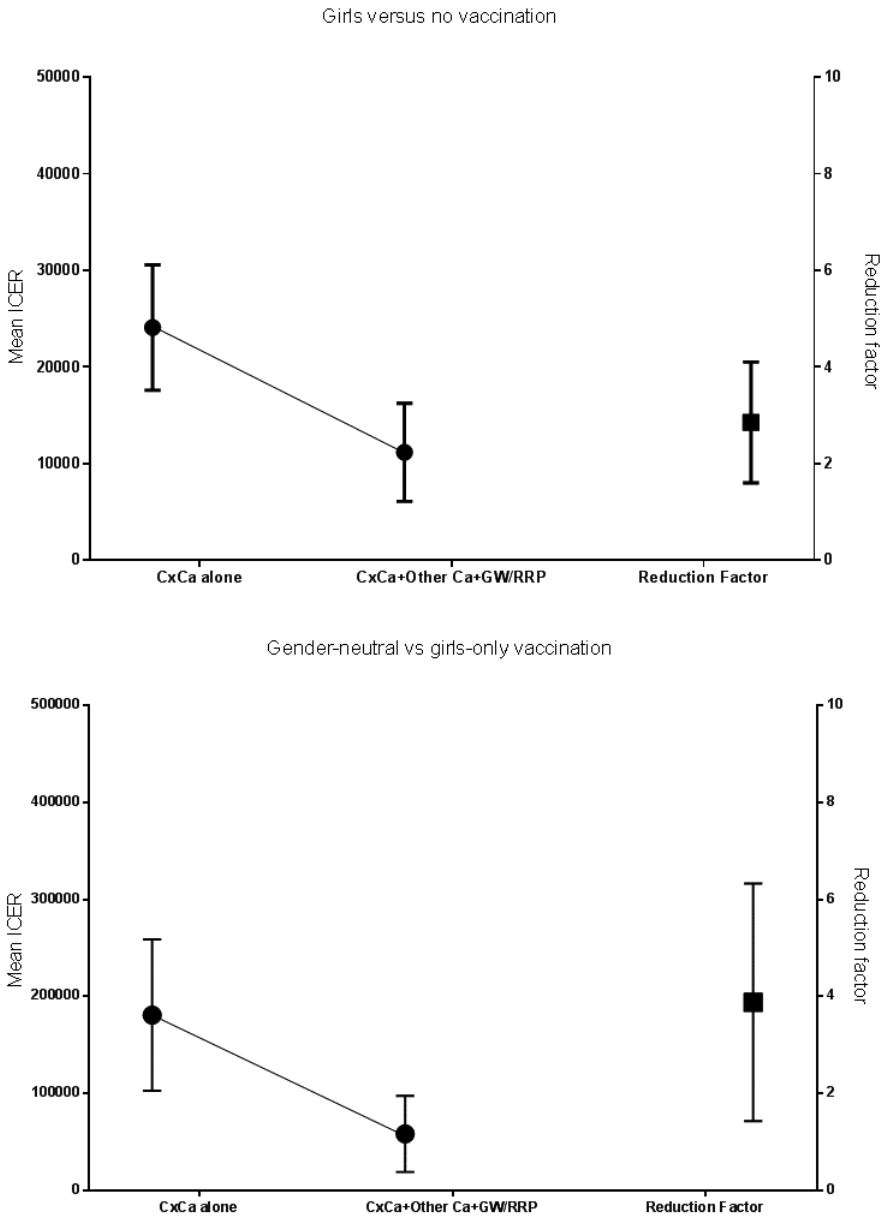


Figure 3. Mean ICERs (±1.96*se) for scenarios using only cervical cancer compared to all HPV-associated diseases and the corresponding mean of the factors.

Expert commentary

The inclusion of all HPV-associated cancers in an economic evaluation resulted in substantially more favorable cost-effectiveness estimates than evaluations where only cervical cancer was taken into account. Interestingly, anal, vaginal, vulvar and oropharyngeal cancers all do occur many years later than cervical cancer, and their prevention will typically yield less QALYs than the prevention of a case of cervical cancer, especially after discounting of future health benefits in vaccination programs. Even so, scenarios that considered the effect of vaccination on non-cervical disease outcomes showed substantially more favorable ICERs than those that only considered the effect on cervix carcinoma. The mean ICER of a girls only vaccination program (compared to no vaccination) was €15,216 per QALY gained (or DALY averted) when all HPV-associated diseases were taken into account and €24,080 when only cervical cancer was considered. The ICERs of vaccination strategies considering vaccination of boys and girls versus girls only deviated even more: €95,444 per QALY gained (or DALY averted) when all HPV-associated diseases were taken into account versus €80,823 when only cervical cancer was included. For some countries, inclusion of all HPV-associated diseases could result in an ICER which is considered cost-effective (i.e. lies below the threshold used for cost-effective interventions) when boys' vaccination is valued conditional on girls' vaccination. Hence, acknowledging the total vaccine-preventable burden of HPV-related diseases could widen the opportunities for gender neutral vaccination, as this could increase the likelihood of gender neutral vaccination to become acceptable according to current standards to determine cost-effectiveness.

In recent reviews, most studies included were only targeted at cervical cancer [22, 45]. In 2012, Seto et al published a comprehensive systematic review of 29 HPV vaccine studies [20]. Seventeen of the included articles considered only cervical disease outcomes, and 12 studies also included non-cervical disease outcomes. Similar to our results, studies that focused on female-only vaccination programs in general proved to be cost-effective compared with inclusion of cervical cancer screening alone. However, Seto et al. found that the addition of boys to preadolescent vaccination programs exceeded accepted thresholds for cost-effective interventions, even if all recognized HPV-associated cancer outcomes were included. These findings are largely influenced by the economic evaluation of Kim and Goldie [34], whereas we included more recent studies with more economically favorable outcomes. As described in our results, six of the 18 studies included all currently known HPV-associated diseases, whereas eleven studies considered most but not all presently known HPV-associated diseases. In addition, eight out of 18 studies did not report the incorporation of cross-

protection in the model. The inclusion of a larger number of diseases and cross-protection will result in a more favorable cost-effectiveness profile of vaccination, as there will be more vaccine preventable diseases included in the analysis [27, 33, 34, 39].

Many studies included in this review report a lack of available national cancer data regarding incidence, costs and utilities. The reason for variability in utilities for example stems from the difficulty of assigning the values and the different methods to arrive at these values [46]. Moreover, in general the assumption is made that the incidence of HPV-associated cancers will be constant over time. For oropharyngeal, penile and anal cancer the incidence seems to increase [47-49], and also the proportion of oropharyngeal cancers attributed to HPV appears to increase. In the economic evaluations however, the assumptions are made that HPV vaccination affects a constant proportion of these cancers. Additionally, the etiological fraction assumed among these cancers could vary largely between countries and influences the assumed effectiveness of the vaccine. Also the impact of HPV vaccination may vary widely between the different diseases and is determined based on prevalence, utilities and survival (to determine the number of gained QALYs by vaccination) and the costs of illness being combined in the cost-effectiveness model, resulting in one ICER.

Elbasha et al. demonstrated a greater effect of including all HPV-associated diseases compared to the other economic evaluations [39]. This is probably due to the construction of the model in which HPV-associated cancers happen earlier in life, resulting in more QALYs gained and a more favorable ICER after introduction of a vaccination program. It should also be noted that Elbasha assumed a vaccine protection of 32 years whereas the other studies assumed lifelong protection from vaccination. We compared the mean and median reduction factors for the ICERs including non-cervical disease outcomes or not, which were not very different, suggesting that the results of this particular study had only limited impact on the overall conclusions. In only two of the studies transmission of HPV among men having sex with men (MSM) was explicitly reported [27, 43]. In nine other studies vaccination was targeted at boys. In only two studies, cost-effectiveness of the nonavalent vaccine was assessed. Given the recent licensure of the nonavalent vaccine, less data is available in comparison to the bivalent and quadrivalent vaccine, that is regarding the duration of protection. Not all costing data was included in the analysis: for example, none of the economic evaluations included productivity losses. Finally, in all studies future changes in existing screening programs were not taken into account. For example, the implementation of HPV-testing as a primary screening tool instead

of cytology, might lead to a different cost estimation than compared to the existing screening program, as other patterns of referral might occur. Besides, the number of detected carcinomas might differ using different screening programs [50].
Among included studies, the efficacy of the vaccine between genders varied widely. While for women in most cases an efficacy above 95% was reported, for men no efficacy higher than 90% was included with a minimum of only 41%. Clinical trials have shown remarkable differences in efficacy among males, depending on the population studied [51, 52]. Assuming that vaccination occurs in most countries before onset of sexual activity, the higher efficacy from the per-protocol population might be the most representative. Using a lower efficacy might result in a higher ICER and is therefore less likely to support cost-effective implementation of boys' vaccination [53].

This review quantifies the impact of inclusion of non-cervical cancers on the cost-effectiveness of preadolescent HPV vaccination. A Dutch study suggested that a decrease in cost-effectiveness ratio (CER) of 10% to 31% after addition of non-cervical cancers could be expected from inclusion of non-cervical HPV-positive cancers [54]. However, this was neither an explicit modelling study nor a full economic evaluation and several simplifications may have led to a biased estimate. First, it only considered the prevention of cancer deaths, not cancer incidences. Second, it only considered the mean age at cancer death, not its age distribution. Hence, in a discounted analysis, the importance of preventing early cancers is lost entirely. Third, it did not include indirect benefits that arise through herd immunity nor cross-protection to non-vaccine types. Fourth, it used a discount rate of 1.5% per year, as commonly used in the Netherlands, whereas 3% discount rates are the international norm. Finally, the HPV-attributable fraction of oropharyngeal cancers was set at 11%, which is much lower than currently assumed.

In this review, the search was restricted to the English language therefore neglecting eight papers in other languages. However, based on the English abstracts, those papers did not seem to include other HPV-associated diseases than cervical cancer. The vaccine prices used in the included papers are remarkably higher than the actual prices achieved in several vaccination programs [31]. Therefore, the cost-effectiveness at present of including all HPV-associated diseases might even be more favorable than discussed in published papers. We did not adjust for the kind of included HPV-associated diseases, when computing the mean ICERs. This might influence the reduction factor, as not every study included the same number and type of HPV-associated diseases. Also, most of the included studies considered a three-dose schedule, while more recently the two-dose schedule has been licensed in several countries [55]. Moreover, it has also been suggested that even one dose might

be enough to reach the same protection against infection [56, 57]. Finally, possibly not all HPV-associated health outcomes are considered in economic evaluations. Some cancers are currently classified as having a possible link with HPV, for example cancer of the oral cavity [58, 59]. As this cancer occurs frequently, even a small proportion that could be due to HPV would already lead to many cases that could be prevented by vaccination. In this review, three studies considered head/neck cancer instead of oropharyngeal cancer, [30, 39, 44] whereas Kim et al. included oral cancer besides oropharyngeal cancer [33, 34]. Additionally for other cancers known to be related to HPV, such as oropharyngeal cancer, estimating vaccine efficacy is difficult due to absence of intermediate endpoints; this might influence the ICER as the efficacy might be in fact higher or lower than what is currently assumed [60]. This also means that effects are assumed in this review for some diseases against which the vaccines are not (yet) licensed, for example oropharyngeal and penile cancer. Finally, Foresta et al. suggested that HPV vaccination in men is effective in decreasing average clearance time in patients featured by HPV semen infection [61]. This evidence may be promising for patients with a long-lasting HPV semen infection, especially for those infertile patients eligible for medical reproduction techniques. Including all these aspects in future cost-effectiveness studies could further improve the ICER.

Five-year view

Future cost-effectiveness analyses, both for implementation of new vaccination programs or adjustments of existing vaccination programs, should consider the overall benefits of HPV vaccination, that is, regarding recognized HPV-associated diseases. Evidence of the efficacy of the HPV-vaccines against other HPV-associated cancers than cervix, such as anal and vaginal carcinoma, has increased over the past years. With regard to the already existing vaccination programs targeting girls only, our results imply that the cost-effectiveness might be considerably more favorable than estimated at the time of introduction of the HPV-vaccine, when most analyses incorporated only benefits related to cervical cancer incidence.

More importantly, considering the impact of vaccination on known HPV-associated diseases could support policymakers to broaden the target group of HPV-vaccination to males; especially when taking account of the reduced vaccine prices and dosing strategies, as well as the advent of HPV vaccines providing broader protection, even beyond the nonavalent vaccine [35, 38, 62, 63]. In addition, specific programs for groups at increased risk, for example, MSM, could be considered since HPV vaccination of girls will not significantly affect the burden of anal cancer in men, which is above all existent in MSM [64-66]. Further studies on immunogenicity and effectiveness of HPV vaccination in general should enable better assumptions on for example duration

of protection and long-term efficacy. Additional information on utilities, survival and etiological fractions of non-cervical cancers is more sparse than data on cervical cancer itself, and further research might help to unravel the overall cost-effectiveness profile of HPV vaccination.

Key issues

- Human papillomavirus (HPV) is associated with the development of cervical, vaginal, vulvar, penile, anal, and oropharyngeal cancers as well as genital warts and recurrent respiratory papillomatosis
- Currently three vaccines (bivalent, quadrivalent and nonavalent) are available that protect individuals against HPV-associated diseases
- Earlier systematic reviews concerning the cost-effectiveness of gender neutral vaccination also include economic evaluations targeted at the effects on cervical cancer and genital warts in girls only.
- In this review 18 full economic evaluations including other cancers than only cervical cancer could be identified
- The incremental cost-effectiveness ratios (ICERs) of analyses including all currently recognized HPV-associated diseases were substantially lower compared to analyses that only included cervix carcinoma
- The mean ICER in a girls only vaccination program versus no vaccination is €15,216 / quality adjusted life year (QALY) including all HPV-associated diseases and €24,080 / QALY considering only cervical cancer
- The mean ICER in a gender neutral vaccination program versus a girls only vaccination is €95,444 / QALY including all HPV-associated diseases and €180,823 / QALY considering only cervical cancer
- Within-study comparisons demonstrated that the mean ICERs were 2.85 times more favorable (95%CI 1.35-4.36) for girls only vs. no vaccination, and 3.89 times (95% CI -0.10-7.85) for gender neutral vs. girl-only vaccination
- Considering the impact of vaccination on all known HPV-associated diseases could support policymakers to broaden the target group of HPV-vaccination to males
- Future research on impact on the health-related quality of life, survival and etiological fractions of non-cervical cancers might help to gain insight in the cost-effectiveness profile of HPV vaccination.

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APPENDIX FILES

Table A1. Search strategy

Search	Query
#12	Search #10 NOT #11
#11	Search letter[pt] OR news[pt] OR (comment[pt] NOT editorial[pt]
#10	Search #8 NOT #9
#9	Search ((testing[ti] OR screening[ti]) NOT (vaccin*[ti] OR immunisat*[ti] OR immunizat*[ti] OR vaccination[majr]))
#8	Search #5 AND (#6 OR #7)
#7	Search (papillomavir*[ti] OR hpv*[ti] OR cervical[ti] OR cervix[ti]) AND (vaccin*[tiab] OR immunisat*[tiab] OR immunizat*[tiab] OR vaccines[mh] OR vaccination[mh] OR immunization[mh:noexp])
#6	Search papillomavirus vaccines[mh] OR ((alphapapillomavirus[mh] OR papillomavirus infections[mh]) AND (vaccines[mh] OR vaccination[mh] OR immunization[mh:noexp]))
#5	Search #1 OR #2 OR #3 OR #4
#4	Search (cost-effectiveness[tiab] OR cost-benefit[tiab] OR cost-utility[tiab] OR cost-beneficial[tiab] OR cost-effect*[tiab] OR cost-efficiency[tiab]) AND (value[ti] OR valuing[ti] OR impact[ti] OR evaluat*[ti] OR benefit*[ti])
#3	Search (economic evaluation*[tiab] OR economical evaluation*[tiab] or economic study[tiab] OR economic studies[tiab])
#2	Search (cost*[ti] AND (effect*[ti] OR benefit*[ti] OR beneficial[ti] OR quality[ti] OR efficien*[ti] OR efficac*[ti])) OR (cost*[ti] AND economics[majr]) OR "value-for-money"[ti]
#1	Search "cost-benefit analysis"[mh] OR cost benefit*[ti] OR cost beneficial*[ti] OR cost effect*[ti] OR cost utilit*[ti] OR cost efficien*[ti] OR cost efficac*[ti] OR econom*[ti] OR pharmacoeconomic*[ti] OR pharmaco-economic*[ti]

Table A2. Quality of life parameter values

Author	Methodology*	RRP	Genital warts	Cervix cancer	Vulvar cancer	Vaginal cancer	Anal cancer	Penile cancer	Oropharyngeal cancer
Blakely [28]	Disability weights	-	0.03	0.288 (DT) 0.487 (PT) 0.495 (T) w	0.295 (DT) 0.487 (PT) 0.495 (T) 0.161 (R)	-	0.295 (DT) 0.487 (PT) 0.495 (T) 0.161 (R)	-	0.375 (DT) 0.584 (PT) 0.94 (T) 0.248 (R)
Pearson [29]	Disability weights	-	0.03	0.288 (DT) 0.487 (PT) 0.495 (T) 0.134 (R)	0.295 (DT) 0.487 (PT) 0.495 (T) 0.161 (R)	-	0.288 (DT) 0.487 (PT) 0.495 (T) 0.134 (R)	-	0.375 (DT) 0.584 (PT) 0.94 (T) 0.248 (R)
Bresse [36]	Utility weights	-	0.91	Stage 1: 0.76 2-3: 0.67 4: 0.48	Stage 1: 0.65/0.59 2-3: 0.65/0.59 4: 0.48	Stage 1: 0.65/0.59 2-3: 0.65/0.59 4: 0.48	Stage 1: 0.57 2-3: 0.57 4: 0.48	Stage 1: 0.79 2-3: 0.67 4: 0.48	Stage 1: 0.76 2-3: 0.58 4: 0.48
Brisson [37]	Utility weights	-	0.98	Stage 1: 0.70 2-3: 0.70 4: 0.52	0.68	0.68	0.49	0.71	0.75
Brisson [35]	Utility weights	-	0.98	Stage 1: 0.72 2-3: 0.61 4: 0.55	0.68	0.68	0.49	0.71	0.75
Burger [31]	Utility weights	0.69	0.93	0.48-0.76	0.65	0.59	0.57	0.79	0.58
Elbasha [39]**	Utility weights	0.80	0.91	Local: 0.76 Reg: 0.67 Dist: 0.48	0.64	0.64	0.64	0.64	0.64
Drolet [38]	Utility weights	-	0.98	Stage 1: 0.70 2-3: 0.70 4: 0.62	0.68	0.68	0.49	0.71	0.75
Haeussler [30]**	Utility weights	-	0.6961	0.5769 (FIGO 1)	NR	NR	males: 0.664, females: 0.7275	0.7922	males: 0.81, females: 0.7413
Jit [40]	Utility weights	-	0.971	Year of treatment: 0.48-0.65 Year of post-treatment: 0.62-0.90	Same as cervical cancer	Same as cervical cancer	Same as cervical cancer	Same as cervical cancer	Same as cervical cancer
Jit [41]	Utility weights	1.3*	0.982	0.67-0.76	0.68	0.68	0.49	0.71	0.75
Jit [42]	Utility weights	1.3*	0.982	0.715	0.68	0.68	0.49	0.71	0.75
Kim [33]	Utility weights	0.69	0.91	0.48-0.76	0.68	0.68	0.68	-	0.68
Kim [34]	Utility weights	0.69	0.91	0.48-0.76	0.68	0.68	0.68	0.68	0.68

Laprise [43]	Utility weights	-	0.98	Stage 1: 0.70 2-3: 0.70 4: 0.62	0.68	0.68	0.49	0.71	0.75	
Luttjeboer [27]	Utility weights	-	-	0.71-0.92	0.76-0.92	0.72-0.96	0.75-0.92	-	0.65-0.90	
Olsen [44]**	Utility weights	-	0.91	0.76-0.67	0.76-0.67	0.76-0.67	0.76-0.67	0.76-0.67	0.76-0.67	
Chesson [32]	QALYs lost per case	1.05	0.025	3.95	3.28	4.59	3.05	2.78	5.16	

*-=not included, *=QALY loss per episode, NR=not reported, DT= diagnosis and treatment, PT= pre-terminal, T=terminal, R=remission, spreading cancer cells stage Stage 1: not outside the uterus, stage 2: beyond the cervix and uterus, stage 3: to lower part of the vagina or walls of the pelvis, stage 4: to the bladder, rectum or outside the pelvis*

*Note that disability weights and utility weights use a different scale: for disability weights 0 reflects no disability and 1 reflects most serious disease, while for utility weights this is reverse, with 1 reflecting full health and 0 reflecting death. ** Olsen et al, Elbasha et al, and Haeussler et al considered head/neck cancer instead of oropharyngeal cancer*

Table A3. Case fatality ratios or survival rates

Author	Methodology	Cervix cancer	Vulvar cancer	Vaginal cancer	Anal cancer	Penile cancer	Oropharyngeal cancer
Blakely [28]	EMR*	Same as all cancer	0.77	-	0.81	-	Same as all cancer
Pearson [29]	EMR*	Same as all cancer	0.77	-	0.81	-	Same as all cancer
Bresse [36]	NR						
Brisson [37]	Case fatality rate**	Stage 1: 0.08 2-3: 0.44 4: 0.83	0.38	0.38	0.19	0.21	0.24
Brisson [35]	Case fatality rate**	Stage 1: 0.72 2-3: 0.09 4: 0.42	0.33	0.33	0.31	0.32	0.39
Burger [31]	5-year survival	0.20-0.91	0.73	0.49	0.70	0.81	0.58
Chesson [32]	5-year survival	Local: 0.41-0.94 Reg: 0.46-0.60 Dist: 0.13-0.20	Local: 0.59-0.96 Reg: 0.36-0.80 Dist: 0.05-0.39	Local: 0.38-0.80 Reg: 0.38-0.64 Dist: 0.25-0.53	Local: 0.56-0.87 Reg: 0.33-0.74 Dist: 0.09-0.30	Local: 0.61-0.79 Reg: 0.35-0.51 Dist: Dist: 0.05-0.16	Local: 0.11-0.82 Reg: 0.70-0.75 Dist: 0.13-0.33
Drolet [38]	Case fatality rate	Stage 1: 0.08 2-3: 0.44 4: 0.83	0.38	0.38	0.19	0.21	0.24
Elbasha [39]****	Mortality rate per year	Local: 0.006-0.12 Reg: 0.9-0.29 Dist: 0.41-0.70	Local: 0-0.05 Reg: 0.05-0.36 Dist: 0.60	Local: 0.006-0.12 Reg: 0.9-0.30 Dist: 0.42	Local: 0.6-0.10 Reg: 0.14-0.18 Dist: 0.33-0.59	Local: 0.06-0.10 Reg: 0.14-0.18 Dist: 0.33-0.58	Local: 0.82-0.84*** Reg: 0.51-0.56 Dist: 0.31-0.34
Haeussler [30]****	1-year survival	0.98 (stage 1)	0.78 (stage 1)	0.95 (stage 1)	0.98 (stage 1,2)	0.83 (stage 1)	0.98 (stage 1)
Jit [40]	NR						
Jit [41]	NR						
Jit [42]	NR						
Kim [33]	5-year survival	0.17-0.92	0.78	0.56	0.66	-	0.63
Kim [34]	5-year survival	0.17-0.92	0.78	0.56	0.66	-	0.63
Laprise [43]	Case fatality rate	Stage 1: 0.08 2-3: 0.44 4: 0.83	0.38	0.38	0.24	0.21	0.25
Luttjeboer [27]	NR						
Olsen [44]****	NR						

*NR=not reported, *EMR=excess mortality rate, **100%- 5-year survival, *** 5-year survival, **** Olsen et al, Elbasha et al, and Haeussler et al considered head/neck cancer instead of oropharyngeal cancer*

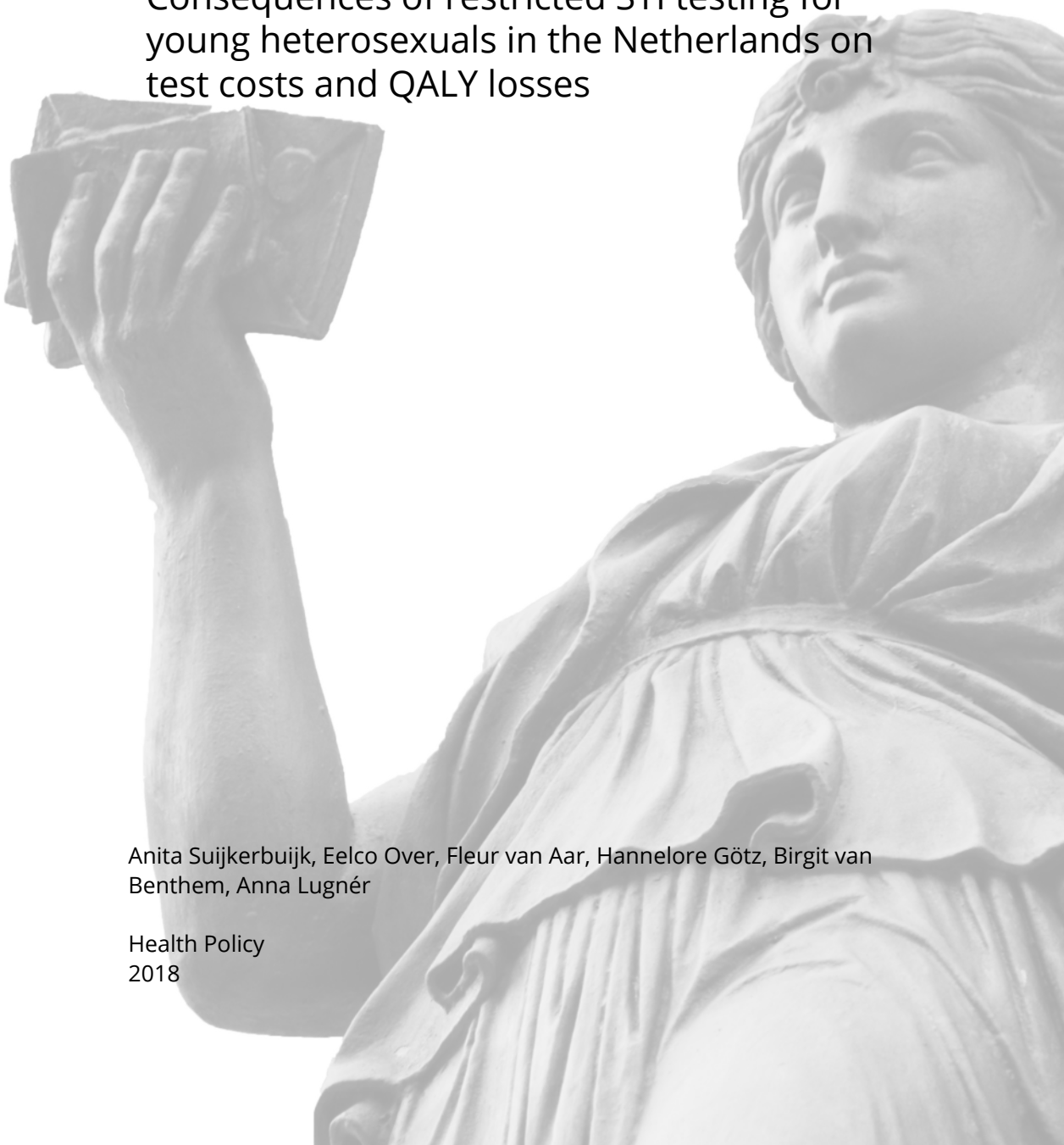
Table A4. Sources and figures of cancer incidences

Author	Sources cancer incidence	Cancer incidences					
		Cervical cancer	Vulvar cancer	Vaginal cancer	Anal cancer	Penile cancer	Oropharynx cancer
Blakely [28]	Previous publications/ New Zealand Cancer Registry Data	*	*	Excluded; small burden	*	Excluded; small burden	*
Bresse [36]**	Previous publications (Hartig et al.)	♀ 380 (100)	♀ 37 (70)	♀ 147 (40.4)	♀ 80 (85) ♂ 34 (85)	♂ 58 (46.7)	♀ 68 (39.7) ♂ 329 (39.7)
Brisson [37]	HPV-advise	*	*	*	*	*	*
Brisson [35]	HPV-advise	*	*	*	*	*	*
Burger [31]	Norwegian Cancer Registry	♀ 24/100.000	♀ 3.4/100.000	♀ 0.6/100.000	♀ 1.9/100.000 ♂ 0.9/100.000	♂ 2.0/100.000	♀ 1.5/100.000 ♂ 3.8/100.000
Chesson [32]	Previous publications	12.5/100.000	4.8/100.000	1.5/100.000	5.3/100.000	2.8/100.000	5.2/100.000
Drolet [38]	HPV-advise	*	*	*	*	*	*
Elbasha [34]***	Previous publications	♀ HPV-16 5.5/100.000 ♀ HPV-18 1.0/100.000	♀ HPV-16 0.43/100.000 ♀ HPV-18 0.03/100.000	♀ HPV-16 0.21/100.000 ♀ HPV-18 0.03/100.000	♀ HPV-16 1.29/100.000 ♀ HPV-18 0.12/100.000 ♂ HPV-16 0.99/100.000 ♂ HPV-18 0.09/100.000	♂ HPV-16 0.73/100.000 ♂ HPV-18 0.06/100.000	♀ HPV-16 1.02/100.000 ♀ HPV-18 0.11/100.000 ♂ HPV-16 4.14/100.000 ♂ HPV-18 0.46/100.000
Haeussler [30]***	Previous publications (Myers et al.)	*	*	*	*	*	*
Jit [40]	Office of national statistics	*	*	*	*	*	*
Jit [41]	Cancer registration England	*	*	*	*	*	*
Jit [42]	HPV-advise/UK-data	*	*	*	*	*	*
Kim [33]	National Cancer Institute	♂4.2-62.8/100.000	♂ 0.2-19.6/100.000	♂ 0.1-6.0/100.000	♀0.0-5.6/100.000		♀0.0-1.1/100.000
Kim [34]	Previous publications	♂4.2-62.8/100.000	♂ 0.2-19.6/100.000	♂ 0.1-6.0/100.000	♀0.0-5.6/100.000 ♂ 0.1-4.3/100.000	♂0.0-7.6/100.000	♀0.0-1.1/100.000 ♂ 0.0-2.9/100.000
Laprise [43]	HPV-advise	*	*	*	*	*	*
Luttjeboer [27]	Previous publications	*	*	*	*	*	*
Olsen [44]***	Cancer registry	♀ 12.7/100.000	♀ 6.4/100.000	♀ 6.4/100.000	♀ 6.4/100.000 ♂ 3.6/100.000	♂ 3.6/100.000	♀ 8.9/100.000 ♂ 19.6/100.000
Pearson [29]	Previous publications	*	*	Excluded; small burden	*	Excluded; small burden	*

** Exact data not mentioned in publication, ** Number of cases per year (between brackets is the etiological fraction), *** Elbasha et al, Haeussler et al, and Olsen et al considered head/neck cancer instead of oropharyngeal cancer*

CHAPTER 8

Consequences of restricted STI testing for young heterosexuals in the Netherlands on test costs and QALY losses



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ABSTRACT

Background

Due to rising costs caused by increasing demand for sexually transmitted infection (STI) care, the Dutch government changed the funding of STI clinics. In 2015, a more restrictive testing policy was introduced with syphilis and HIV tests only on indication for younger, heterosexual clients. We evaluated intended savings and missed syphilis and/or HIV infections and explored efficiency of possible test policies.

Methods

Using surveillance data from 2011- 2013 with extensive testing for all, we estimated effects of restrictive testing on test costs, number of infections missed, costs per Quality Adjusted Life Year (QALY) lost, and calculated the net monetary benefit from a government perspective.

Results

The 2015 policy led to estimated savings of €1.1 million, while missing approximately three HIV infections and seven syphilis infections annually. Savings were €435,000/QALY lost. If testing second-generation immigrants for syphilis and HIV, savings rose to €525,000/QALY lost. Offering an HIV test when diagnosed with chlamydia or gonorrhoea savings were €568,000/QALY lost. In a sensitivity analysis, the willingness-to-pay threshold had the highest impact on results.

Conclusions

The 2015 testing policy resulted in a modest decline of detected HIV and syphilis infections, generating substantial savings. Syphilis and HIV tests for both first- and second-generation immigrants and an HIV test in case of positive chlamydia or gonorrhoea diagnosis could reduce missed infections in a cost-effective way.

INTRODUCTION

West European countries differ in the organisation of sexually transmitted infection (STI) control and in their level of implementation of primary prevention and STI services [1]. Moreover, the reimbursement of costs of consultation, diagnosis, and treatment varies largely across Europe. In the Netherlands, testing for and treatment of STI are performed at general practices and at special STI clinics. STI clinics provide additional care alongside the regular healthcare system (general practitioners), and the service is intended for specific target groups being considered as at high risk of contracting STIs. As in many west European countries, the most frequently diagnosed STI in the Netherlands is chlamydia: at STI clinics, positive test results were found in 14.5% (20,698 diagnoses) of all consultations at STI clinics in 2016 [2]. Chlamydia is mainly found in heterosexual men and women up to 25 years of age. The second most frequent diagnosed STI is gonorrhoea (6,092 infections), mostly diagnosed in men who have sex with men (MSM). In 2016, 1,223 syphilis infections and 285 HIV infections were detected at STI clinics, more than 90% in MSM. MSM are also the group at highest risk for acquiring syphilis and HIV: more than 90% of all infectious syphilis and HIV infections are among MSM at STI clinics. In addition, STI positivity rates are relatively high among first-generation immigrants from STI endemic countries. In general, the number of STI diagnoses at general practices is higher than at STI clinics: 35,000 chlamydia diagnoses and 7,900 gonorrhoea diagnoses in 2016 [2]. The number of syphilis and HIV diagnosis in general practices is unknown, however 32% of all new HIV diagnoses among heterosexuals are diagnosed in general practice [2].
To be eligible for testing at the STI clinic, a risk assessment of criteria is performed, including: age (younger than 25 years), symptoms of STI, individuals being notified for an STI, MSM, individuals or their partners originating from an STI endemic country, commercial sex workers (CSW) and their clients [3]. Individuals, who are not eligible for testing at the STI clinic, are referred to a general practitioner. The STI clinics are publicly financed by the government, in contrast to general practices which are paid by health insurers. Due to the rising costs caused by an increasing demand for STI care each year, an aspiration towards more efficiency and a reduction in healthcare expenditures of the Dutch government arose steadily [4].
As from 2015, the funding of the STI clinics has changed. Instead of reimbursing a fixed amount per STI consultation, an overall fixed budget was set, based on total costs in 2013. Additionally, the testing policy was restricted based on STI epidemiology in the STI clinics [5]. Heterosexual clients younger than 25 years without other risk factors for having an STI are now offered chlamydia and gonorrhoea testing only. The other groups receive additional testing for syphilis and HIV: first-generation immigrants

from an STI endemic country or those with partners born in STI endemic countries, CSW and their clients, MSM, and heterosexual clients older than 25 years. In addition, the STI clinic offers full laboratory testing to clients who report symptoms related to syphilis or HIV and clients who are notified for syphilis or HIV by a sex partner.

In California, in 2009, the budget cuts by 80 percent for HIV prevention programs, including education and testing activities, were evaluated [6, 7]. As a result, the number of HIV tests and new HIV diagnoses declined. Redirecting remaining HIV funds from risk reduction education to testing activities mitigated the negative effects of the budget cuts [6, 7].

A less extensive testing policy could be detrimental to finding and treating STIs, as was seen in California [6, 7]. Infections that remain undetected could possibly lead to an increase in both the total and individual burden of disease, due to transmission and the need for more intensive treatment that will cause higher healthcare costs in the long term.

In this paper, we evaluate the new Dutch testing policy from a government perspective. We assess the intended savings of test costs in relation to the number of missed infectious syphilis and HIV infection in the Dutch setting. Besides the 2015 policy we explore whether other possible test policies would lead to fewer missed infections at acceptable costs.

METHODS

General approach

In this evaluation, we assessed savings on test costs, missed infections and related quality of life on a yearly basis. Most cost-effectiveness studies analyse new interventions and more treatment rather than restricted care. We therefore do not report the costs per QALY gained, but the savings per QALY lost. We include the threshold of savings per QALY lost that is implicitly used by Dutch policymakers. We also identify other testing policies that could withdraw the negative effects of restricted testing, and therefore will be more efficient than the restricted testing policy implemented in 2015.

Data

Each consultation of a client visiting an STI clinic is anonymously recorded in the national STI surveillance database, including demographic details, country of birth of client and parents, current symptoms, notification by an infected partner, number of recent sexual partners, sexual orientation, and sexual risk behaviour along with test results. We used data from 2011 to 2013 to assess the annual number of visits to the STI clinic as well as the test results for the target group of the 2015 policy that is all heterosexual clients up to 25 years, excluding first-generation immigrants from STI endemic countries and commercial sex workers and their clients. To minimize the effect of annual fluctuations we used the average number of visits and test results of these three years. As the testing policy between 2011 and 2013 still included syphilis and HIV testing for this group, we were able to explore the number of syphilis and HIV infections that would have remained undiagnosed if they had been tested for chlamydia and gonorrhoea only. Potential test cost savings by only testing these individuals for chlamydia and gonorrhoea and not including syphilis and HIV tests were related to numbers of missed syphilis and/or HIV infections. HIV and syphilis test prices were both €11.35 and were gathered from list prices available online of the Dutch Health Authority and were expressed in Euros at the price level of 2014 [8].

Quality of life

As a missed syphilis infection has a different impact on a person's quality of life than an HIV infection we also calculated test cost savings per Quality Adjusted Life Year (QALY) lost. The QALY is a composite health measure combining quality of life and duration of disease, in which a QALY weight of 1.0 represents full health and 0.0 represents death. HIV infection is a chronic disease; whereas a syphilis infection not always leads to a chronic manifestation. In both cases, different disease stages with

different impact on the quality of life can be expected. The QALY lost for missing an HIV infection was based on an economic evaluation for the United States of Jusoola et al, assuming average disease duration of seven years of asymptomatic HIV as well as the time to detect infection [9]. In order to assess an appropriate QALY weight to each disease stage, we calculated the difference between the lowest value of unidentified HIV (0.72) and an HIV infection treated with ART (0.83). Following Jusoola et al. we multiplied this with the time to detect infection (7 years), resulting in a cumulative QALY loss per case of 0.77 (0.11*7) due to a missed HIV infection. In addition, QALY losses were discounted at 1.5% annually according to the Dutch manual for health economic evaluations [10]. Discounting is an economic concept that is used to project future QALY losses or gains into a present value, implying that future QALY losses are valued lower than immediate QALY loss. The cumulative QALY loss of a missed HIV infection after discounting is calculated at 0.74. We used a loss of 0.005 for syphilis. This loss is based on estimates using the disability weight assessed for the DALY approach (Disability Adjusted Life Year) [11] in the absence of an existing QALY estimate for syphilis. DALYs are calculated as the sum of the years of life lost due to premature mortality and the years lost due to disability for individuals living with the disease. Part of the DALY approach combines morbidity of a health state with the duration of the state, corresponding with the QALY under the assumption that: QALY weight = 1.00 – disability weight [12].

Net monetary benefit

We calculated the net benefits in terms of net monetary benefit by giving a monetary value to the benefit of the intervention. First, we assume a “willingness to pay (WTP)” threshold for a QALY, that is, the maximum amount society is willing to invest to avoid one QALY lost. Consequently, we assumed that compensation for a QALY lost would have to be at least equal to the WTP threshold to gain a QALY. We converted health losses into Euros by multiplying QALY lost with the threshold value in order to have a monetary value of the health loss. The cost due to health losses associated with each testing strategy is then subtracted, resulting in the net benefit of each strategy expressed in monetary units. The net monetary benefit can be used to rank the most cost-effective strategy. Currently, in the Netherlands, a WTP threshold for a preventive intervention of €20,000 per QALY has been used [13]. In short, our outcomes were: the number of missed infections (syphilis and HIV), the test cost savings per missed infection, the test cost savings per QALY lost and the net monetary benefit.

Other groups and test options

We expanded the analyses to assess efficiency of the 2015 policy for other groups visiting the STI clinics besides younger heterosexuals. These groups were classified by sexual preference: heterosexual or MSM, age: older or younger than 25 years, and origin: western country, being a first- or second-generation immigrant from an STI endemic country. As it was determined that CSW and their clients were not eligible for chlamydia and gonorrhoea testing only in the 2015 testing policy, we excluded them from all analyses. Table 1 presents the characteristics of the different groups in this study.

Table 1. Characteristics of the groups for which restricted testing policy could apply

Target group	Age	MSM	First generation immigrant	Second generation immigrant
2015 target group: young heterosexuals, including second generation immigrants[a]	<25	No	No	Yes
Young heterosexuals, from a western origin	<25	No	No	No
Young heterosexuals, including all immigrants[b]	<25	No	Yes	Yes
Young MSM, from a western origin	<25	Yes	No	No
Older heterosexuals, from a western origin	≥25	No	No	No
Older MSM, from a western origin	≥25	Yes	No	No

[a] immigrants from an STI endemic country, not being a first-generation immigrant, [b] first- and second-generation immigrants from an STI endemic country

We calculated costs per missed infection, costs per QALY lost, and net monetary benefit for the 2015 testing policy and in three additional scenarios that potentially can further increase the testing efficiency with respect to missed infections and costs. The following STI testing policy options were assessed:

- Option 1: chlamydia and gonorrhoea testing required only (T2, 2015 testing policy);
- Option 2: T2 with a subsequent HIV test in case of a positive chlamydia or gonorrhoea test result;
- Option 3: T2 with a subsequent HIV and syphilis test in case of a positive chlamydia or gonorrhoea test result;
- Option 4: chlamydia, gonorrhoea, and HIV testing (T3);

Sensitivity analysis

We performed one-way sensitivity analyses to assess the effects of important parameters in the model on the net monetary benefit. We varied the QALY loss per missed STI (with a 25% increase and decrease), the number of missed infections (with a 50% increase and decrease), and the WTP threshold (set at the higher amounts of €30,000 and €50,000).

Results

Table 2 presents the total number of consultations at STI clinics and the number of STI diagnoses between 2011 and 2013. In the group related to the new 2015 testing policy, 22,223 chlamydia and gonorrhoea infections were diagnosed, as well as 20 syphilis and 10 HIV infections. The number of consultations was highest among persons up to 25 years of age, including first- and second-generation immigrants. In addition, in this group the highest number of chlamydia and gonorrhoea infections is diagnosed. Most syphilis and HIV infections were diagnosed in MSM, especially among those older than 25 years.

Table 2 Total numbers of consultations and the numbers of STI diagnoses by target group, 2011-2013

Target group	Number of consultations	Chlamydia and/or gonorrhoea infection	Recent (infectious) syphilis infection	Coinfection syphilis[b]	HIV infection	Coinfection HIV[b]
Aged < 25 years						
2015 target group: young heterosexuals, including second-generation immigrants[a]	143,612	22,223	20	5	10	2
Young heterosexuals, from a western origin	121,288	17,350	12	2	7	1
Young heterosexuals, including all immigrants[c]	154,309	24,590	25	6	19	3
Young MSM, from a western origin	8,865	1,521	115	30	62	29
Aged ≥ 25 years						
Older heterosexuals, from a western origin	77,703	7,380	53	5	40	11
Older MSM, from a western origin	49,731	8,288	1,031	294	590	209

[a] immigrants from an STI endemic country, not being a first-generation immigrant, **[b]** *with chlamydia or gonorrhoea, (subsets of syphilis and HIV infection columns), [c] first- and second-generation immigrants from an STI endemic country*

Applying the new testing policy to the 2015 policy target group would have led to test cost savings and net monetary benefit of about €1 million per year (Table 3). Savings per missed syphilis or HIV infection or per QALY lost were €109,000 and €435,000 respectively. Results are more favourable with respect to savings per QALY lost in young heterosexual visitors from a western country. The groups younger and older MSM, as well as the older heterosexuals showed rather low savings at the cost of a missed syphilis or HIV infection or per QALY. The net monetary benefit showed negative results in MSM, both younger and older than 25 years.

Table 3 Test cost savings and net monetary benefit following T2[b], option 1, 2011-2013

Target group	Test cost savings (€)	Savings (€) / missed hiv/syphilis	Savings (€) / QALY lost	Net monetary benefit (€)
2015 target group: young heterosexuals, including second-generation immigrants[a]	3,260,000	109,000	435,000	3,110,000
Young heterosexuals, from a western origin	2,753,000	145,000	525,000	2,648,000
Young heterosexuals, including all immigrants[c]	3,503,000	80,000	247,000	3,219,000
Young MSM, from a western origin	201,000	1,000	4,000	-728,000
Older heterosexuals, from a western origin	1,764,000	19,000	59,000	1,167,000
Older MSM, from a western origin	1,129,000	696	3,000	-7,706,000

[a] *immigrants from an STI endemic country, not being a first-generation immigrant, [b] only a chlamydia and gonorrhoea test, [c] first- and second-generation immigrants from an STI endemic country*

Additional test options

For the three upper groups with the highest test cost savings and net monetary benefits of table 3 three additional test options on savings per QALY lost were explored with the aim to optimize results and avoid negative consequences of a restricting testing policy. Results of the additional Options 2, 3 and 4 are shown in Table 4. In addition, savings per lost QALY of option 2 and 3 are also presented in Figure 1 in an appendix file. Overall, offering a limited number of tests following the three test options resulted in highest savings per QALY lost in the group young heterosexuals from a western origin. In all three groups, Option 2, a subsequent HIV test if diagnosed with chlamydia or gonorrhoea, led to higher savings per QALY lost compared to Option 3. In case all clients are offered an HIV test by default (Option 4) the savings per QALY lost were much higher than offering T2 only, since no HIV infections would be missed. Applying this Option 4, the test cost savings and net monetary benefits were lower than in case of offering T2. Figure 2 and 3 in the appendix file present the incremental savings and QALYs per test option. In table A1 (appendix file) the incremental cost-effectiveness ratio per test option is given.

Table 4 Test cost savings and net monetary benefit in additional test options, 2011-2013

Target group	Test cost savings (€)	Savings (€) / missed hiv/ syphilis	Savings (€) / QALY lost	Net monetary benefit (€)
Test option 2: additional HIV test if positive chlamydia/gonorrhoea				
2015 target group: young heterosexuals, including second-generation immigrants[a]	3,008,000	107,000	500,000	2,887,000
Young heterosexuals, from a western origin	2,556,000	142,000	568,000	2,466,000
Young heterosexuals, including all immigrants[b]	3,224,000	79,000	269,000	2,984,000
Test option 3: additional HIV and syphilis test if positive chlamydia/gonorrhoea				
2015 target group: young heterosexuals, including second-generation immigrants[a]	2,756,000	120,000	460,000	2,636,000
Young heterosexuals, from a western origin	2,359,000	147,000	525,000	2,270,000
Young heterosexuals, including all immigrants[b]	2,945,000	84,000	247,000	2,706,000
Test option 4: chlamydia, gonorrhoea and HIV testing				
2015 target group: young heterosexuals, including second-generation immigrants[a]	1,630,000	82,000	16,300,000	1,628,000
Young heterosexuals, from a western origin	1,377,000	115,000	22,944,000	1,375,000
Young heterosexuals, including all immigrants[b]	1,751,000	70,000	14,011,000	1,749,000

[a] immigrants from an STI endemic country, not being a first-generation immigrant, [b] first- and second-generation immigrants from an STI endemic country, chlam=chlamydia, gon=gonorrhoea

Sensitivity analysis

Figure 4 in the appendix file shows the change in net monetary benefit when applying other input parameters than included in the model. A WTP threshold set at €50,000 had the highest impact and resulted in a €225,000 decrease of the net monetary benefit in a three years' period. Both a WTP threshold set at €30,000 and 50% more missed HIV and syphilis infections, resulted in a €75,000 decrease in net monetary benefit. 50% less missed infections led to a €75,000 increase in net monetary benefit. A 25% increase or decrease in QALY weights resulted in a €37,500 decrease or increase of the net monetary benefit. Changes in the WTP threshold had the highest impact on the other testing scenarios, however to a lesser extent than regarding the 2015 testing policy.

DISCUSSION

In this study we assessed the consequences of the 2015testing policy at STI clinics: the number of missed infections and cost savings, and the impact on the burden of disease. The 2015testing policy is applied to all heterosexual persons up to 25 years visiting the STI clinic; except for those who are first-generation immigrants to the Netherlands and CSW. Based on data from 2011 to 2013, the new policy could have led to 20 missed syphilis infections and 10 missed HIV infections, which is limited compared to the total number of 1673 syphilis infections and 1129 HIV infections over this three-year period. In the same period, about €3.3 million would have been saved by excluding syphilis and HIV testing for this group. Savings are €109,000 at the costs of one missed infection and €435,000 per QALY lost. Applying the threshold value of a QALY gain in the Netherlands for a preventive measure of €20,000, the net monetary benefit would be €3.1 million, corresponding to approximately €1 million a year. Results from the sensitivity analysis showed that the net monetary benefit varied the most when assuming other STI missing percentages, and when the WTP threshold was higher. The maximum decrease in net monetary benefit was €75,000 a year.

Limitations

Data limitations did not allow assessing the number of syphilis or HIV infections among clients visiting the STI clinic with syphilis or HIV specific symptoms or having been notified for syphilis or HIV infection, nor among those clients with a partner born in an STI endemic country. In addition, the assessment of clients' STI risks at the STI clinic offers the clinician the opportunity to deviate from the default testing policy and

perform supplementary tests. Therefore, in reality the number of missed infections will be lower, resulting in outcomes that are more favourable in terms of less QALY losses. The scope of this study was insufficient to model the long-term transmission effect of the new testing policy. Our cost analysis neither included treatment costs, nor the costs and QALY losses due to transmission of undetected syphilis and HIV infection, influencing results less favourable. Potentially, complications in non-detected cases could lead to higher future costs.We did not account for costs and effects of extra-genital testing. A high burden of rectal and pharyngeal chlamydia and gonorrhoea infections in MSM has been well documented. Moreover, extra-genital testing in heterosexual women should be considered and is advised in Dutch STI clinic guidelines when oral or anal sexual activity is reported [14, 15]. The inclusion of extra-genital testing for MSM and heterosexual women would lead to overall higher test costs but would most likely not give a significant rise to savings per QALY lost since the latter depend on the number of missed syphilis and HIV infections. We also have to acknowledge that the results in this analysis apply for the epidemiological situation that is based on 2011-2013 data while in the meantime the epidemiological situation might shift. We therefore might underestimate the true number of missed cases. In recent years (2015/2016) there were small geographical clusters of heterosexual syphilis cases showing the importance of evaluating the test policy (unpublished data). Finally, the restricted testing policy at STI clinics could lead to additional tests and associated costs in general practice.

Willingness to pay versus willingness to accept

The study results regarding the net monetary benefit should be interpreted with caution since they are directly depending on the WTP threshold and the WTP is not carved in stone. In this study we applied the Dutch WTP threshold of €20,000 per QALY gained which is low compared to the US' threshold of $50,000 per QALY gained [16]. Using a higher threshold in the sensitivity analysis resulted in a lower net monetary benefit. Furthermore, we considered the WTP for health gain equal to the willingness to accept (WTA) health loss. It has been discussed that the WTA threshold is usually higher than the WTP threshold; people have an averseness to loose health gains and need a higher compensation to accept the removal of healthcare interventions than they are willing to pay for the introduction of new therapies [17]. However, the WTA threshold should be increased to €434,666 to result in a zero net monetary benefit, which supports the decision of implementation of the restricted STI testing policy.

Quality of life

The results in our analysis are sensitive to the QALY loss of a missed HIV infection. Using the lowest QALY value of unidentified HIV and a QALY value of an HIV infection treated with ART for calculating a QALY loss per case and assuming a time of 7 years to detect infection would both possibly result in an overestimation of QALY loss per case. Since no evidence on health states due to a missed infection exists, we chose this conservative approach. The 25% increase or decrease of the QALY loss per case in the sensitivity analysis however, did not have much impact on the net monetary benefit.

Restricted care

Our recommendations are in contrast with the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) which are recommending that HIV testing and counseling should be accessible to all adolescents in order to reduce the number of undetected HIV infections [18, 19]. However, the WHO recognizes the heterogeneity of adolescents in different settings (generalized, low and concentrated epidemics). The impact of the economic crisis has led to flattening of budgets in many European countries across social sectors including infection prevention and control in healthcare [20, 21]. Reducing ineffective expenditures remains one of the most obvious opportunities to contain the increasing costs in the healthcare sector. Other industrialised countries are also concerned about finite health care resources, resulting in discussions about the avoidance of low-value practices. In 2012, the American Board of Internal Medicine and Consumer Reports launched the Choosing Wisely campaign to encourage physicians, patients, and other healthcare stakeholders to reconsider commonly used clinical services that provide little or no benefit for most patients [22]. Other countries followed this initiative, e.g., England, Canada, Australia, the Netherlands and Germany [23]. Up to now, none of the items of Choosing Wisely is targeted at STI testing.

Recommendations

We demonstrated that the efficiency of the testing policy could be improved. First, in addition to first-generation immigrants, STI clinics could offer second-generation immigrants a syphilis and HIV test. If we would include this target group for full laboratory testing, the savings per QALY lost would rise to €525,000. Second, STI clinics could offer an additional HIV test to visitors diagnosed with chlamydia or gonorrhoea. This would result in savings of €568,000 per QALY lost. However, in both cases, the net monetary benefit would reduce to respectively €2.6 million and €2.5 million. Third, the scenario in which young heterosexual visitors from a western origin

would be provided an HIV test by default would cause a dramatic increase of savings per QALY lost: €22.9 million. Conversely, the net monetary benefit will have a large decline down to €1.4 million in a three years period. In addition, it has to be noted that the costs as reported here are only laboratory costs. The potential expansions of the 2015 testing policy should be discussed with clinicians and policy makers, taking all aspects of its possible implementation regarding costs, extra consultations, burden of disease, and logistics into account.

CONCLUSION

We found that the implemented testing policy at STI clinics leads towards a modest decline of HIV and syphilis infections identified of at most 0.02% of all consultations at the STI clinics, generating substantial test cost savings for the Dutch government. In the Netherlands, the restricted testing policy seems to be an adequate decision for this purpose, especially since clinicians at STI clinics are given flexibility in how to assess clients' STI risks and add testing if they feel this is warranted. It is important to launch a debate with policy makers and clinicians for further improvements of the 2015 testing policy. In this debate, finding those with undetected HIV and syphilis infection outside the scope of the STI clinics is of importance and requires adequate financing. Finally, monitoring the effects of the restricted testing policy in the long term is essential.

ACKNOWLEDGEMENTS

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APPENDIX FILE

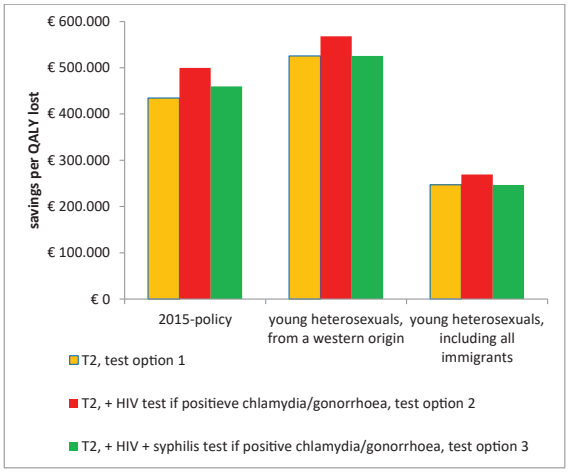

Figure 1: savings per QALY lost in three test options

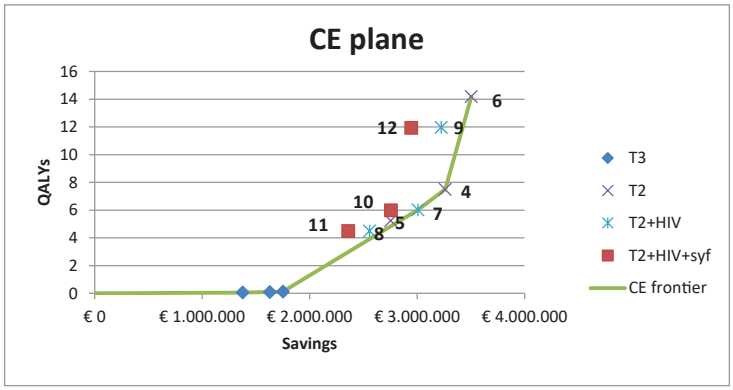

Figure 2: Cost-effectiveness plane in case of the 2015 testing policy (T2), T2 with a subsequent HIV test if positive chlamydia or gonorrhoea test result (T2+HIV), T2 with a subsequent HIV and syphilis test if positive chlamydia or gonorrhoea test result (T2+HIV+syphilis). For zoom in on T3 options, see Figure 3.

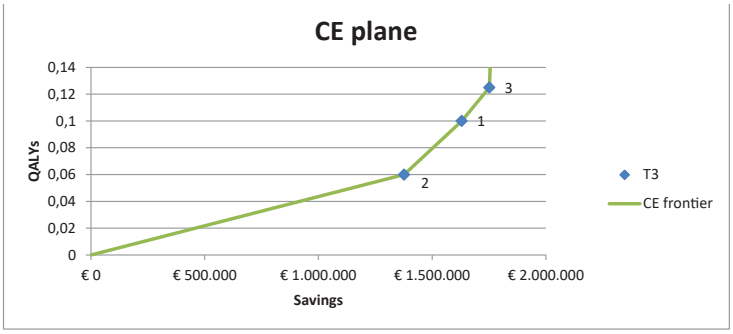

Figure 3: Cost-effectiveness plane in case of chlamydia, gonorrhoea, and HIV testing (T3)

Explanation of the numbers used in figure 2 and figure 3

1 T3 (test option 4), 2015 target group
2 T3 (test option 4), from a western origin
3 T3 (test option 4), incl. all immigrants
4 T2 (test option 1), 2015 target group
5 T2 (test option 1), from a western origin
6 T2 (test option 1), incl. all immigrants
7 T2, +HIV (test option 2), 2015 target group
8 T2, +HIV (test option 2), from a western origin
9 T2, +HIV (test option 2), incl. all immigrants
10 T2, +HIV+syphilis (test option 3), 2015 target group
11 T2, +HIV+ syphilis (test option 3), from a western origin
12 T2, +HIV+ syphilis (test option 3), incl. all immigrants

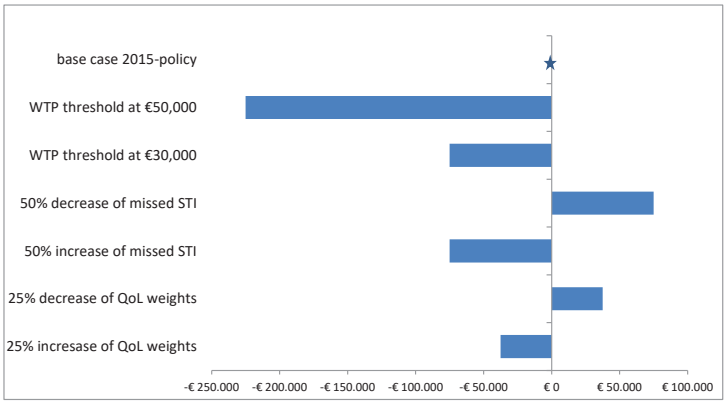

Figure 4: effects of variation in input parameters on the net monetary benefit

Table A1: QALYS, savings and incremental cost-effectiveness ratio (ICER) per test option

	QALYs lost	savings	ICER
Test option 1 (T2)			
2015 target group: young heterosexuals, including second-generation immigrants[a]	7.5	3,259,992	€ 170,426 compared to T2+HIV, 2015 target group
Young heterosexuals, from a western origin	5.24	2,753,238	Dominated by T2+HIV, 2015 target group
Young heterosexuals including all immigrants[b]	14.185	3,502,814	€ 36,323 compared to T2, 2015 target group
Test option 2: additional HIV test if positive chlamydia/gonorrhoea (T2+HIV)			
2015 target group: young heterosexuals, including second-generation immigrants[a]	6.02	3,007,761	€ 213,122 compared to T3, young heterosexuals including all immigrants
Young heterosexuals, from a western origin	4.5	2,556,315	Dominated by T2+HIV, 2015 target group
Young heterosexuals including all immigrants[b]	11.965	3,223,718	Dominated by T2, 2015 target group
Test option 3: additional HIV and syphilis test if positive chlamydia/gonorrhoea (T2+HIV+syphilis)			
2015 target group: young heterosexuals, including second-generation immigrants[a]	5.995	2,755,530	Dominated by T2+HIV, 2015 target group
Young heterosexuals, from a western origin	4.49	2,359,393	Dominated by T2+HIV, 2015 target group
Young heterosexuals including all immigrants[b]	11.935	2,944,621	Dominated by T2+HIV, 2015 target group
Test option 4 chlamydia, gonorrhoea and HIV testing (T3)			
2015 target group: young heterosexuals, including second-generation immigrants[a]	0.1	1,629,996	€ 6,334,435 compared to T3, young heterosexuals from a western origin
Young heterosexuals from a western origin	0.06	1,376,619	€ 22,943,647 compared to policy before 2015
Young heterosexuals including all immigrants[b]	0.125	1,751,407	€ 4,856,438 compared to T3, 2015 target group

[a] immigrants from an STI endemic country, not being a first-generation immigrant, [b] first- and second-generation immigrants from an STI endemic country

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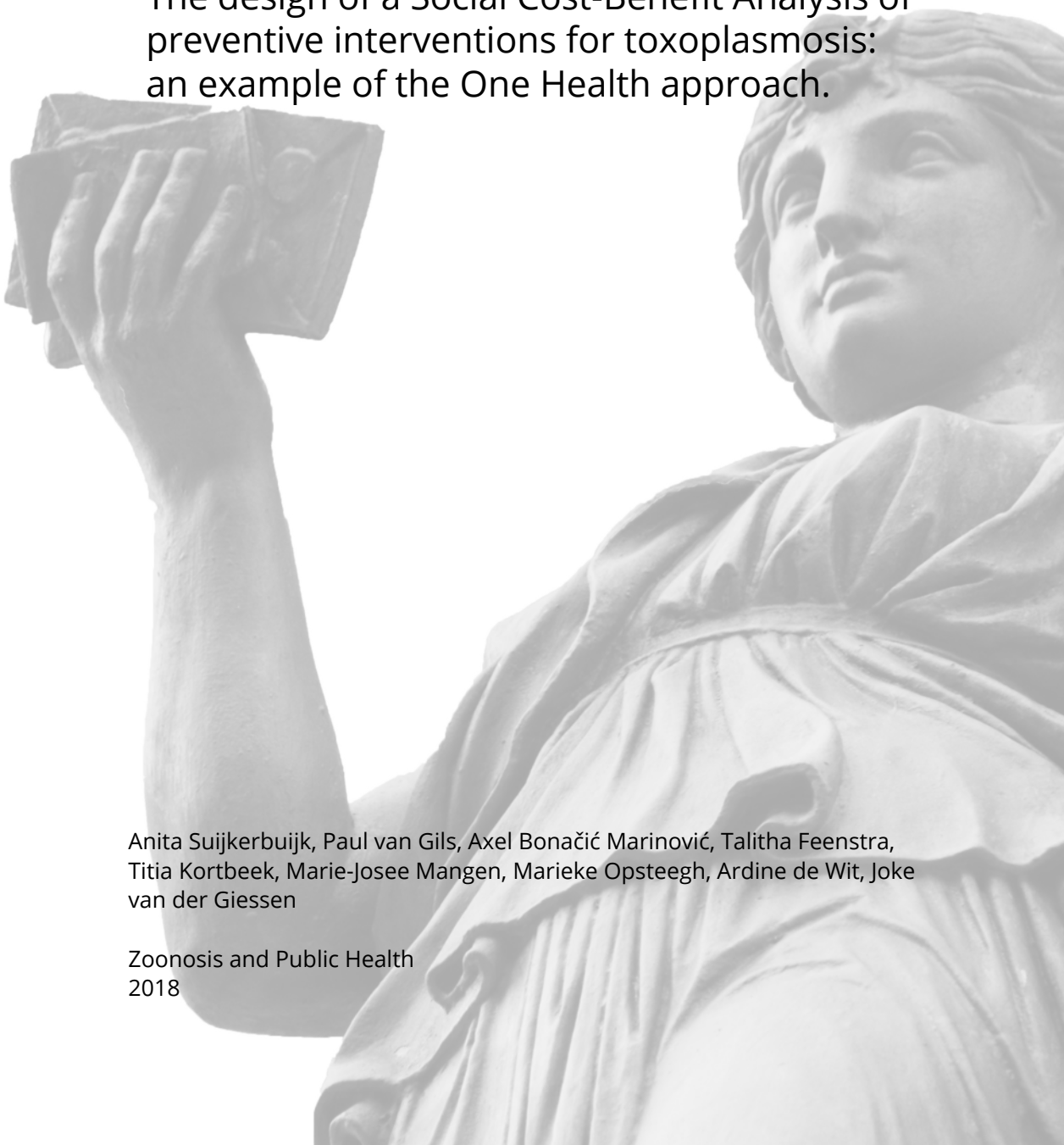
CHAPTER 9

The design of a Social Cost-Benefit Analysis of preventive interventions for toxoplasmosis: an example of the One Health approach.



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SUMMARY

Toxoplasma gondii infections cause a large disease burden in the Netherlands, with an estimated health loss of 1,900 Disability Adjusted Life Years and a cost-of-illness estimated at €44 million annually. Infections in humans occur via exposure to oocysts in the environment and after eating undercooked meat containing tissue cysts, leading to asymptomatic or mild symptoms, but potentially leading to the development of ocular toxoplasmosis. Infection in pregnant women can lead to stillbirth and disorders in newborns. At present, prevention is only targeted at pregnant women. Cat vaccination, freezing of meat destined for undercooked consumption, and enhancing biosecurity in pig husbandries are possible interventions to prevent toxoplasmosis. As these interventions bear costs for sectors in society that differ from those profiting from the benefits we perform a social cost-benefit analysis (SCBA). In an SCBA, costs and benefits of societal domains affected by the interventions are identified, making explicit which stakeholder pays and who benefits. Using an epidemiological model, we consider transmission of *T. gondii* after vaccination of all owned cats or cats at livestock farms. To identify relevant high-risk meat products that will be eaten undercooked, a quantitative microbial risk assessment model developed to attribute predicted *T. gondii* infections to specific meat products will be used. In addition, we evaluate serological monitoring of pigs at slaughter followed by an audit and tailor made advice for farmers in case positive results were found. The benefits will be modelled stochastically as reduction in DALYs and monetized in euro's following reference prices for DALYs. If the balance of total costs and benefits is positive, this will lend support to implementation of these preventive interventions at the societal level. Ultimately, the SCBA will provide guidance to policy makers on the most optimal intervention measures to reduce the disease burden of *T. gondii* in the Netherlands.

INTRODUCTION

Toxoplasmosis is caused by the protozoan parasite *Toxoplasma gondii*. This parasite can infect a wide range of warm-blooded animals such as birds, mice, rats, cats, sheep, pigs and cattle, as well as humans. Most species function as intermediate hosts and they will not shed *T. gondii* in the environment, but infection will lead to the development of infectious tissue cysts. Cats and other felids function as definitive hosts, meaning that *T. gondii* can complete its sexual cycle resulting in shedding of millions of oocysts in their feces for up to three weeks [1]. These oocysts can remain viable in the environment for about a year [2, 3], where they can infect other animals, both farm and non-farm animals as well as humans. Infections in humans occur mostly via exposure to oocysts in the environment or after eating raw or undercooked meat containing tissue cysts, often leading to an asymptomatic infection or mild flu-like symptoms (Elmore et al., 2010), but potentially leading to the development of ocular toxoplasmosis [4]. Besides, toxoplasmosis is also well-known as a cause of congenital disease in humans. Infection in naïve pregnant women can lead to abortion, stillbirth and serious disorders in newborns such as hydrocephalus, microcephalus and chorioretinitis later in life [4].

As a consequence of these serious health risks, *T. gondii* is an important pathogen in terms of burden of disease in humans in the Netherlands. The burden of toxoplasmosis can be distinguished into the number of years of life lost (premature mortality) and the number of years lived in less than full health (morbidity). The aggregate of both measures is a quantification of the years of healthy life lost due to a certain disease or infection, better known as the DALY (Disability Adjusted Life Years). It is recently estimated that toxoplasmosis is responsible for a disease burden (undiscounted) of about 1,903 DALYs per year [5]. With this disease burden, *T. gondii* ranks third among all foodborne-related pathogens, after *Campylobacter spp.* that is associated with 3,573 DALYs and norovirus with 2,248 DALYs in the Netherlands [5]. In 2016, the estimated mean annual number of infections of toxoplasmosis in the Netherlands was 767, of which 344 were congenital and 423 were acquired in later life [5]. In the same year, the estimated mean annual number of deaths was 12. About half of all toxoplasmosis related DALYs are associated with congenital toxoplasmosis. Mangen et al. assessed the cost-of-illness of toxoplasmosis in 2016 at € 44 million, considering disease-related costs from a societal perspective, which means that in addition to healthcare costs also productivity losses due to work absence of caregivers and patients and the

cost of special education were included [5]. In order to reduce the burden of disease and associated costs, additional strategies to prevent both congenital and acquired toxoplasmosis in the population should be considered.

In the Netherlands, toxoplasmosis prevention currently is only targeted at educating and counselling pregnant women [6]. No intervention is applied in the food chain. Opsteegh et al. described that cat vaccination, freezing of meat destined for raw or undercooked consumption and enhancing biosecurity in pig husbandries are potential interventions to further prevent *T. gondii* infections [6]. Implementation of these interventions would most likely reduce the number of infections, but increase costs in several domains of society at the same time. Toxoplasma infections in animals are generally asymptomatic, preventing infections in animals results mostly in additional costs. However, there are some additional benefits for the farmers/food chain, such as a reduction in abortions in ewes when implementing the cat vaccination intervention and less spilled feed due to rodent control when increasing biosecurity at pig farms. Freezing high-risk meat products has economic consequences for both the meat processing industry and consumers of the high-risk meat products. There may be a disbalance between stakeholder groups that have to pay for these interventions and stakeholder groups that will benefit from such interventions.

A social cost benefit analysis (SCBA) is an established method to map the distribution of the short-term and longer-term costs and benefits of implementing new interventions over the different stakeholders involved in these interventions. Performing an SCBA implies the identification and valuation of all costs and all benefits of a certain intervention in monetary terms. The valuation of the costs and benefits in an SCBA allows comparison and ranking of the results of the various interventions [7]. Within an SCBA, the overall sum of benefits and costs is reported as net social costs or net social benefit. This is the sum of all the valued benefits minus the sum of all the valued costs. If the monetized balance of the total costs and total benefits is positive, then this will lend support to implementation of these preventive interventions at the societal level. By allowing a ranking of these net social benefits of different interventions, the SCBA will help to decide which intervention is most worthwhile to be implemented.

SCBAs are rarely performed when evaluating interventions affecting both human and animal health. Most evaluations focus either on the stable to slaughterhouse (animal health), or on public health domains and ignoring the other sectors. There are a few exceptions; some economic evaluations of zoonosis included a range of social costs and effects. For example, Sundström et al. assessed the net benefits of introducing alternative Salmonella control strategies taking expected changes in

human and cattle morbidity and the associated monetary effects into account [8]. Quality of life loss due to Salmonellosis could not be incorporated into the model. Babo Martins et al. evaluated the economic effects of zoonosis surveillance. In the case of *Campylobacter,* costs of an animal and human monitoring system were included [9, 10]. In another economic evaluation, the social costs and effects of combined rabies control interventions such as dog vaccination, and pre-and post-exposure prophylaxis in humans were assessed [11]. Unlike our study, in the latter two studies the benefits were not monetarized in Euros but only expressed in human infections and DALYs averted. Within healthcare, most economic evaluations concern cost-effectiveness analyses (CEAs). In a cost-effectiveness study, a scenario with a new intervention is often compared to a scenario without this intervention (mostly the current situation) and sometimes several interventions are compared among each other. In a CEA, the incremental cost-effectiveness ratio (ICER) shows the net costs of health improvement, for example in terms of costs per Life Year Gained (LYG) or DALY averted of the new intervention, compared to care as usual or to not implementing that intervention. Although most guidelines for economic evaluation advocate the use of a societal perspective, in reality many analyses use a healthcare perspective [12, 13]. In case a societal perspective is taken, this often is limited to the inclusion of productivity losses and additional patient costs, such as travel costs. Wider societal costs, such as those for the food production industry, are not taken into account in general. In addition, CEAs pay little attention to distributional aspects, regarding the stakeholders who pay for an intervention and who get the benefits. In contrast to CEAs, health benefits in SCBAs are expressed in a monetary unit (e.g., dollars or euros), and not in a specific health outcome, such as DALYs or infections averted [7, 14-16]. The SCBA requires availability of data from all relevant domains. A well-performed SCBA is attractive because it takes into account both the inter-sectoral costs and benefits as well the distributional issues since the interventions impact several domains of society.

The aim of this paper is to present the design of an SCBA investigating the costs and (monetarized) benefits of three preventive interventions with the objective to reduce the disease burden of toxoplasmosis in the Netherlands: 1. Cat vaccination 2. Freezing of high-risk meat products from cattle, pigs, and sheep 3. Enhancing biosecurity on pig farms. Since SCBA is rarely applied in the field of zoonoses research, the design of such an approach might be of interest for all working in the One Health community.

METHODOLOGY OF A SOCIAL-COST BENEFIT ANALYSIS

For Dutch government decisions that involve several domains of society, SCBA is the recommended analytical technique. The study will be performed according to the Dutch general guidelines for SCBAs and will follow steps recommended in these guidelines (see Fig. 1) (Romijn & Renes, 2013 [14, 15].

Fig. 1 Research steps of a Social Cost Benefit Analysis (adapted from [7])

As shown in Fig 1, the guideline prescribes 8 steps that will be explained below.

Step 1 Scoping the problem.

In this first step, the initial situation with regard to the problem at hand is determined. What is the size of the problem? What is the prevalence and incidence of toxoplasmosis, both in the animal and the human population, what are the consequences of toxoplasmosis in terms of disease burden in humans, and what are the consequences of toxoplasmosis in animals, if any, and what will be the trend

into the future under the current interventions? Will the problem diminish, increase or stabilize and what are the main drivers for these future trends? The main aim of this step is to portray the current state of affairs (including the main actors) for toxoplasmosis in the Dutch society. This step also includes an inventory of current interventions to prevent toxoplasmosis.

Step 2 The reference scenario

In this step, the reference scenario will be described in terms of costs and consequences of continuing current interventions (unchanged policies). Essentially, this is limited to creating awareness among pregnant women and advising on preventive measures that pregnant women can take themselves. No other interventions are currently in place, neither in the public health domain, nor at the farm or in the food chain. At the start of the project all relevant stakeholders are identified based on information from websites, grey and scientific literature and on interviews with experts in the field and from scientific institutes [17-22] (Table 1). Human healthcare, agriculture in particular livestock holders, veterinarians, animal feed companies, food processing industry, and education are involved with the interventions under study. The stakeholders will experience a change in costs and benefits due to the interventions. Furthermore, higher or lower prices will influence the producer and consumer surplus. A crucial assumption is that we assume that interventions will be supported and adopted by all European countries. Therefore, we do not take into account import of non-frozen meat from abroad, nor the jeopardy for competitiveness should only one European country require food industry to freeze certain types of meat. Ultimately, the net benefits per stakeholder are presented. Defining the reference scenario is crucial, because this will be the scenario to which the costs and benefits of new interventions will be compared.

Step 3 Define the interventions

People can become infected via three main ways of transmission: ingesting uncooked meat containing tissue cysts, ingesting food and water contaminated with oocysts from infected cat feces, and congenitally [6]. Since an effective human vaccine is lacking, prevention of zoonotic transmission from animals or environment to humans is therefore the most optimal alternative. Cats are the main reservoir. Food animals can become infected via the environment or by ingesting water contaminated with oocysts from infected cat feces. Reducing exposure to oocysts or tissue cysts in humans can be achieved through 1. Cat vaccination 2. Freezing of high-risk meat products, and 3. Enhancing biosecurity on pig farms. The different domains and their effects for the different interventions are shown in Table 1 and described below.

Ad 1. Vaccination of cats may be an effective way to reduce oocyst shedding by cats in the environment [6]. The intervention will directly influence human infections via oocysts in the environment but also infections via meat as it will reduce the prevalence of infection in livestock. The effects of cat vaccination in animals and humans will be modelled based on available literature or expert opinion.
Unfortunately, no vaccine is commercially available at this moment. However, in a vaccination-challenge experiment, use of a prospective vaccine prevented oocyst shedding in 31 of 37 kittens [23]. Depending on the proportion of cats that is domestic and the proportion that is not bound to a certain owner, it may be difficult to reach sufficient vaccination coverage. In this study we consider both vaccination of all owned cats or of cats that are kept at livestock farms only. Vaccination of cats can lead to fewer toxoplasma-related abortions in ewes. Most of all, there will be fewer human infections and consequently fewer cost-of-illness and disease burden.

Ad 2. Freezing meat at −20°C for 2 days will render tissue cysts nonviable [19]. Freezing (and thawing) of meat will have effects on the physical quality of meat. The formation of ice crystals during freezing damages the structure in the meat and leads to changes in the biochemical reactions that occur at the cellular level of the meat [24, 25]. Amongst other effects, it will lead to changes in moisture loss, colour, and pH, shear force and microbial spoilage [26]. In general, frozen meat is less juicy and tender, influencing consumers' attitudes towards freezing of meat negatively. Consequently, the price consumers are willing to pay for such products may be affected. Freezing meat will extend the meat production chain and therefore increases the risk of cross-contamination with other pathogens such as *Salmonella* spp. This may happen at the consumer level, but also during the freezing process or via staff at the freezing company. Due to data limitations, the aspect of cross-contamination will not be taken into account. Several mechanisms are available to mitigate the effects of freezing and thawing including the use of novel methods of freezing and thawing and modified atmospheric packaging [24]. To reduce costs and increase acceptance of consumers, the freezing meat intervention will only be targeted at high-risk meat products. This will include meat products from animal species with a high prevalence of *T. gondii* such as sheep, and products that are commonly consumed raw or undercooked, such as steak, raw meat-slices, and raw meat spreads. To identify the most relevant high-risk meat products, the quantitative microbial risk assessment (QMRA) model developed to attribute predicted *T. gondii* infections to specific meat products will be updated for this SCBA, based on data from the new Dutch National Food Consumption Survey [27, 28]. More information on this QMRA model is given in the model section below. Freezing will not affect the farm practice, and we therefore assume no impact of this intervention on food animal production. We only consider effects on human health.

Ad 3. Controlled indoor husbandry (housing) has drastically reduced the prevalence of *T. gondii* infection in pigs and is considered an important factor in the decrease of seroprevalence observed in human populations [6]. As in most European countries, a quality system is established in the Netherlands for the solid production of pork. Independent organizations monitor and assess working procedures and conditions of animal welfare, quality, and food safety on pig farms. Everyone in the production chain, from farmer to butcher, can participate in this scheme. An European Food Safety Authority (EFSA) working group has suggested the following controlled housing conditions to prevent *Toxoplasma* infection in pigs [18]:

1. keeping the animals indoors
2. keeping cats away from stables, feed, and bedding production and storage, more specifically avoid contact of (feces of) cats with the feed
3. avoiding dead birds and rodents in the feed
4. implementing strict vermin control
5. availability of suitable clean clothing, shoes and protective equipment for employees and visitors; use of separate boots, wheelbarrow and other equipment to avoid bringing soil into the stables
6. providing clean drinking water and blocking access to surface water

These conditions are already partly included in the Dutch quality system (integrated quality control) for pig farms. Serological monitoring can be a tool in detecting farms infected with *T. gondii* [29]. Preliminary results of collected sera showed an average of 2% serological prevalence in pigs. Pigs from organic farms had a prevalence of 3.6% [29]. Also in Italy, anti-*Toxoplasma* antibodies were detected in 2.1% of pig carcasses from intensively reared pigs suggesting for additional on-farm preventive measures [30]. It seems that at high risk farms having seropositive pigs, rodent control is less well performed and many of these farms have outside bulk storage of some feed constituents, which may be accessible for rodents and/or cats [31]. In this SCBA, we assume serological monitoring of pigs at moment of slaughter; seropositive results will lead to an audit and tailor made advice for farmers with for example the imposition of additional rodent control etc. Stricter biosecurity measures might result in a lower prevalence in pigs, and consequently fewer human infections. A side-effect of the better biosecurity measures might be that rodents spoil fewer feed, resulting in lower feed costs.

Step 4 Define and value benefits

Following step 3 where the effects and impacts of the new policies were defined, monetary values (in Euro) have to be assigned to the benefits of the interventions for the Netherlands. Three models are used to assess these effects with respect to number of infections, transmission of *T. gondii,* and burden of disease (see model

section). Using Havelaar's model, and recent European disability weights, health gains of avoided infections in terms of DALYs averted will be estimated [32, 33] and valued in monetary terms. Based on the same outcome tree Mangen et al. estimated the healthcare costs, patients costs, and costs in other sectors (i.e. productivity losses and special education). We will use updated estimates for the year 2016 when estimating savings in healthcare costs, patients cost as well as gain in productivity and savings regarding special education due to less complications of toxoplasmosis [5, 34]. The monetary value of an averted DALY will be taken from Dutch recommendations for SCBA in the social domain in which the value of a Quality Adjusted Life Year is described. We assume that the monetary value of a DALY corresponds with the monetary value of the QALY ranging between 50.000 and 100.000 Euro [15]. The benefits will mostly affect consumers since they experience less *Toxoplasma*-related infections, productivity losses, and special education.

Step 5 Define and value costs

The aim of this step will be to use state of the art valuation methods for carefully costing all resource use involved in the different interventions for the Netherlands. Various approaches will be needed, either using reference values for healthcare costs [35] or for non-health outcomes [15, 36], or using a relevant valuation method (hedonic pricing or contingent valuation). Intervention costs will be estimated based on literature and via field experts. The price for freezing meat is based on market prices; however consumers' preferences on frozen meat are unknown. Therefore, we will perform a Discrete Choice Experiment (DCE), a type of contingent valuation in which preferences of consumers can be assessed. The so-called attributes, items that are important for consumers' decisions, will be taken from the literature and interviews with experts. Using a price proxy, we come close to estimation for the willingness to pay for frozen meat (hence, the willingness to pay for avoidance of infection risk) or the amount of compensation consumers may want for frozen meat (hence, the compensation needed to forego consumption of fresh meat). We can use this estimate to determine the consumers' surplus, the monetary value of the benefit that they accrue from consuming types of meat important in the transmission of toxoplasmosis. The costs will initially affect the pig farmers who pay for the enhanced biosecurity, the cat owners who pay for the vaccination (who are in practice also consumers), and the freezing companies for freezing meat. Serological costs will be paid by the slaughterhouse who, we might assume transfer these costs to the consumer. The same applies for the freezing costs which are spilled-over to the consumer, resulting in slightly higher consumer prices.

Step 6 Assess the net present value

This step considers the summation of the monetized costs and benefits using an Excel model (see model section) to obtain a net present value in euros per intervention measure. It also includes presenting a list of different stakeholders involved and provides detailed insight into the gains and losses for the different stakeholders over time.

Step 7 Conduct sensitivity analyses

Uncertainty is interpreted in a broader sense than merely statistical uncertainty (as represented by 95% intervals). This assessment involves the identification and characterization of all uncertainties of the models using an uncertainty typology [37]. Such a typology helps to characterize uncertainty sources with respect to the place where the source of uncertainties manifested (e.g. study boundaries or in the model structure), the nature of the uncertainty (lack of knowledge or variability) and its range (probabilistic or scenario-based).

Step 8 Present outcomes

Here we present a conclusion of the economic consequences for society with respect to the interventions under study. We report the outcomes of both the main analysis and the sensitivity analyses in agreement with the pertinent guideline for reporting economic evaluations in a transparent and replicable way [38]. This will be done for each of the interventions under review and include a list of the non-monetised costs and benefits and will be complemented by a research agenda to address the most salient knowledge gaps identified by our study.

Because costs (investments) have to be made now and effects will spread out over many years, it is common in an SCBA to use a time horizon that covers as many costs and effects as possible. A discount rate is used because costs and benefits in the future are valued less than in the present. The time horizon used in our model will be 10 years and the discount rate of 3% is conform the advice of the Dutch Ministry of Finance [39].

Table 1. Domains in the society related to the three interventions

Domains	Effects, resulting in changes in costs and benefits	Cat Vaccination	Freezing Meat	Enhancing biosecurity at pig farms
Consumer	• *Toxoplasma* –related patient costs will be assessed	X	X	X
	• Consumer surplus[a]		X	
	• Consumption of meat may change due to change in meat price	X		
	• Costs for cat vaccination			
Human health	• Healthcare costs	X	X	X
	• Morbidity and premature mortality due to toxoplasmosis are expressed in DALYs. All short and long term effects of infection will be included	X	X	X
Producers	• Producer surplus[b]. Since we consider freezing meat as an international intervention the consequences for the producer surplus will be limited as additional costs might spill-through to the consumer.		X	X X X
	• Biosecurity measures will lead to additional costs for pig farmers.			
	• Serological testing in slaughterhouses are additional costs for slaughterhouse that might be put through to the consumer, since we assume that this is an international intervention	X		
	• Toxoplasmosis is an important cause of abortion among sheep. Vaccination of cats at farms can reduce these losses.		X	
	• Facilities at companies will be needed such as freezers, extra surface area, and electricity costs. These facilities will have additional annual recurrent costs (e.g. electricity, maintenance) leading to higher productivity costs for slaughterhouses and the meat processing industry.			
Employees	• *Toxoplasma* –related productivity losses will be assessed	X	X	X
	• Freezing of meat will lead to extra employment.	X	X	
	• The development, campaign, distribution and vaccination of cats will lead to extra employment for veterinarians			X
	• The biosecurity measures will affect employment of pig breeders, and fatteners, but also persons involved in rodent control and persons who perform the audits.			
Social security, pensions	• A change in employment rate will affect social security and pensions.	X	X	X
Education	• Less infections will lead to less special education	X	X	X

[a] Consumer surplus is an economic measure of consumer benefit, which is calculated by analyzing the difference between what consumers are willing and able to pay for a good or service relative to

its market price, or what they actually do spend on the good or service. A consumer surplus occurs when the consumer is willing to pay more for a given product than the current market price.
[b] Producer surplus is an economic measure of the difference between the amount that a producer of a good receives (the market price) and the minimum amount that he or she would be willing to accept for the good. The difference, or surplus amount, is the benefit that the producer receives for selling the good in the market.

The Models

Four different models will be employed to estimate the societal costs and benefits of three different interventions:

1. The QMRA model: relative attribution of meatborne infections in humans

The QMRA makes it possible to quantify the contribution of sheep, pork and beef products to predicted *T. gondii* infections in the Dutch population [6]. The model takes the following steps: a). calculating the number of bradyzoites per infected portion b). estimating the reduction by salting, followed by freezing and finally heating c). estimating the probability of human infection per infected portion using a dose-response relation d). multiplying the outcome of c. with the prevalence of *T. gondii* per livestock species to estimate the probability of infection per portion, and e). multiplying the probability of infection per portion with the consumed number of portions per year to predict the total number of infections per meat product. The previously published model, which uses consumption data from 1997 and 1998, will be updated with new data from the Dutch National Food Consumption Survey. The incidence of human infections without and with intervention (i.e. freezing, improved biosecurity) will be the outcome of this model, and the estimated difference will be the input for the SCBA model. Improving biosecurity measures on pig farms is assumed to result in a lower prevalence in pigs, and consequently in pork. Since prevalence data on the expected effectiveness of improved biosecurity are still in process in a current project, we will assume that the effectiveness of this intervention will result in a lowered prevalence in pigs and anticipate that the lower prevalence in pigs results in a lower number of contaminated pork products. This will lead to a lower number of human toxoplasma cases in the QMRA model.

2. The T. gondii transmission model in cats and their environment

In an epidemiological model *T. gondii* transmission with respect to cat vaccination as described by Lelu et al. [40] will be modified. This is a so called SIR-model, a disease compartment model existing of 3 compartments: S=susceptible, I=infectious and R=recovered. The cat population is split into these three compartments and the prey population (mice) is divided into two compartments, susceptible and infected mice. Because cats are assumed to defecate in the area of their habitat there is a limited surface that can be contaminated by oocysts. Therefore, the environment exists of

two compartments: uncontaminated and contaminated defecating areas. The model will consider different proportions of vaccinated cats, ranging from 0 to 1, to study to what extent these various vaccination levels would reduce the presence of oocysts in the environment. Encountering an infectious oocyst dose is assumed to follow a Poisson process. Therefore, due to the relatively small disease incidence rate, the risk of exposure to any oocyst dose becomes proportional to the number of oocyst present in the environment. By combining a dose-response relation with risk of exposure, we will calculate the expected number of oocyst-driven infections, and how their number is reduced with the various vaccination levels. There is no clear human dose-response relation with regard to oocyst exposure, but data from several animal studies suggest that the response is similar among mice, rats, and pigs [41-45]. We will construct a dose-response relation based on these data as we have no reason to assume that for humans it would be different.

3. Disease burden model

The outcome of infection in terms of diseases caused by *T. gondii* is expressed in DALYs [32], in which a DALY is the sum of the number of years of life lost (YLL) due to diseases caused by *T. gondii* and the number of years lived with a disability (YLD) caused by *T. gondii* (DALY =YLL+YLD). YLL is calculated by summation of all fatal cases due to all health outcomes of *T. gondii* multiplied by the expected individual life span at the age of death. YLD is the sum of outcomes of all cases of which duration of the illness and the disability weights of a disease caused by *T. gondii* are multiplied.

We attribute toxoplasma disease incidence, disease burden and the cost-of-illness to different exposure pathways, based on an expert elicitation study [46]. This study estimated the fraction of all human cases by five major pathways (i.e. food, environment, direct animal contact, human-human transmission, and travel). The foodborne pathway was further subdivided into 11 food groups (e.g. pork, sheep, cattle).

4. The SCBA model (Figure 2).

The SCBA model is implemented as a Microsoft Excel model. The SCBA model synthesizes all available input from the above mentioned models. Results are transformed into overall costs and benefits associated with the interventions considered in this project.

The model includes:

1. the costs of implementing (and enforcing) the three different interventions directed at diminishing exposure to *T. gondii* ;
2. the effects of the interventions on the exposure to *T. gondii* ;

3. the costs and benefits associated with reduced *T. gondii* exposure for the different domains as listed in Table 1.

There are several types of input data to the SCBA model:

1. Pig farm data (number of farms, pigs, tested pigs at slaughter, amount of pig feed);
2. Cat population data (owned cats, stray cats, and cats at farms);
3. Meat consumption data (annual number of portions of risk meat per person, total amount of consumed risk meat);
4. Cost data (costs with respect to cat vaccination, freezing meat, enhancing biosecurity pig farms as well as healthcare costs, productivity losses, and special education costs)
5. Quality of life data (toxoplasma-related disease burden and premature deaths)

The Excel model determines the net costs and benefits of the three interventions by comparing the reference scenario (with no additional policies) with alternative scenarios including reduced *Toxoplasma* transmission by simply calculating the difference between the costs in the alternative and the reference scenario. Net results are presented per intervention: undiscounted per year, discounted for the 10-years period, and also per stakeholder: consumers, freezing meat companies, farmers, slaughterhouses, and government.

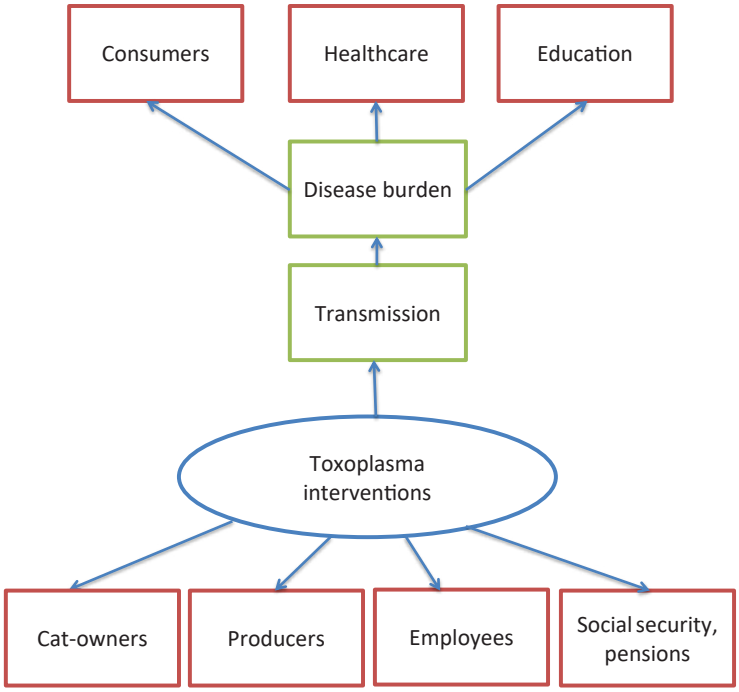

Figure 2. Flowchart of the SCBA-Model

CONCLUSION

This SCBA will provide evidence on the effectiveness and net benefits of promising interventions targeted at toxoplasmosis. In addition, this study will clarify potential barriers and facilitators of implementation. As toxoplasmosis has a high disease burden and prevention is currently limited to health education for specific risk groups, more effort to reduce transmission of *T. gondii* is warranted. As far as we know this study is the first that investigates the long-term social costs and benefits for society of toxoplasmosis related preventive interventions. The SCBA will present which intervention leads to the greatest welfare gains and shows who has to pay for these welfare gains and who ultimately benefits most. Both aspects are of importance for policy measures. Since SCBAs in the field of public health are relatively scarce, the study will contribute to our understanding of the feasibility of SCBAs targeted at other zoonoses with high consequences for society. Other challenging issues during this project will be the unraveling of data targeted at avoidance of double counting in the domains affected, as well as the management of impaired data in the several domains of society for valid calculations in the SCBA.
The research described herewith will present a full picture of socio-economic benefits of preventive strategies against a zoonosis with a high disease burden in order to give decision makers recommendations and guidance to reduce morbidity and mortality of toxoplasmosis.

Impacts:

- *Toxoplasma gondii* infections cause a large disease burden in the Netherlands, with an estimated health loss of 1,900 Disability Adjusted Life Years and a cost-of-illness estimated at €44 million annually.
- Three possible preventive interventions: cat vaccination, freezing meat destined for undercooked consumption, and enhancing biosecurity in pig husbandries bear costs for stakeholders in society that differ from those profiting from benefits.
- In a social cost-benefit analysis (SCBA), all costs and benefits are identified, making explicit which stakeholder pays and who benefits. The results of the SCBA will guide policy making. If the balance of costs and benefits is positive it will lend support to implementation of these preventive interventions.

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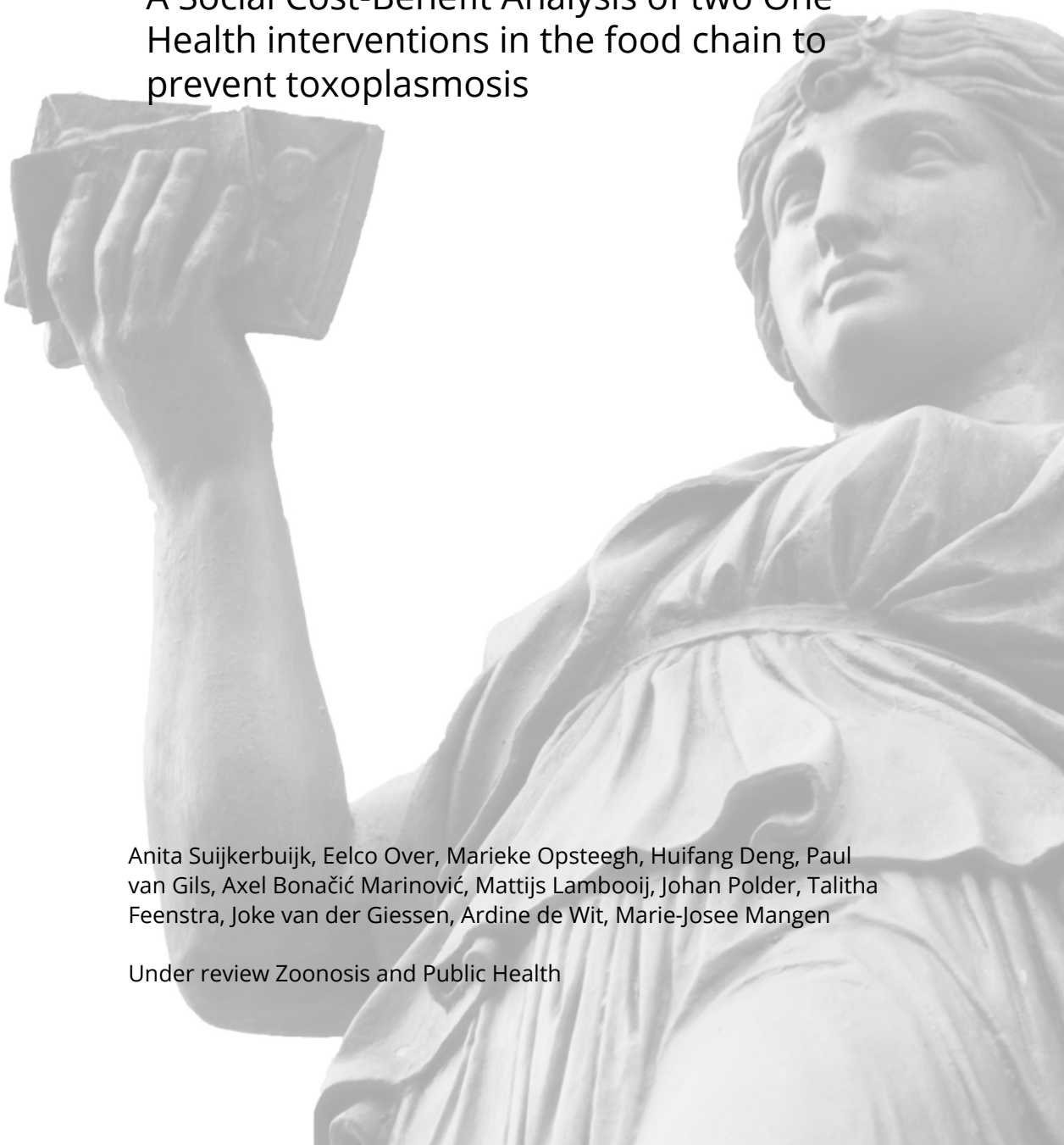
CHAPTER 10

A Social Cost-Benefit Analysis of two One Health interventions in the food chain to prevent toxoplasmosis



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SUMMARY

In the Netherlands, toxoplasmosis ranks third in disease burden among all foodborne pathogens. Therefore, effective and preferably cost-effective preventive interventions are warranted. Freezing meat intended for raw or undercooked consumption and improving biosecurity in pig farms are promising interventions to prevent *Toxoplasma gondii* infections in humans. Putting these interventions into practice would expectedly reduce the number of infections; however, the net benefits for society are unknown. Stakeholders bearing the costs for these interventions will not necessary coincide with the ones having the benefits. We performed a Social Cost-Benefit Analysis to evaluate the net value of two potential interventions for the Dutch society. We assessed the costs and benefits of the two interventions and compared them with the current practice of education, especially during pregnancy. The freezing meat intervention was far more effective than the biosecurity intervention. Despite high freezing costs, freezing two meat products: steak tartare and mutton leg yielded net social benefits in both the minimum as maximum scenario, ranging from €3 million to €12 million for steak tartare and €6 million to €15 million for mutton leg. The biosecurity intervention would result in net costs in all scenarios ranging from €1 million to €2.5 million, due to high intervention costs and limited benefits. From a public health perspective (i.e. reducing the burden of toxoplasmosis) freezing steak tartare and leg of mutton is to be considered.

1. INTRODUCTION

The protozoan parasite *Toxoplasma gondii* is infecting globally a third of the human population and may cause toxoplasmosis [1]. Acquired toxoplasmosis in immunocompetent persons in general occurs without clinical symptoms, while in immunocompromised individuals uncontrolled multiplication of the parasite can have severe and potentially fatal implications, such as encephalitis [2]. During pregnancy, the parasite might be transmitted via the placenta and infect the fetus with varying severity from asymptomatic infection to life-threatening risk for the fetus and infant [2].

Cats are the definitive hosts of *T. gondii*: infected cats spread the parasite via oocysts excreted in their feces infecting warm blooded animals and humans either via direct contact or indirectly via the environment. In livestock, toxoplasmosis mostly goes unnoticed as asymptomatic, except for pregnant sheep that might have an abortion [3]. However, tissue cysts can develop in all organs and tissues including muscles of meat producing animals. Consumption of undercooked or raw meat products is therefore an important exposure pathway to humans. Humans can also become infected by ingestion of cat-shed oocysts via contaminated water or food, or via direct contact with cat feces [2, 4]. Additionally, congenital transmission can occur after primary infection during pregnancy [4].

In the Netherlands, toxoplasmosis ranks third in disease burden among all foodborne diseases with in total 1900 Disability Adjusted Life Years (DALY) in 2016, and additional cost-of-illnesses of €24 million [5]. Given the burden of disease associated with *T. gondii*, effective and cost-effective preventive interventions are warranted. In the Netherlands, with an observed seroprevalence of 18.5% in pregnant women [6], toxoplasmosis prevention is merely targeted at education during pregnancy [7], similar to most other western European countries [8]. However, these interventions do not prevent acquisition of infections in the general population, whereby exposure via food (~56% of all symptomatic *T. gondii* infections in the Netherlands) is considered to be the most important route of infection [5]. Opsteegh et al. suggested - based on a quantitative risk assessment model - that freezing of raw consumed meat products would in the short-term be effective to reduce the burden of disease [7]. Other potential intervention measures are improving biosecurity of meat producing animals to reduce the exposure to oocysts, and improved education to pregnant women and the general public [9].

Putting new interventions targeted at toxoplasmosis into practice would expectedly reduce the number of human infections; however, the net benefits for society are unknown. A Cost-Benefit Analysis, also referred to as a Social Cost-Benefit Analysis (SCBA), expresses human health, animal health and costs in comparable terms (i.e. monetary units) and is therefore the methodology to apply when evaluating the net benefits of a new One Health intervention [10, 11]. An SCBA assesses the costs and benefits for a range of social domains and stakeholders and identifies those who benefit and parties that have to pay for the intervention. Here, we describe an SCBA studying two interventions in the food chain to prevent *T. gondii* infections in humans in the Netherlands.

2. METHODS

2.1 Evaluation of intervention measures

The costs and benefits of implementing two interventions were calculated: freezing meat intended for undercooked and raw consumption and improving biosecurity on pig farms (hereafter called freezing meat intervention and biosecurity intervention, respectively). We assumed that both interventions would be implemented by law, at least at European Union (EU) level, or globally. Following the assumption of large-scale introduction of interventions, trade effects were ignored in the current study.

2.2 Design of the SCBA

The design of this SCBA has been described in [11]. In short, several types of input data, partly derived from primary data, partly derived from models, were incorporated in the SCBA, see Figure 1, and are discussed in more detail hereafter. Not all data were available and assumptions had to be made. We defined a 'minimum scenario' and a 'maximum scenario', using input parameters with least benefits to society and input parameters with most benefits to society, respectively.

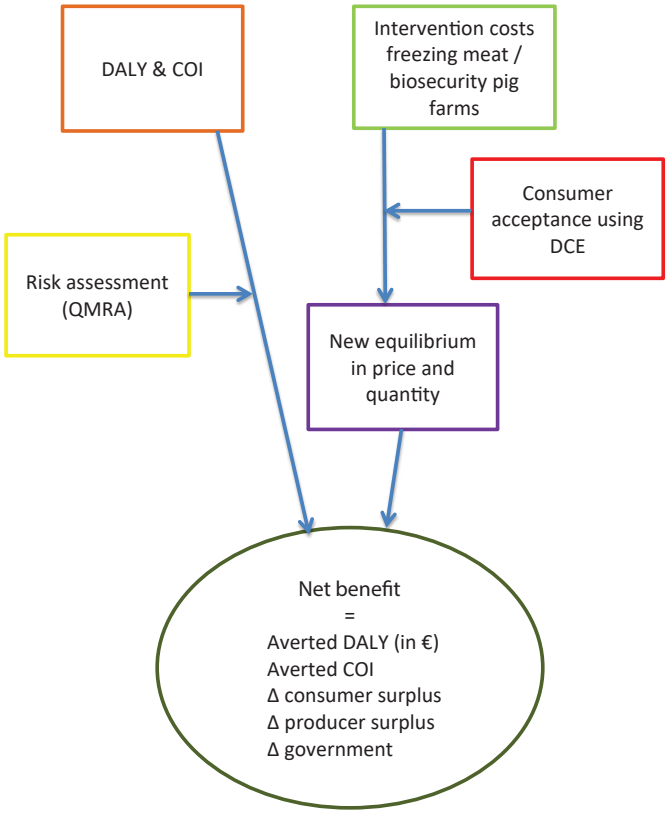


Figure 1 Design of the SCBA

DALY=Disability Adjusted Life Year, COI=cost-of-illness, DCE=Discrete Choice Experiment, QMRA=Quantitative Microbial Risk Assessment

2.3 Estimation of incidence, disease burden, cost-of-illness and attribution to meat

At first, we need *T. gondii*-related incidence, burden of disease (BoD), and cost-of-illness (COI) estimates. Using an incidence- and pathogen-based approach,[12] BoD and COI for toxoplasmosis and associated sequelae were estimated for 2016. Incidence, mortality rates and sequelae of congenital toxoplasmosis were estimated based on described methods and data [13, 14] and updated to 2016 using the number of live births as reported by Statistics Netherlands[15][15][15][15]. Chorioretinitis was the only health outcome considered for acquired toxoplasmosis [13]. The outcome

tree for congenital *T. gondii* infections considers the health outcomes: chorioretinitis, intracranial calcification, hydrocephalus, central nervous system abnormalities, and fetal death [13].

BoD was expressed in Disability Adjusted Life Years (DALY), a metric combining the Years of Life Lost (YLL) due to premature mortality and the Years Lost due to Disability (YLD) [16]. The estimation of the BoD is described in detail in the Appendix file.

Healthcare costs, patient costs, special education costs, and productivity losses due to temporary work absences of patients or their caregivers were considered in the COI estimates. These were based on Mangen et al. [17] and updated to 2016 prices (see Appendix 1).

Using an expert elicitation study, human *T. gondii* cases and associated BoD and COI were attributed to five major exposure pathways (food, environment, direct animal contact, human-human transmission and travel) and eleven food groups [18]. Based on these estimates we calculated the meatborne-attributable fraction of BoD and COI for the year 2016 (see Appendix 1 Table A1).

2.4 Quantitative Microbial Risk Assessment (QMRA)

To determine the reduction in the number of human toxoplasmosis cases following implementation of the two interventions as well as associated BoD and COI, we used output data from an update of the quantitative microbiological risk assessment (QMRA) model for meatborne *T. gondii* infections [19] (see Appendix 2).

2.5 Interventions

2.5.1 Freezing meat intervention

Freezing meat at −20°C for 2 days effectively eliminates infectious *T. gondii* tissue cysts [20]. To limit the intervention costs and increase acceptance by consumers, the freezing meat intervention was considered for meat products with a high relative contribution: spicy steak tartare (also known as filet American), beef steak, lamb chop, and leg of mutton [19]. The numbers of the specific meat products consumed were retrieved from the Dutch National Food Consumption Survey performed in 2010 [21], see Table 1. Total consumption of all meat products was based on a Dutch report [22]. Additional assumptions are described in Appendix 3.

2.5.2 Biosecurity intervention

Controlled housing at pig farms has the potential to prevent *T. gondii* infections of pigs. The biosecurity intervention in this study entails a practical risk-based surveillance program on top on the currently established quality assurance and monitoring at pig farms in the Netherlands. When *T. gondii* seropositive pigs are detected during screening at the slaughterhouse, the fattening farm is assumed to conduct additional

or intensified on-farm intervention measures to control toxoplasmosis. This includes an additional audit and additional measures to limit exposure to the risk factors identified (see Appendix 3 for additional information), resulting in additional costs of €400 (minimum) and €4000 (maximum)/affected farm (Table 1) and an improved rodent control resulting in reduced production costs (Table 1).

Table 1. Input parameters for the economic model

Description	Point estimator	Unit	Min	Max	Source
BoD and COI attributable to meatborne toxoplasma infections in 2016					
DALYs by toxoplasmosis via meatborne infections[a]	326				Estimated*
DALY value	50,000	€			[23]
COI of toxoplasmosis via meatborne infections[a]	7.9	million			Estimated*
Freezing meat intervention					
Pork meat consumption[b]	37.4	Kg			[22]
Beef meat consumption[b]	14.2	Kg			[22]
Mutton meat consumption[b]	1.2	Kg			[22]
Steak tartare portion size[d]		g	11	53	[21]
No of portions steak tartare[cd]	330	million			[21]
Meat percentage steak tartare/portion[d]		%	50.84	73.96	QMRA
Steak (beef) portion size		g	44	224	[21]
No of steak portions[d]	14	million			[21]
Lamb chop portion size		g	28	214	[21]
No of lamb chop portions[d]	3	million			[21]
Leg of mutton portion size	158	g			[21]
No of leg of mutton portions[d]	0.8	million			[21]
Price elasticity meat	-0.7				[24]
Freezing costs/kg		€	0.10	0.15	[e]
Biosecurity intervention					
No of fattening pig farms	4,000				[25]
No fattening pigs/farm	1,450				[25]
No fattening pigs slaughtered/year	15,034,000				[25]
Fattening pigs/lorry when delivered	200				[e]
No of fattening pigs tested/lorry			1	10	[e]
Cost serological test	5	€			[26]
Positive tested farms[f]		%	12	20	[27, 28]
Annual costs rodent control/pig farm		€	400	4000	[g]
Feed cost/fattening pig/year[f]	65	€			[25]
Less spilled feed		%	0	0.1	Assumption
Costs for an additional audit (4 hours)	132	€			[29][d]
Effectiveness	1	%			[30]

*[a] discounted at 3% a large part of the associated BoD (in particular the sequelae) and costs do not occur in the year of the infection itself, but happen later in life, [b]per person and year in the Netherlands, [c]steak tartare also known as filet American, [d]consumed in the Netherlands per year, [e]personal communication VION Food group, [f]assumption based on quadrupling the % of positive tested farms, based on the % of infected pigs in a recent study which is four times higher than found in a previous study, [g]personal communication branch organisation of rodent control, averaged 2013-2015, BoD= Burden of Disease, COI= Cost-of-Illness, DALY=disability adjusted life year, *We used the average as point estimator, for more details see Table A1 and Table A2 in Appendix 1.*

2.6 Discrete Choice Experiment (DCE)

Freezing and thawing of meat will result in safer meat but might impact the physical quality of meat (e.g. moisture loss, and changes in color, and pH) [31-34] potentially influencing consumers' attitudes. Preference of meat consumers for different attributes of frozen meat were studied in a Discrete Choice Experiment (DCE), (Lambooij et al submitted, see Appendix 4). As consumers demonstrated to have a preference for fresh, non-frozen meat in the DCE, the willingness-to-pay was negative (Table 2).

2.7 Stakeholders

The stakeholders included in this SCBA were consumers (meat consumers, toxoplasmosis patients), producers (farmers, slaughterhouses, freezing companies, meat processing industry, retailers), and government (including health care and special education). Both interventions would affect consumers: fewer human *T. gondii* infections would result in better health (fewer DALYs lost), lower patients' costs and fewer productivity losses. Due to additional intervention costs, meat prices would change. The negative WTP estimates in combination with extra costs due to freezing resulted in a double decline in consumers' demand for these high-risk meat products. The confidence intervals around the WTP estimates comprised the '0', therefore, no change of WTP was considered in the maximum scenario. As consumers' preferences in experiments may differ from their behavior in daily life [35] only 50% of WTP calculations were taken into account in the minimum scenario. The assessment of the consumer surplus (an economic measure of consumer benefit) is explained in Appendix 4.

The interventions will affect the producer surplus, as higher prices of meat will influence consumers' demand for meat. As we assume perfect competition among freezing meat companies and slaughterhouses, the supply curve is horizontal and there is no difference between market price and supply curve; therefore, we do not take the producer surplus (the benefit for selling the product, see Appendix 4 for explications) of the freezing meat intervention into account [23]. The same applies to the slaughterhouses in the biosecurity intervention. Since only small changes in the supply of meat throughout the meat chain are expected, we assumed that changes in supplies of meat had no effect on the profit of any of these stakeholders (i.e. slaughterhouses, transport companies, freezing industries, food retailers) in the Netherlands. Additional interventions costs were assumed to be passed through to the consumer, so that welfare changes for these stakeholders were assumed to be zero. Only in case of the biosecurity intervention, affected pig farmers will experience

a negative welfare effect. The incurred costs for improving biosecurity cannot be fully compensated by the additional benefits (fewer feed costs) and cannot be passed on to consumers, since they will involve only a selection of all pig farmers.

The final stakeholder is the government who, with decreasing number of *T. gondii* infections will incur less healthcare costs and less special education costs. However, when farmers have a lower income due to toxoplasma-related investments, and the freezing meat intervention leads to a lower production of meat, the government will receive less tax revenue. As lower tax revenues will be compensated by consumers in higher taxes elsewhere, we did not include these in our study.

2.8 Economic evaluation

All available input for the SCBA (see Table 1 and 2) was synthesized using a Microsoft Excel model. For the reference scenario, we assumed existing preventive measures to be unchanged and no changes in incidence or prevalence of *T. gondii* infections over time. The model estimates the net value by comparing the reference scenario with the two alternative scenarios including reduced *T. gondii* transmission by calculating the difference between the costs and benefits in the alternative and the reference scenario. The net values of costs and benefits are presented per intervention per year, per stakeholder, using DALY and COI estimates. The monetary value of a DALY was assumed to be €50,000 [23]. All costs were expressed for the year 2016, and we indexed price levels using Dutch consumer price indices as provided by Statistics Netherlands.

2.9 Sensitivity and scenario analyses

For both interventions, we performed different scenario analyses. We varied the baseline value of a DALY from €50,000 (baseline) to € 100,000/ DALY for both interventions [23].

For the freezing meat intervention, we calculated results with similar bradyzoites concentration for all meat products, so including beef products, in the QMRA (versus 100 times lower for beef in baseline). Furthermore, we did not assume perfect competition between the freezing companies and in this case included the producer surplus in the model. We varied the meatborne attribution (44% of all toxoplasmosis infections in the baseline analysis) with a 50% higher and 50% lower estimate and we varied the annual BoD (expressed as DALYs/year) and COI in the population using the 2.5% and 97.5% (748 DALY/year and €18.3 million/year in baseline versus 506

DALY/year and €5.1 million/year (2.5%) and 1063 DALY/year and €53.2 million/year (97.5%), see Table A.1 in Appendix 1). Lastly, we combined the 50% higher meatborne attribution estimate with a scenario of 1143 DALYs/year and €53.2 million/year.

For the biosecurity intervention, we changed the attribution of pig meat products to toxoplasmosis as provided by the QMRA with attribution of pig meat products based on expert elicitations (66% versus 14% in the baseline). In addition, because the effects and the endurance of effects in the biosecurity measure are mostly unknown, we varied effectiveness in additional sensitivity analyses to 10% effect (versus 1% in baseline), and endurance of 5 and 10 years were used (versus 1 year in baseline), whereby using a 3% discount rate [23].

3. RESULTS

3.1 Freezing meat products

The products steak tartare, lamb chops, leg of mutton, and beef steaks are considered to attribute a risk for meatborne *T. gondii* infection according to the QMRA and the amount of these meat products to be frozen is shown in Table 2. Depending on the assumptions on portion sizes this varies from 8,100 tons up to 43,700 tons for all five products annually for the Netherlands. QMRA results show that freezing these meat products would lead to a decline of 82% of all meatborne *T. gondii* infections and its corresponding DALYs, ranging from 215 to 322 DALYs averted.

Table 2. Attribution to meatborne toxoplasmosis, meat to be frozen, DALYs averted, and WTP for the freezing meat intervention

	Attribution to meatborne toxoplasmosis (%)	Meat to be frozen (tons)		DALYs averted (N)		WTP/kg
		Min[a]	Max[b]	Min[a]	Max[b]	
Steak tartare	31.56	887.7	6,502.1	82.32	123.49	-€1.64
Beef steak	12.23	6,254.8	32,072.3	31.91	47.86	-€1.13
Lamb chop	0.30	84.7	654.5	0.78	1.17	€0.05
Leg of mutton	38.19	70.8	177.5	99.59	149.38	€0.05
Total	82.28	7298	39406.4	214.6	321.9	

[a] using least economically favorable input parameters, [b] using most economically favorable input parameters, [c] preferences for leg of mutton were not assessed by DCE, we assumed the same WTP as for lamb chop, WTP=willingness-to-pay

Table 3 presents costs and benefits for freezing the four meat products from Table 2. Using the least economically favorable input parameters in the model (the 'minimum scenario') the intervention would lead to annual net benefit of €3.0 million and €6.0 million for respectively steak tartare and leg of mutton, but would not render benefits for the other two products. Using the most favorable input parameters (the 'maximum scenario') the intervention would lead to annual total net benefits for all four meat products ranging from €0.1 million for lamb chops to €15 million for leg of mutton. Monetized DALYs contribute most to benefits of the freezing intervention, followed by avoided healthcare costs (Table 3). Freezing costs are lowest for leg of mutton (€0.007 to €0.027 million) and highest for beef steak (€0.6 to €4.8 million) in line with the volume consumed in the Netherlands. Freezing beef steak would result in the lowest consumer surplus (ranging from -€0.6 million to -€2.7 million).

Table 3. Net benefits for the stakeholders involved with the freezing meat interventions in 2016 (€)*1000

	Steak tartare		Beef steak		Lamb chop		Leg of mutton	
Stakeholders[a]	**Min**	**Max**	**Min**	**Max**	**min**	**max**	**min**	**max**
Freezing companies[b]	-975	-89	-4,811	-626	-98	-9	-27	-7
	+975	+89	+4,811	+626	+98	+9	+27	+7
Consumers								
Freezing costs	-975	-89	-4,810.9	-626	-98	-9	-27	-7
DALYs averted	4,116	6,174	1,595.3	2,393	39	59	4,979	7,469
Patient costs	4.8	9.5	1.9	3.7	0.0	0.1	5.8	12
Productivity losses	79	143	30	55	0.7	1.4	95	173
Consumer surplus	-907	-112	-2,722	-622	-10	-8	-4	-3
Government								
Healthcare costs	726	5986	281	2,320	7	57	878	7,241
Special education costs	1.3	56.7	0.5	22.0	0.0	0.5	1.6	68.6
Net benefits[c]	**3,044**	**12,169**	**-5,623**	**3,546**	**-61**	**101**	**5,930**	**14,964**

Min: using input parameters that result in economically least favorable outcomes, Max: using input parameters that result in economically most favorable outcomes, [a] we assumed no change in costs for farmers and retailers [b] Intervention costs occurring in freezing companies will be put through to consumer (so at slaughterhouse level it will be zero), [c] note: a negative number corresponds with costs, a positive number with savings

3.2 Improving biosecurity on pig farms

Improving biosecurity on pig farms results in costs ranging from €1.1 million in the 'maximum scenario' to €2.5 million in the 'minimum scenario' as costs easily outweigh the benefits of the intervention (Table 4). In both scenarios, farmers have the highest costs by implementing rodent control. In addition, consumers incur costs

as serological costs paid by slaughterhouses would be put through to consumers; leading to higher consumer prices. Most benefits are realized by monetized DALYs, ranging from 53 to 36 DALYs averted, and from avoided healthcare costs.

Table 4. Net benefits for the stakeholders involved with the biosecurity interventions in 2016 (€)*1000

	Biosecurity intervention	
Stakeholders	**Min**	**Max**
Producers		
Farmers	-2,103	-701
Slaughterhouses[a]	-439	-482
	+439	+482
Consumers		
Intervention costs slaughterhouses	-439	-482
DALYs averted	18	27
Patient costs	0.0	0.0
Productivity losses	0.3	0.6
Government		
Healthcare costs	3	26
Special education costs	0.0	0.2
Net benefits[b]	**-2,522**	**-1,129.7**

Min: using least economically favorable input parameters, Max: using most economically favorable input parameters, [a]Intervention costs occurring in slaughterhouses will be put through to consumer (so at slaughterhouse level it will be zero), [b] note: a negative number corresponds with costs, a positive number with savings

3.3 Sensitivity analyses

Results of the sensitivity and scenario analyses are presented in Table 5. In all cases, freezing steak tartare and leg of mutton would still lead to savings to society. Using an equal number of bradyzoites concentration in beef had the highest impact on results, followed by increasing the DALY value to €100,000, both making freezing steak tartare even more favorable. Increasing the meatborne attribution estimate with 50% in combination with a higher annual burden (expressed as higher number of DALYs/ year and COI/year) also resulted in more net benefits to society. Assuming no perfect competition between the freezing companies did hardly influence results.

A higher DALY value and increasing the effectiveness of the biosecurity intervention to 10% instead of 1% would not result in net benefits for society. In addition, when an attribution of pig meat products to toxoplasmosis was based on expert elicitations (66%) instead of the pig meat attribution from the QMRA of 14%, it did not result in net benefits for society (Table 5). Results for higher effectivity that lasts for more than one year are presented in Appendix 5.

Table 5. Results sensitivity and scenario analysis, net benefits in €1000

Freezing meet intervention				
	Min	Relative change compared to main analysis %	Max	Relative change compared to main analysis %
Main analysis				
Steak tartare	3,044		12,169	
Beef steak	-5,623		3,546	
Lamb chop	-61		101	
Leg of mutton	5,930		14,964	
DALY valuation €100,000				
Steak tartare	7,161	135	18,343	51
Beef steak	-4,028	-28	5,939	67
Lamb chop	-22	-64	159	58
Leg of mutton	10,909	84	22,423	50
Assuming equal dose of bradyzoites in all meat products				
Steak tartare	10,623	249	31,196	156
Beef steak	-5,391	-4	4,128	16
Lamb chop	-106	72	-10	-110
Leg of mutton	281	-95	772	-95
No perfect competition between freezing companies				
Steak tartare	2,964	-3	12,147	0
Beef steak	-5,844	4	3,421	-4
Lamb chop	-63	3	99	-2
Leg of mutton	5,929	0	14,953	0
Meatborne attribution 50% lower (22% versus 44% in baseline)				
Steak tartare	2,639	-13	9,072	-25
Beef steak	-5,780	3	2,346	-34
Lamb chop	-65	6	71	-29
Leg of mutton	5,440	-8	11,206	-25
Meatborne attribution 50% higher (66% versus 44% in baseline)				
Steak tartare	3,450	13	15,267	25
Beef steak	-5,466	-3	4,747	34
Lamb chop	-58	-6	101	0
Leg of mutton	6,420	8	14,954	0
Lower estimate (2.5%) for BoD and COI in the population				
Steak tartare	1,896	-38	8,147	-33
Beef steak	-6,244	11	1,987	-44
Lamb chop	-77	25	63	-38
Leg of mutton	3,992	-33	10,088	-33
Higher estimate (97.5%) for BoD and COI in the population				
Steak tartare	5,100	68	17,330	23
Beef steak	-4,827	-14	5,546	31
Lamb chop	-42	-32	150	26
Leg of mutton	8,416	42	21,196	23

Freezing meet intervention				
	Min	Relative change compared to main analysis %	Max	Relative change compared to main analysis %
Meatborne attribution 50% higher & higher estimate (97.5%) for BoD and COI in the population				
Steak tartare	5,674	86	21,719	78
Beef steak	-4,604	-18	7,247	104
Lamb chop	-37	-41	191	90
Leg of mutton	9,111	54	26,506	77
Biosecurity intervention[a]				
Main analysis	-2,522		-1,130	
DALY valuation €100,000	-2,504	-1	-1,103	-2
Effectiveness 10%	-2,337	-7	-652	-42
Attribution of pig meat products based on expert elicitations	-2,469	-2	-1,007	-11

[a] additional sensitivity analyses are presented in figures in the appendix file, BoD= Burden of Disease, COI= Cost-of-illness

4. DISCUSSION

In this SCBA we compared the costs and benefits of adding two interventions targeted at reducing the *T. gondii*-related BoD to current practice which is focused solely on educating pregnant women and other risk groups. The intervention related to freezing high-risk meat (products) is far more effective in reducing BoD than the intervention to improve the biosecurity on pig farms. Freezing steak tartare and mutton leg yield annual net social benefits in both the minimum and maximum scenario, ranging from €3 million to €12 million for steak tartare and €6 to €15 million for leg of mutton. These results remained robust in sensitivity analysis. The estimated risk of infection per portion is low (2.35E-05) however in the Netherlands, steak tartare is highly appreciated as a meat spread for sandwiches. Leg of mutton is not a meat product traditionally eaten in the Netherlands, but in this case the risk of infection per portion is high (1.2%) due to the high prevalence and bradyzoite concentration in sheep and the heating distribution that allows for the possibility of undercooking.

The DCE performed in this study revealed that consumers do not prefer to buy industrially frozen (and thawed) meat. Additional information for consumers seems necessary to convince them to buy 'toxoplasma-safe' meat. On the other hand, half of the meat intended for producing steak tartare and similar meat products is currently frozen, and consumers do not seem to have knowledge on this fact nor notice a difference between the two variants of the product. The intervention related

to improve biosecurity on pig farms would result in net costs in all scenarios ranging from €1 to €2.5 annually. These results are driven by high costs for farmers and consumers and by an assumed 1% effectivity of the intervention with DALYs averted and associated benefits being low. This could be influenced by the already high level of biosecurity on pig farms in the Netherlands since the larger part of pig production is under controlled housing conditions [36].

Although vaccination of the cat population was identified as being a potential effective intervention [11], there is yet no vaccine available and the feasibility of such an intervention is questionable (Appendix 6, Bonacic Marinovic et al. in preparation), therefore cat vaccination was not further studied in the current SCBA.

This SCBA reveals several strengths and limitations. As far as we know, only Van Asseldonk et al evaluated the costs and benefits of an intervention for toxoplasmosis by improving biosecurity at pig farms, considering relevant stakeholders [37].
Strengths of the current study are the incorporation of updated information of attributing risk meat products for obtaining toxoplasmosis and the assessment of consumers' preferences towards frozen meat. The main limitations of the study are the uncertainty of incidence of *T. gondii* infections and the corresponding BoD and COI, the attribution to the main pathways of toxoplasmosis and to the meat products, and the lack of effectiveness data applied to the biosecurity intervention. Currently, we assumed effectiveness of 1%. If the effectiveness turns out to be more than 1%, that would lead to a higher net value for the biosecurity intervention in this SCBA. The intervention, therefore, might be more favorable than we can conclude from our best estimates, although the scenario analysis indicates that increasing biosecurity would still result in net costs at 10% effectivity. By freezing and thawing meat, additional steps are introduced in the meat chain, with a risk of introducing additional hazards with a negative impact on human health. On the other hand, freezing may also negatively impact the viability of other foodborne pathogens such as *Campylobacter* [38]. Both facts were not considered in the current study.

A main assumption was that the interventions would be imposed by law in the European Union (at the least), and that trade/market distortion could be ignored. However, if this assumption does not hold, our results are no longer valid. In the Netherlands around 75% of all meat is exported, mostly to EU countries [39].

Regarding congenital infections, we only included productivity losses for caregivers, not for children born with these complications, based on a French study [40]. In France, contrary to the Netherlands, screening during pregnancy is implemented,

with possibly a different population of congenital toxoplasma cases. Furthermore, DALY estimations were based on fetal losses from only 24th week of gestation and onwards. Finally, productivity losses for fetal and neonatal deaths were excluded from our calculation based on Dutch SCBA guidance [23]. This differs from other cost-benefit analyses (e.g. [41]) and other SCBA guidelines.
Price elasticity of meat was not specifically targeted at the separate meat products, and consumers shifting to consuming other meat products with a different predicted probability of causing *T. gondii* infection [42, 43] were disregarded.

To evaluate the full economic impact of interventions to control a zoonosis, the influence on the human and animal health sector need to be integrated for decision makers in all sectors [10, 44]. We performed an SCBA to assess interventions targeted at the prevention of toxoplasmosis and gained insight in a range of mechanisms that influenced total net monetary results. Using conservative input parameters for the biosecurity intervention in the SCBA model, the intervention would result in high net costs for farmers and consumers, with only limited positive effects for consumers. On the contrary, freezing high risk meat products would result in net benefits for society. More specifically, freezing steak tartare and leg of mutton are expected to be efficient options to reduce the burden of toxoplasmosis and increase food safety.

APPENDIX

Appendix 1 - Incidences, Burden of disease (BoD) and cost-of-illness (COI)

BoD methods

BoD was expressed in Disability Adjusted Life Years (DALY), a metric combining the Years of Life Lost (YLL) due to premature mortality and the Years Lost due to Disability (YLD) [16]. YLL is calculated by multiplying the number of deaths due to congenital toxoplasmosis with their remaining life expectancies in years (i.e. 85.68 years [45]), whereby only fetal losses starting from 24 weeks of gestation were taken into account [13]. YLD was derived by accumulating over all cases and all health outcomes the product of the duration of the illness and the disability weight of a specific disease (scale ranging from 0 (perfect health) to 1 (dead)). We used the DALY estimation recently updated with European disability weights [46], for more details see Mangen et al [5, 17]. Non-fatal symptomatic *T. gondii* infections resulted in life-long remaining symptoms [13]. We assumed that the monetary value of a DALY corresponds with the monetary value of the Quality Adjusted Life Year (QALY) with a Dutch standard value of €50.000 [23].

COI calculations

Acquired and congenital chorioretinitis was assumed to never result in blindness in both eyes [47, 48]. Blindness in one eye, however, seldom results in work inability, and these costs were disregarded. The long-term implications of non-fatal congenital toxoplasmosis with respect to special education and temporary productivity losses of caregivers were included. In addition, therapeutic help (between age 2 and 7 years), allowing them to catch up with their peers and neurological examination up to 20 years of age was also included [49, 50]. Following Berrébi et al. we assumed that academic and cognitive development in children with a chronic manifestation of toxoplasmosis would be the same as that of non-infected children at adulthood [40], and therefore the long-term production losses of these children were assumed to be negligible. Finally, we did not include production losses associated with premature mortality as recommended by the Dutch guidance on SCBA [23].

Table A1 Attribution of toxoplasmosis to main pathways in the Netherlands, 2016 – Average and 95% uncertainty intervals in brackets[a]

	Food	Whereof meatborne	Environment	Human	Animal	Travel-related[b]	Total
Incidence	428 (256-638)	**334** (200-497)	278 (166-414)	6.9 (4-10)	19 (11-29)	35 (21-53)	767 (459-1143)
Deaths	6.7 (4.3-11)	**5.3** (3.3-8.3)	4.4 (2.8-6.9)	0.1 (0.1-0.2)	0.3 (0.2-0.5)	0.6 (0.4-0.9)	12.1 (8-19)
DALY per year							
undiscounted (0%)	1,062 (711-1530)	**827** (554-1192)	689 (462-992)	17 (11-25)	48 (32-69)	88 (59-126)	1,902 (1275-2741)
discounted (3%)	418 (282-560)	**326** (220-462)	271 (183-385)	6.7 (4.6-9.6)	19 (13-27)	34 (23-49)	748 (506-1063)
Cost-of-illness[c]	10.2 (2.8-29.7)	**7.9** (2.2-23.1)	6.6 (1.8-19.3)	0.2 (0.05-0.5)	0.5 (0.1-1.3)	0.8 (0.2-2.4)	18.3 (5.1-53.2)

This table is adapted from Mangen et al [5]. More details on incidence, deaths, DALYs and COI, and the underlying assumptions and uncertainty ranges are presented in Mangen et al. [5]. Note they used a 1.5% discount rate for DALYs and 4% for costs.

[a] Values represents the uncertainty w.r.t. incidence estimates and health outcomes, but not the uncertainty w.r.t. attribution, here we had used the most likely values as estimated by experts (for details see Havelaar et al [18].

[b] Travel-related infections were acquired outside the Netherlands by one of the four major route of transmissions, i.e. food, environment, direct animal contact and human-human transmission.

[c] M€ per year, discounted at 3% and expressed in 2016 euros

Table A2 Annual average costs for patients, healthcare, special education, and productivity losses due to *T. gondii* infection in the Netherlands, 2016 (*1000 in 2016 euros)[a]

	Patients	Healthcare	Special education	Productivity losses
Undiscounted				
Beef and lamb	11	5480	33	174
Pork	25	12012	71	382
Poultry	2	1149	7	36
Dairy	2	1101	7	35
Fish & shellfish	2	885	5	28
Produce	3	1388	8	44
Other foods	1	550	3	17
Humans and animals	3	1364	8	43
Total	49	23929	142	760
Discounted at 3%				
Beef & Lamb	11	2202	24	104
Pork	25	4828	25	228
Poultry	2	462	5	22
Dairy	2	442	5	21
Fish & shellfish	2	356	4	17
Produce	3	558	6	26
Other foods	1	221	2	10
Humans and animals	3	548	6	26
Total	49	9617	103	454

[a] The reference scenario in the SCBA, This table is adapted from Mangen et al [5]. These authors estimated the costs for the year using a 0% and 4% discount rate. For more details and the uncertainty range, see Mangen et al. [5]

Appendix 2 – Quantitative Microbial Risk Assessment (QMRA)

The Quantitative Microbial Risk Assessment (QMRA) model calculates the predicted number of human *T. gondii* infections and the relative attribution of different meat products using meatborne exposure data including food consumption data of the Netherlands [21]. The previously published QMRA for toxoplasmosis [19] was updated with:

- information from the Dutch National Food Consumption Survey in 2007-2010 [21],
- with a lower bradyzoite concentration of *T. gondii* for beef products,
- and a new estimate for the effect of salting on *T. gondii* viability

and are described in detail in Deng et al. (in preparation).

The results of the updated QMRA model were used to simulate the number of meatborne *T. gondii* infections for the current situation as well as after implementation of the two interventions. The relative attributions to the total number of predicted infections in the QMRA, were used to attribute the total meatborne BoD and COI to specific meat products.

Appendix 3- Assumptions regarding the interventions

Freezing meat intervention

According to several people from the Dutch meat industry who were interviewed, 50% of all steak tartare is currently already produced from meat that was frozen previously. Therefore, for steak tartare, total future freezing costs were calculated for the remaining 50%. Total capacity of freezing companies for freezing meat in the Netherlands was assessed at 4,500,000 m^3 (Davey Gerlings, Nekovri, personal communication 9-28-2017). Given the low quantity of meat to be frozen (45-252 m^3/day) we assumed that an investment neither in new freezing installations, nor in transport facilities would be required. We further assumed that both freezing and transport companies would realize the same profit independent of the type of good that is being frozen or transported. Freezing and thawing was assumed to be implemented at the freezing company, with partly additional transport from slaughterhouse to freezing company. Additional freezing and transport costs were estimated to be €0.10-€0.15 per kg (Table 1). Presuming that the intervention would be implemented by law, the intervention costs were assumed to be passed through to the consumer in the form of a higher consumer meat price.

Biosecurity intervention

In the Netherlands, working procedures including quality assurance and monitoring to improve food safety are already established at pig farms [51][51][16]. The biosecurity intervention in this study entails a practical risk- based surveillance program on top on the currently established quality assurance and monitoring at pig farms in the Netherlands. When *T. gondii* seropositive pigs are detected during screening at the slaughterhouse, the fattening farm is assumed to conduct additional or intensified on-farm intervention measures to control toxoplasmosis. This includes an additional audit for the presence of risk factors and recommendations to the pig farmer how to limit exposure to these risk factors. Interventions on pigs farms such as additional covering of feeders and storage of feed; extra measures to control rodents and extra measures to exclude cats from the stables were taken into account in our study [52]. All these measures resulted in additional costs to be incurred by the affected farmers (€400 (minimum) and €4000 (maximum) based on information from the branch organisation of rodent control, Table 1. As *T. gondii* infections are usually asymptomatic in pigs [53] the intervention was expected not to improve animal health, growth or reproduction figures. However, improved rodent control was assumed to result in reduced feed spillage (0% (minimum) and 0.1% (maximum)), and consequently reduced production costs for the farmer concerned (Table 1).

The number of farms (4000) and pigs (around 15 million) were taken from agrimatie.nl [25], the number of infected pigs (2%) and farms (16%) was based on the literature [27, 28] (Table 1). In the absence of scientific evidence on the effectiveness of existing biosecurity interventions for *T. gondii* prevalence on pig farms, we assumed, similar to Mangen et al., a conservative effectivity of the intervention of 1% [30]. That is, in 1% of the infected and detected farms, the intervention will eliminate *T. gondii*, and the farms remain *T. gondii* free for the duration of 1 year. Serology costs (Table 1) are paid by the slaughterhouses and were assumed to be passed through to the consumer as a higher meat price.

Appendix 4 – Glossary

Discrete Choice Experiment (DCE)

A DCE is a stated preference survey technique that enables the calculation of Willingness-to-Pay (WTP) for different aspects of frozen meat, such as food safety, expiration date, quality of meat, production method, and price [54]. In a DCE-model, the probability that a person chooses a particular alternative is estimated. Consumers' preferences are provoked by quantifying the relative importance of freezing and other characteristics of consuming risk meat products. Therefore, 671

(response=75%) respondents participating in a panel study were invited to complete a set of online tasks by choosing between two or more scenarios when buying the toxoplasma-related risk meat products identified in this SCBA: beef steak, lamb chop, and steak tartare. The description of the meat product in these tasks was based on its characteristics or 'attributes', i.e. price, type of production, expiration date, quality, and either or not freezing during production. The results indicate to which extent the values of the levels of the attributes determine the preference of respondents for a certain scenario. By dividing the coefficients of the attribute that expressed the meat to be frozen by the price parameter, the change in WTP between frozen and unfrozen meat was estimated. The WTP was estimated for certain classes of consumers. For the SCBA we used the weighted mean of the WTP estimates.

Consumer surplus

We assessed the consumer surplus of freezing meat, which is an economic measure of consumer benefits: in practice the difference between what consumers are willing to pay for a product and the current market price.

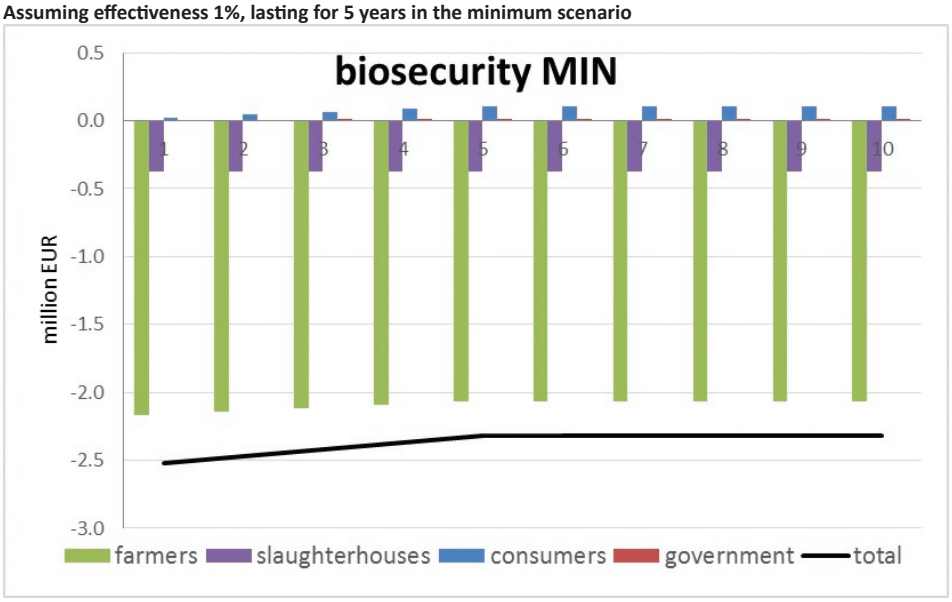
Using a linear demand equation (based on a price elasticity of -0.7 and current market prices at Dutch supermarkets) the consumer surplus can be estimated as the area between the demand curve and the current market price in a plot of price versus quantity.

Producer surplus

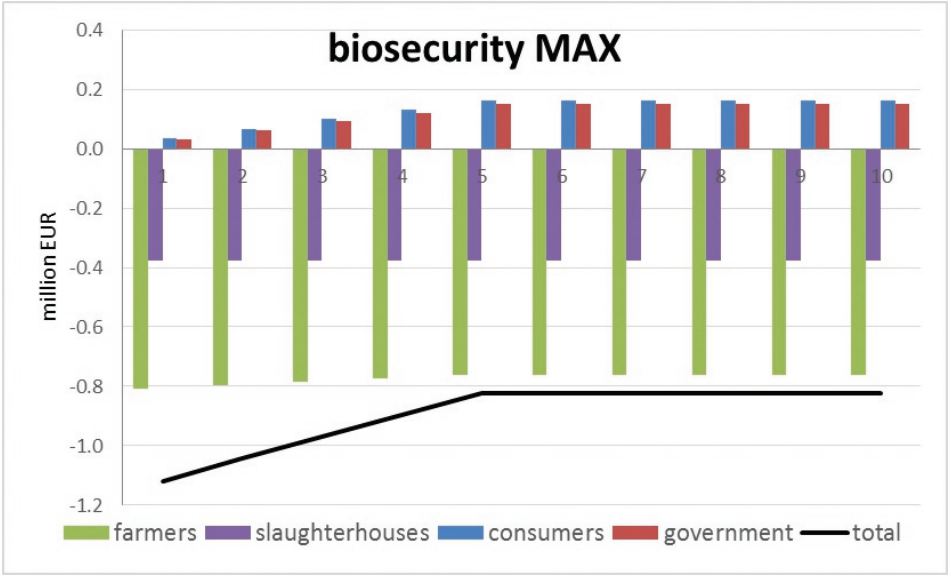
The producer surplus represents the difference between the amount a producer of a product receives i.e. the market price and the minimum price at which the producer still would be willing to sell the product, in short the benefit for selling the product.

Appendix 5 – Additional sensitivity analyses for the biosecurity intervention

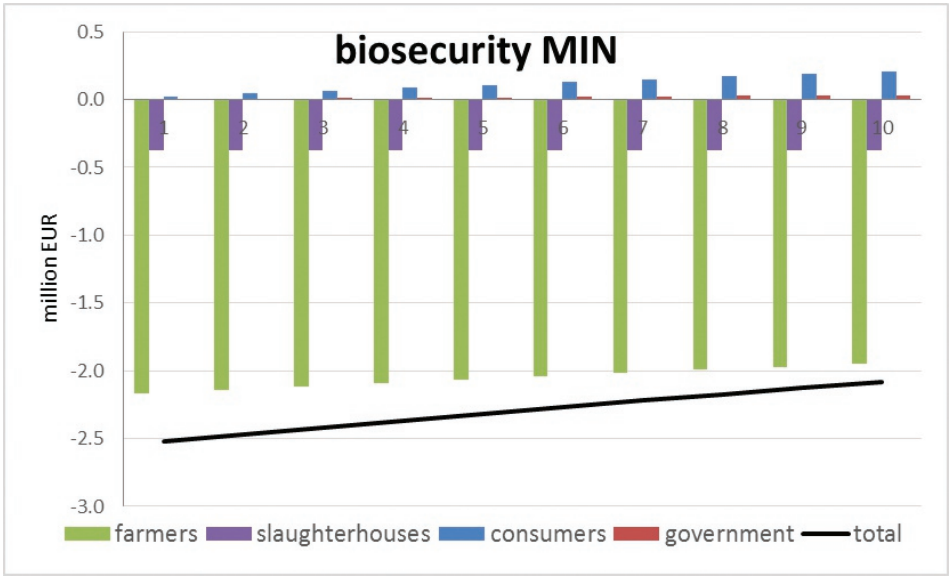
Assuming effectiveness 1%, lasting for 5 years in the minimum scenario



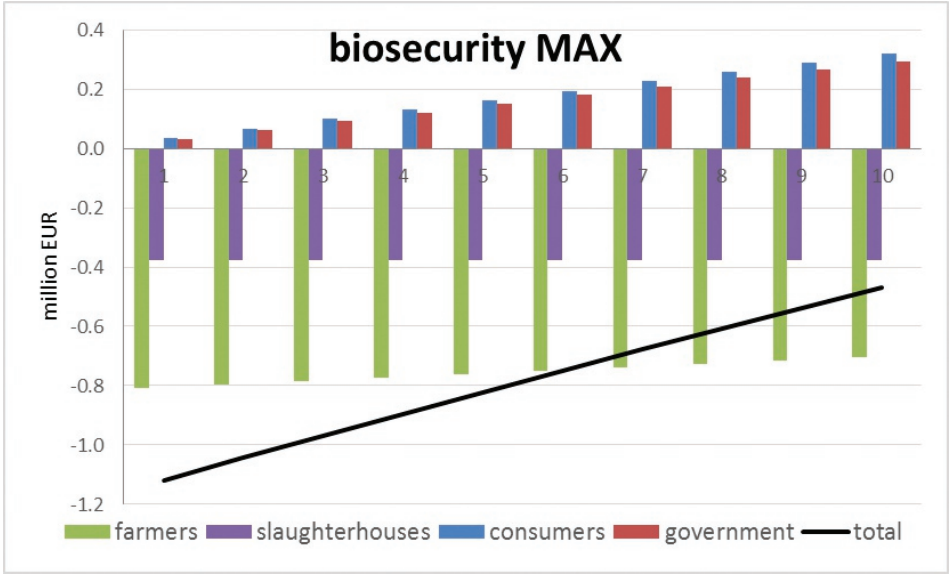
Assuming effectiveness 1%, lasting for 5 years in the maximum scenario



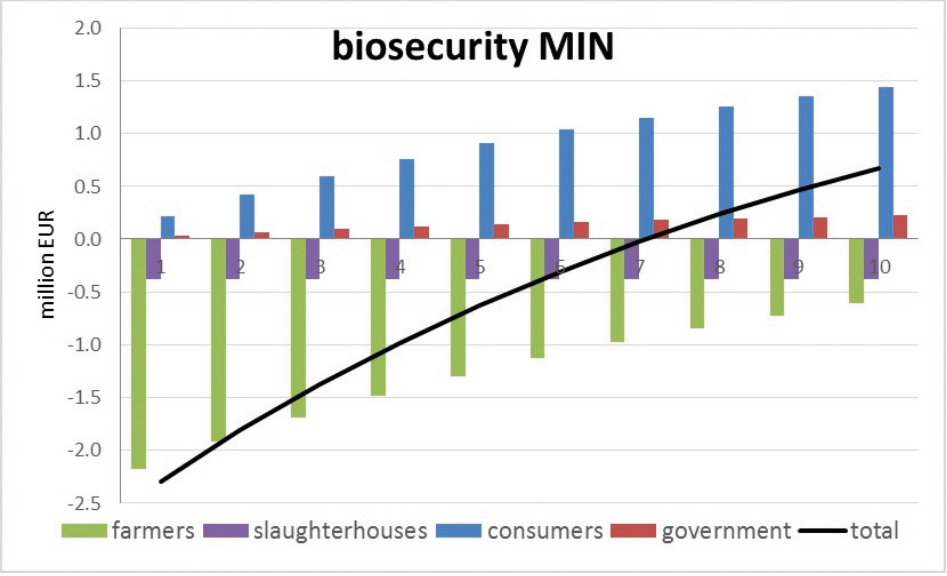
Assuming effectiveness 1%, lasting for 10 years in the minimum scenario



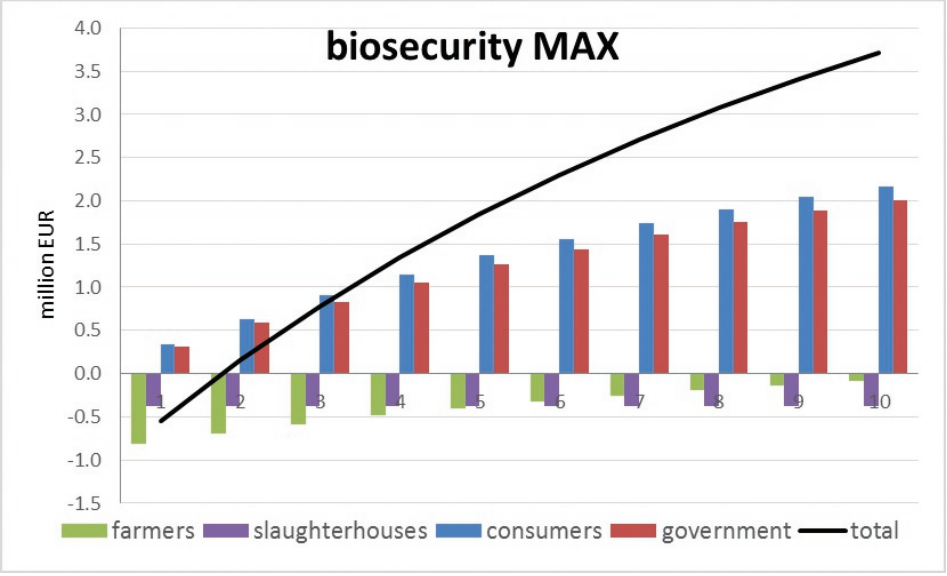
Assuming effectiveness 1%, lasting for 10 years in the maximum scenario



Assuming effectiveness 10%, lasting for 10 years in the minimum scenario



Assuming effectiveness 10%, lasting for 10 years in the maximum scenario



Appendix 6 – Cat vaccination

Using a disease dynamics model for *T. gondii* infections in cats and mice combined with an estimation of oocyst dose response, the impact of potential cat vaccination on human infections was assessed. Preliminary data revealed that it may not be feasible to carry out this intervention effectively, because reducing transmission to humans would require a cat vaccination coverage of more than 95% in populations of the order of 100 cats (and higher in larger populations), which is unlikely to be achieved and this was considering a hypothetical 100% effective vaccine. More details in Bonacic Marinovic et al. (in preparation)

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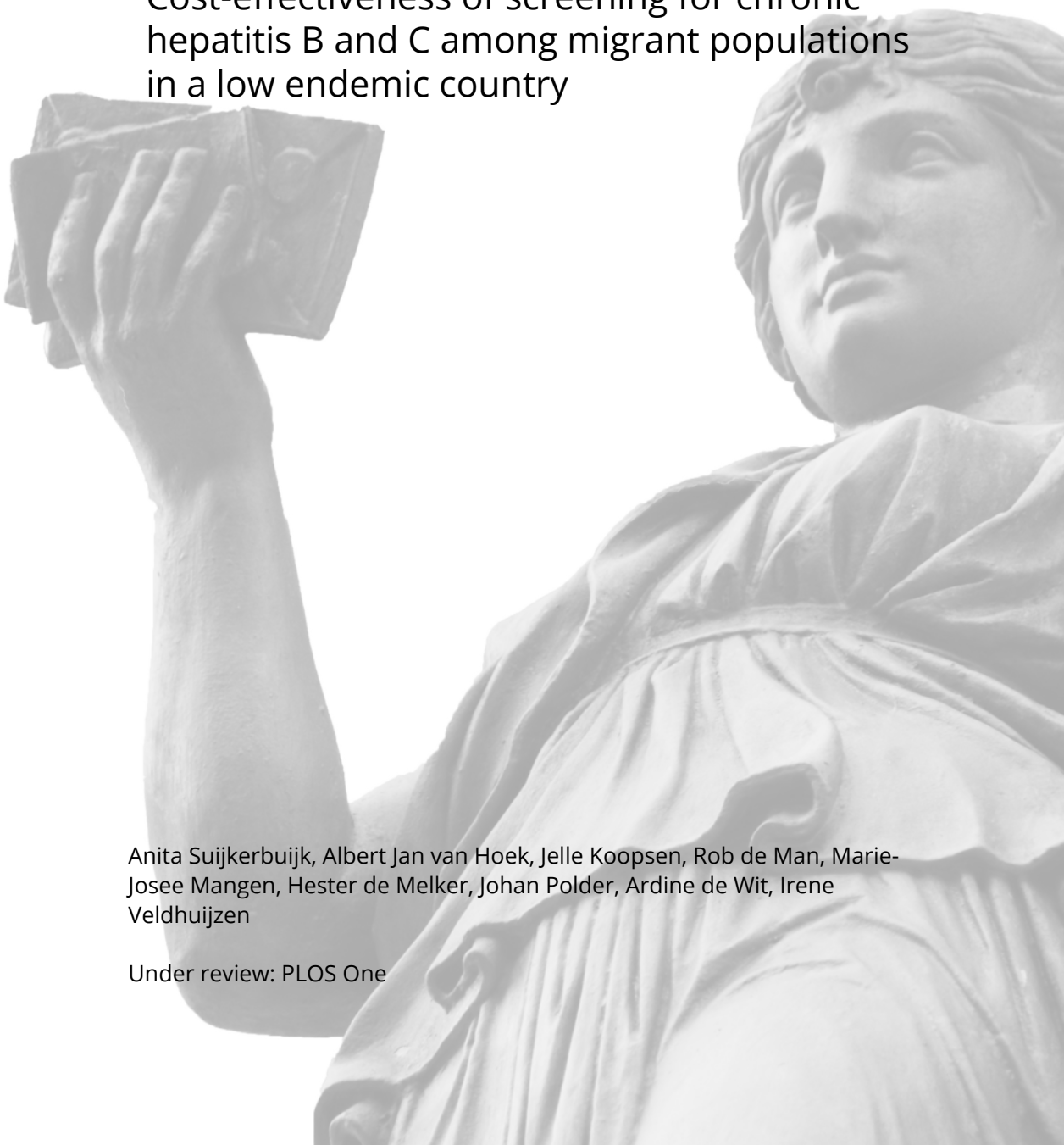
CHAPTER 11

Cost-effectiveness of screening for chronic hepatitis B and C among migrant populations in a low endemic country



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Under review: PLOS One

ABSTRACT

Background

Chronic infection with hepatitis B or C virus (HBV/HCV) can progress to cirrhosis, liver cancer, and even death. In a low endemic country as the Netherlands, migrants are a key risk group and could benefit from early diagnosis and antiviral treatment. We assessed the cost-effectiveness of screening foreign-born migrants for chronic HBV and/or HCV using a societal perspective.

Methods

The cost-effectiveness was evaluated using a Markov model. Estimates on prevalence, screening programme costs, participation and treatment uptake, transition probabilities, healthcare costs, productivity losses and utilities were derived from the literature. The cost per Quality Adjusted Life Year (QALY) gained was estimated and sensitivity analyses were performed.

Results

For most migrant groups with an expected high number of chronically infected cases in the Netherlands combined combined screening is cost-effective, with incremental cost-effectiveness ratio's (ICERs) ranging from €4,962/QALY gained for migrants originating from the Former Soviet Union and Vietnam to €9,375/QALY gained for Polish migrants. HBV and HCV screening proved to be cost-effective for migrants from countries with chronic HBV or HCV prevalence of ≥0.41% and ≥0.22%, with ICERs below the Dutch cost-effectiveness reference value of €20,000/QALY gained. Sensitivity analysis showed that treatment costs influenced the ICER for both infections.

Conclusions

For most migrant populations in a low-endemic country offering combined HBV and HCV screening is cost-effective. Implementation of targeted HBV and HCV screening programmes to increase early diagnosis and treatment is important to reduce the burden of chronic hepatitis B and C among migrants.

INTRODUCTION

People with chronic hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infection are at risk of serious illness and death from liver disease, such as liver cirrhosis and hepatocellular carcinoma [1]. Transmission of HBV can occur vertically (mother-to-child) and via sexual or blood contact, while HCV is mainly transmitted via blood contact [2]. The risk of developing chronic HBV infection is highly age dependent; 90% of infants infected at birth develop later in life a chronic infection, compared to less than 10% of those infected as adults [3]. Infection with HCV results in a chronic infection in 50–80% of patients [4]. Patients with chronic hepatitis B (CHB) or C (CHC) can eventually develop cirrhosis (up to 50%) and liver cancer (1–5%) over a period of 20-30 years [4, 5].

Effective antiviral treatment is available for CHB and can achieve long-term viral suppression in up to 94% of patients [5]. More recently, the treatment options for CHC have greatly improved through the introduction of direct acting antiviral therapy (DAAs), that shows cure rates of over 95% [6] and is, since November 2015, reimbursed by the basic healthcare insurance in the Netherlands for all CHC patients, independent of the stage of liver disease.

To prevent hepatitis-related burden of disease and death, timely diagnosis and linkage to care for treatment of eligible patients is needed [7]. However, this is challenging as many patients with chronic viral hepatitis experience no or few clinical symptoms before major complications (development of ascites, variceal bleeding, hepatocellular carcinoma (HCC) occur. Therefore, active case finding through screening is required.

In a low endemic setting like the Netherlands, migrants originating from endemic regions are an important risk group and are estimated to account for 81% of chronic HBV and 60% of chronic HCV infections [8-10]. The Dutch Health Council advised in 2016 to offer screening for HBV and/or HCV to migrants from countries with a prevalence of chronic HBV or HCV of ≥2% [11]. To inform the implementation of targeted screening interventions we estimated the cost-effectiveness of screening foreign-born migrants for HBV, for HCV, and of combined HBV and HCV screening in the Netherlands.

METHODS

Model

We investigated the cost-effectiveness of screening foreign-born migrants per country of origin using a Markov model programmed in MS Excel 2010. The benefit of the screening programme is early detection of those who are prone to develop complications later in life, where antiviral treatment prevents disease progression, with associated quality of life advantages and cost reductions, as well as increased survival. The lifetime costs and Quality-Adjusted Life Years (QALYs) were calculated for a 40 year old person, based on the average age of migrants participating in several pilot screening projects performed in the Netherlands [12-15]. We present costs and clinical impact of HBV and HCV screening. The incremental cost-effectiveness ratio (ICER) of a HBV or HCV programme was calculated using no screening as comparator strategy. For a combined screening programme the ICER was first calculated for adding HCV testing to an HBV programme, and vice versa depending on the most cost-effective strategy. In addition, we performed country-specific threshold analysis to retrieve the maximum investment per migrant allowed, given the prerequisite that the cost-effectiveness level of €20,000 per QALY should not be exceeded. This value is considered an acceptable value for cost-effectiveness in the Netherlands [16]. The cost-effectiveness model was performed from a societal perspective, including an impact on productivity of those infected. Cost and QALYs were discounted differently, costs with 4% and health benefits with 1.5%, following Dutch guidelines [17].

Hepatitis B

Disease states considered for HBV infection were undiagnosed inactive chronic infection, diagnosed inactive chronic infection, delayed clearance, CHB, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma (HCC), liver transplantation, hepatitis related death, and non-hepatitis related death (for a description of the disease states see Table S1 and Figure S1). The annual transition rates for individuals experiencing natural disease progression and for those undergoing early treatment were taken from the literature and are shown in Table S2. We assumed that all those with decompensated cirrhosis or HCC will seek medical care and have a known HBV status. The screening procedure and follow-up is described in supplementary Section 1. In the initial screening test, 10% of those tested HBsAg positive were classified as CHB patients [18]. The remaining 90% had inactive chronic HBV infection.

Hepatitis C

Disease states for HCV infection were CHC, compensated cirrhosis, decompensated cirrhosis, HCC, liver transplant, hepatitis-related death and non-hepatitis related death (see Table S1 and Figure S2). The annual transition rates for individuals experiencing natural disease progression and for those undergoing treatment were taken from the literature and are given in Table S2. Based on Helsper et al., it was assumed that 11% of CHC patients have compensated cirrhosis.[19] Patients with more severe disease end points, (i.e. decompensated cirrhosis and HCC), were assumed to seek medical care based on impaired health status, and got diagnosed and treated. The screening procedure and follow-up is described in supplementary section 1.

Migrant population size and chronic HBV and HCV prevalence

Foreign-born migrant populations registered in the Municipal Personal Records database (BRP) in the Netherlands on 1-1-2016 (www.statline.nl) were included by country of birth for populations with at least 500 first generation migrants (aged 15 or over), see Table S3 and S4. In the Netherlands, asylum seekers and refugees are registered in the BRP within six months after arrival. As a consequence, unregistered foreign-born migrants and migrants coming from countries with less than 500 first generation migrants living in the Netherlands were excluded. The prevalence of chronic infections with HBV or HCV by country of birth was recently obtained from a review of the (un)published literature on prevalence in migrant populations in the Netherlands or, in absence of data, in countries of origin [10]. Migrant groups with an HBsAg prevalence estimate of at least 1% for HBV [20] and/or HCV-RNA prevalence of at least 0.5% for HCV in the country of origin were included [10, 21].

Baseline testing rate and background mortality

In absence of a specific screening programme we assumed that 2.2% of the cohort migrants would be tested and diagnosed annually for HBV and 2.0% for HCV for other reasons such as pregnancy screening (HBV only), as part of STI testing or due to complaints. For HBV this was based on 900 newly diagnosed chronic HBV infections among foreign-born migrants in 2016 (notification data), of an estimated total of 40,000 chronic HBV infections in this group [10]. For HCV 500 chronic HCV diagnosis were reported by virological laboratories in 2016 of which ~60% were assumed to be foreign-born migrants (~300 cases) divided by an estimated 14,000 cases with chronic HCV infection among migrants [10, 22].

Background mortality for causes of death other than HBV and HCV disease was calculated using age-specific Dutch population averages retrieved from Statistics Netherlands [23]. Migrants, although born elsewhere, were assumed to have the Dutch background mortality rate.

Participation in the screening programme

Based on experiences with earlier Dutch pilot screening programmes targeting migrants originating from Afghanistan, Iran, Iraq, the former Soviet Republics, Vietnam, China, and Egypt we assumed that 30% of all invited migrants would participate in the screening programme [13, 14, 24, 25]. Furthermore we assumed that 80% of individuals that test positive would be effectively linked to care for clinical follow-up and treatment and the other 20% would go through natural disease progression [26].

Quality of life

Utility values to determine loss of quality of life in patients being chronically infected were derived from Stahmeijer et al [27] (Table 1). Given being in a certain health state, we assumed equal utility losses for HBV and HCV disease states, as both infections imply the same course of the disease except for having an inactive chronic infection, a health state only related to HBV.

Costs

Cost estimates were determined for programme implementation and administration, medical care, and productivity losses (Table 1 and Table S5) and are explained in detail in supplementary section 2.

Table 1. Overview of the costs of the screening programme, utilities and costs of HBV and HCV disease and treatment in Euro (2016)

	Hepatitis B	Source	Hepatitis C	Source
Programme costs (in €) per person approached				
	37	[28]	37	[28]
Test costs (in €) per person screened				
Order tariff	11	[29]	11	[29]
Test costs (HBsAg/anti-HCV)	10	[29]	10	[29]
Total test costs	21		21	
Additional costs (in €) if positive				
Outpatient visit	91	[17]	91	[17]
Order tariff	11	[29]	11	[29]
PCR	178	[29]	178	[29]
HBeAg	10	[29]	-	
ALT	2	[29]	-	
Fibroscan	103	[29]	103	[29]
Total additional costs	394		382	
Annual healthcare costs (in €)				
Inactive chronic infection	224	Own calculations[a]	-	-
CHB/ CHC	5386	Own calculations[a]	211	[30]
Compensated cirrhosis	6670	[31]	437	[30]
Decompensated cirrhosis	28,170	[30]	28,170	[30]
HCC	21,592	[30]	21,592	[30]
Liver transplantation	264,446	[31][b]	264,446	[31][b]
Costs (in €) including treatment DAA once only				
CHC	-	-	48,044	Own calculations[a]
Compensated cirrhosis	-	-	48,044	Own calculations[a]
Decompensated cirrhosis	-	-	48,044	Own calculations[a]
Annual costs (in €) after treatment with DAAs				
CHC	-	-	205	[30]
Compensated cirrhosis	-	-	501	[30]
Decompensated cirrhosis	-	-	501	[30]

	Hepatitis B	Source	Hepatitis C	Source
Productivity losses				
Annual number of work days lost				
CHB/CHC (days)	8.4	[32]	13.2	[32]
Cirrhosis	15.6	[32]	25.2	[32]
HCC	18	[32]	27.6	[32]
Liver transplantation	26.4	[32]	38.4	[32]
Employment rate				
35-45 years	0.64	[33]	0.64	[33]
45-55 years	0.63	[33]	0.63	[33]
55-65 years	0.48	[33]	0.48	[33]
Mean costs per working hour				
40-44 years	40.04	[34]	40.04	[34]
45-49 years	41.20	[34]	41.20	[34]
50-54 years	41.61	[34]	41.61	[34]
55-59 years	41.83	[34]	41.83	[34]
60-64 years	41.30	[34]	41.30	[34]
Utility values				
Inactive chronic infection	1	assumption	-	
CHB/CHC	0.81	[27]	0.81	[27]
Compensated cirrhosis	0.74	[27]	0.74	[27]
Decompensated cirrhosis	0.72	[27]	0.72	[27]
HCC	0.72	[27]	0.72	[27]
Liver transplant	0.72	[27]	0.72	[27]
Post-liver transplant	0.79	[27]	0.79	[27]

[a] *see Table S5 for details,* [b] *including 10 year follow-up costs*

Sensitivity and scenario analysis

To identify the most relevant uncertainties of our outcomes a one-way sensitivity analysis was performed**.** All input parameters in the model were decreased and increased with 25% and the ten most important ones are plotted in a tornado diagram. Furthermore, a number of scenario analyses were performed. For international comparison we applied a 3% discount rate for both costs and effects. Additionally, we changed screening participation from 30% to 20% and 40%, we changed the background mortality for the general population with the mortality for

migrants originating from a non-western country [35], and we excluded productivity losses from the model. Finally, we assessed results for lower participation rates in combination with higher screening costs.

RESULTS

The clinical impact of screening ten migrant populations with the expected highest number of chronic HBV and ten migrant populations with the expected highest number of chronic HCV infections in the Netherlands is presented in table 2, resulting in results for 16 countries as four countries had a relatively high number of both chronic HBV and HCV cases. These were Surinam, Vietnam, the former Soviet Union and Indonesia. The largest number of complications due to HBV-infection can be prevented by screening migrants born in Turkey, with an estimated number of 7,463 chronically infected cases in the Netherlands (table S3). The largest number of HCV complications can be averted by screening and treating migrants born in Surinam, with an estimated number of 2,935 chronically infected cases in the Netherlands (table S4).

For most countries listed in Table 3 combining HBV and HCV screening is expected to be the most cost-effective strategy, with ICERs ranging from €4,962/QALY gained for migrants originating from the Former Soviet Union and Vietnam to €9,375/QALY gained for Poland. For those countries, solitary HBV or HCV screening is dominated as, compared to combined screening, for these strategies the costs per QALY gained are higher. For migrants originating from Turkey, screening only for HBV is the most cost-effective strategy. Adding HCV on top of HBV screening results in an ICER for HCV related costs and QALYs just above the Dutch threshold of €20,000 per QALY gained. HCV screening only is the most cost-effective option for migrants originating from Pakistan. However, extending HCV screening with HBV results in an ICER of around €5,000/ HBV related QALY gained, which is below the Dutch threshold. The ICER for combined screening was only marginally less beneficial compared to single HCV screening. The ICERs shown in table 4 include default programme costs of €37 per person approached. Leaving these programme costs out of the model, the maximum investments allowed to arrive at an intervention which cost-effectiveness does not exceed the Dutch threshold of €20,000 per QALY gained can be calculated and is presented in table 4. More resource intensive strategies, i.e. higher program costs than €37 per participant, can be used for screening programmes targeting migrants from several African countries (Figure 1). For instance, combined screening of Somali migrants is still a cost-effective intervention at programme costs as high as €1,697 per migrant.

Considering the Dutch reference value for cost-effectiveness, screening migrant groups included in our study for HBV has a cost-effectiveness level below €20,000/ QALY at an HBV prevalence of 0.41%. HCV screening is cost-effective at a prevalence of 0.22%, taking the same threshold for cost-effectiveness into account.

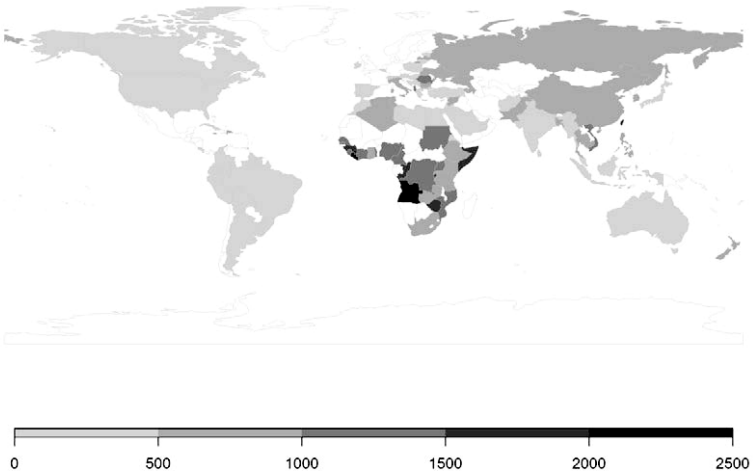

Figure 1. Maximum investment (€2016) allowed per migrant to achieve cost-effective combined HBV/HCV screening (results for migrants from the Former Soviet Union and born before 1991, Former Yugoslavia, born before 1991, and Former Dutch Antilles, born before 2010, are not included in this graph).

Table 2. Averted cases of compensated cirrhosis, decompensated cirrhosis, HCC, liver transplant, and death over a life time period compared to no screening programme for the ten countries of origin with the expected highest number of infected HBV and HCV cases in the Netherlands[a]

		Hepatitis B						Hepatitis C					
Country of origin	Infection with high number of cases	Chronic HBV	Comp. cirrhosis	Dec. cirrhosis	HCC	Liver transplant	Death	Chronic HCV	Comp. cirrhosis	Dec. cirrhosis	HCC	Liver transplant	Death
1. Turkey	HBV	739	333	91	262	80	412	11	4	2	2	0	2
2. Somalia	HBV	325	147	40	116	35	182	25	8	4	4	0	4
3. China	HBV	256	115	32	91	28	143	26	8	4	4	0	4
4. F. Yugoslavia	HBV	196	88	24	70	21	109	91	30	14	14	0	13
5. Surinam	HBV and HCV	178	80	22	63	19	99	597	195	91	89	0	85
6. Indonesia	HBV and HCV	156	70	19	55	17	89	106	35	16	16	0	15
7. F. Soviet Union	HBV and HCV	156	70	19	55	17	87	229	75	35	34	0	33
8. Vietnam	HBV and HCV	96	43	12	34	10	53	57	19	9	9	0	8
9. Cape Verde	HBV	94	43	12	34	10	53	30	10	5	4	0	4
10. Romania	HBV	94	43	12	33	10	53	76	25	12	11	0	11
11. Morocco	HCV	89	40	11	32	10	50	284	93	43	42	0	40
12. Syria	HCV	75	34	9	27	8	42	138	45	21	21	0	20
13. Poland	HCV	45	20	6	16	5	25	109	36	17	16	0	16
14. F. Dutch Antilles	HCV	19	9	2	7	2	11	97	32	15	14	0	14
15. Italy	HCV	63	28	8	22	7	35	87	28	13	13	0	12
16. Pakistan	HCV	31	14	4	11	3	17	77	25	12	12	0	11

Comp. = compensated, dec. = decompensated, HCC=hepatocellular carcinoma, F.=former, for Yugoslavia born before 1991, for Dutch Antilles born before 2010, and for the Soviet Union born before 1991, [a] the number of countries does not sum up to 20 as the F. Soviet Union, Surinam, Vietnam, and Indonesia belong to the countries with the highest number of both HBV and HCV cases in the Netherlands

Table 3. Incremental cost-effectiveness of screening migrant groups for the ten countries of origin with the highest number of infected HBV and HCV cases in the Netherlands[a]

Country		Δ Costs (€*1000)	Δ QALYs	ICER	Max. investment (€*1000)[b]	Max. investment / migrant (€)
1. Turkey	HBV	32,739	5,252	6,233	79,275	421
	HCV	8,408	72	dominated	-	-
	Both	34,174	5,324	dominated	79,270	421
2. Somalia	HBV	11,791	2,313	dominated	35,285	1,590
	HCV	1,538	154	dominated	2,369	107
	Both	12,508	2,467	5,070	37,654	1,697
3. China	HBV	10,488	1,816	dominated	27,537	601
	HCV	2,590	162	dominated	2,352	51
	both	11,381	1,979	5,752	29,889	652
4. F. Yugoslavia	HBV	8,682	1,394	dominated	21,050	423
	HCV	4,279	567	dominated	8,893	179
	both	11,119	1,961	5,670	29,943	601
5. Surinam	HBV	13,541	1,265	dominated	18,291	104
	HCV	21,601	3,722	dominated	59,367	337
	both	28,620	4,988	5,738	77,658	441
6. Indonesia	HBV	9,713	1,110	dominated	16,359	157
	HCV	6,995	661	dominated	10,082	96
	both	12,842	1,771	7,252	26,441	253
7. F. Soviet U	HBV	6,968	1,108	dominated	16,723	407
	HCV	7,149	1,430	dominated	22,970	559
	both	12,596	2,538	4,962	39,693	965
8. Vietnam	HBV	3,732	681	dominated	10,357	826
	HCV	1,882	357	dominated	5,716	456
	both	5,151	1,038	4,962	16,073	1,282

Country		Δ Costs (€*1000)	Δ QALYs	ICER	Max. investment (€*1000)[b]	Max. investment / migrant (€)
9. Cape Verde	HBV	3,646	671	dominated	10,205	876
	HCV	1,196	184	dominated	2,920	251
	both	4,410	855	5,157	13,124	1,126
10. Romania	HBV	3,869	670	dominated	10,155	600
	HCV	2,502	471	dominated	7,547	446
	both	5,744	1,141	5,034	17,702	1,045
11. Morocco	HBV	10,169	634	dominated	8,673	52
	HCV	13,855	1,771	dominated	27,729	166
	both	17,855	2,404	7,426	36,402	218
12.Syria	HBV	3,707	531	dominated	7,957	282
	HCV	4,442	857	dominated	13,751	487
	both	7,104	1,388	5,117	21,708	768
13. Poland	HBV	6,155	319	dominated	4,218	39
	HCV	7,225	682	dominated	10,413	96
	both	9,387	1001	9,375	14,631	136
14. F. Dutch Ant.	HBV	4,067	134	dominated	1,566	-
	HCV	5,705	604	dominated	9,312	117
	both	6,827	738	9,250	10,879	137
15. Italy	HBV	3,187	448	dominated	6,700	265
	HCV	3,129	543	dominated	8,656	343
	both	5,382	990	5,435	15,357	608
16. Pakistan	HBV	1,529	221	dominated	3,320	291
	HCV	2,306	483	4,778	7,769	682
	both	3,413	704	dominated	11,088	973

[a] the number of countries does not sum up to 20 as the F. Soviet Union, Surinam, Vietnam, and Indonesia both belong to the countries with the highest number of HBV and HCV cases in the Netherlands, [b] excluding €37 programme costs for HBV, HCV, or combined screening, F=former, for Yugoslavia born before 1991, for Dutch Antilles born before 2010, and for the Soviet Union born before 1991

Sensitivity and scenario analysis

The ten most influential input parameters for HBV and HCV screening, after decreasing and increasing the input parameters with 25% are presented in figures 2 and 3, using Turkey and Surinam as a high prevalence country for chronic HBV (4.0%) and HCV (1.7%) respectively. For both infections treatment costs highly influenced the ICER. With respect to HBV, the QALY loss for the CHB disease state and the transition probability from CHB to HCC and compensated cirrhosis were relatively important. For HCV, the QALY loss of CHC was important. In addition, discount rates for costs and QALYs were of significance for both infections, see supplementary table S6. If we excluded utility losses for the disease states CHB and CHC, that is assuming perfect health, the ICER increased to €7,519 for HBV and €12,605 for HCV. When the discount rate was changed to 3%, the ICER increased to respectively €10,426 and €6,838. Changing the background mortality and excluding productivity costs from the model, did not have much influence on both ICERs. If we decreased the participation rate to 10% and decreased the number of persons who will seek treatment after a positive test to 60%, the ICER increased to €10,346 for HBV and €11,187 for HCV.

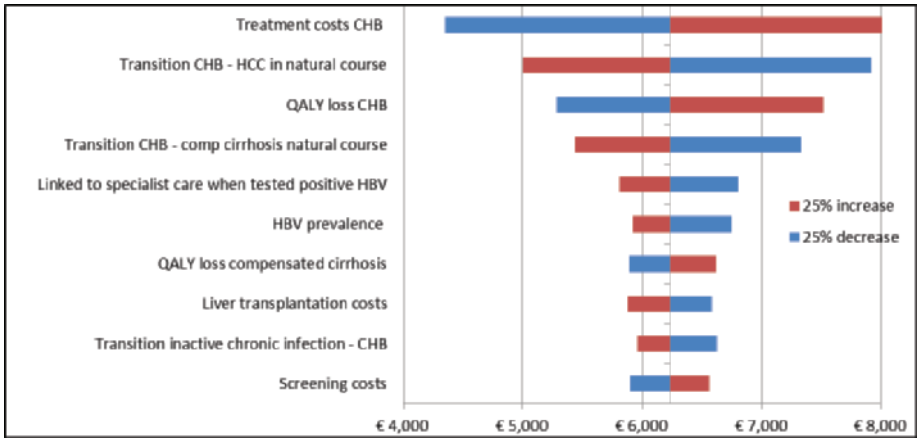

Figure 2. Sensitivity analysis for 10 most important HBV input parameters when decreasing and increasing them with 25% for Turkey, baseline ICER: €6233/QALY

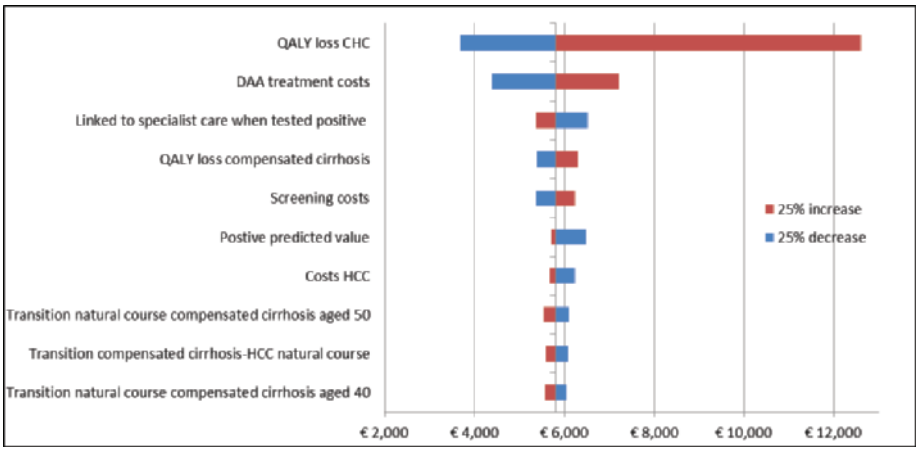

Figure 3. Sensitivity analysis for 10 most important HBV input parameters when decreasing and increasing them with 25% for Surinam, baseline ICER: €5803/QALY

DISCUSSION

Screening foreign-born migrants originating from HBV and HCV endemic countries with a seroprevalence of at least 0.41% for HBsAg and 0.22% for HCV-RNA is expected to be cost-effective in the Netherlands. These findings are driven by the prevention of long-term disease sequelae such as cirrhosis and HCC. For most migrant groups with an expected high number of CHB or CHC cases in the Netherlands this means that offering combined HBV and HCV screening is cost-effective with ICERs far below the reference value of €20,000 per QALY gained. We observed that screening for HBV or HCV alone was more cost-effective than combined screening for some migrant groups. For migrants from Turkey for instance, screening only for HBV was the most cost-effective option. This could be expected as the prevalence estimate for chronic HCV infection in Turkish migrants is 0.03%, which is well below our defined threshold for cost-effectiveness. For migrants from Pakistan screening for HCV only was more cost-effective than combined screening. However, the differences between the ICERS were very small and adding HBV on top of HCV was a cost-effective strategy as well. Therefore, and as the expected prevalence of both infections is over 2%, combined screening for Pakistani migrants is recommended.

Only few economic evaluations targeted at screening migrant populations have been published so far, however, none of these studies combined HBV and HCV screening. The cost-effectiveness of screening migrants in the UK for HCV was £23,200 per QALY gained [36]. However, in this study treatment with DAAs was not included yet. Screening migrants in the Netherlands for HBV was assessed at €8,966 per QALY

gained which is in line with results from our study [18]. Screening refugees for HBV in the U.S.A. was cost-saving [37] while in Canada cost-effectiveness of screening refugees was estimated at $40,880 [38].

Not surprisingly, we found that reducing the currently high DAA treatment costs for CHC would reduce the ICER significantly. DAAs are highly effective in treating CHC, have a short duration of treatment, and are generally well tolerated even in patients with advanced liver disease [39] However, these advantages come with a major increase in treatment costs and financial consequences for health budgets [40]. In some countries, for example in India and Australia, generic DAAs are available at much lower prices [41-43]. Taking these lower prices into account, HCV screening could even be a cost-saving intervention according to Aggarwal et al.[41] However, in the Netherlands, the DAA patent period will last for several years and is unlikely to be violated, as long-term agreements on drug prices between the Ministry of Health and pharmaceutical companies have been made.

In this study, we adopted a societal perspective and included productivity losses in the model based on estimates taken from the literature [32]. However, Scalone et al assessed work days lost only for persons with a paid job while some persons lost their job due to disease. As a result productivity losses are probably underestimated in our study which results in a less beneficial cost-effectiveness.

As in any cost-effectiveness model the final ICER is obtained by combining a selected set of parameter estimates. Therefore there is uncertainty in the final ICER due to both statistical uncertainty in the parameter estimates, as well as due to our modelling decisions. We did not explore the contribution of the statistical uncertainty around each parameter on the ICER but we did explore which parameters are most influential in changing the ICER. This revealed that the ICER was mostly affected by treatment costs and utility losses of CHB and CHC. However, we already used current market prices in baseline and if we excluded utility losses for these disease states from the model, screening remained cost-effective. Additionally, if we combined a low participation rate of only 10% with a relatively low rate of linkage to specialist care and treatment of 60%, screening migrant populations proved to be cost-effective. Given that even with extreme assumptions of the most influential parameters the ICER was still cost-effective we are confident that our conclusions are robust.

Results of this economic evaluation are largely driven by the underlying seroprevalence estimates of chronic HBV and HCV infection in the specific migrant groups. These seroprevalence figures have been retrieved from migrant screening projects and prevalence studies performed in the Netherlands and if unavailable, were taken from literature [20, 21, 44]. Due to several bias mechanisms prevalence rates found in the Netherlands may be lower than in the country of origin. Migrants are not only a very heterogeneous group between countries, but also within countries, where

migrant-groups from the same country can defer in social-economic status, language and culture. Therefore our cost-effectiveness estimates should be interpreted as an indication.

We were not able to estimate the proportion of migrants who have already been tested in the past. Therefore, we may have overestimated the number of people who can still benefit from screening. Furthermore, we used an average age of 40 years, based on the average age that was observed in several Dutch hepatitis screening projects. When the average person screened is older, the cost-effectiveness will be less beneficial as less QALYs can be gained. A younger age, in contrary, would result in a more cost-effective programme, presuming the same prevalence. But this latter is questionable, at least for HBV as vaccination started in some of these countries as early as in 2000 [7].

In our study we assumed a modest participation rate of 30% as baseline. Several interventions at low cost (see supplementary section 3) can improve engagement and compliance along the chronic viral hepatitis care continuum [45, 46]. As in most general practices only a few patients will be eligible for screening, a close collaboration between GPs, Municipal Health Services (MHS) and community-based organisations seems valuable in which MHSs can take responsibility for coordinating the screening programme [12, 13, 24, 25].

WHO launched a global viral hepatitis strategy aimed at reducing mortality by 65% by 2030. To reach this target, increased efforts are needed to scale-up testing and treatment [2]. Several countries have already made progress in recent years implementing interventions targeted at specific risk groups such as injecting drug users [47]. In addition, many countries have introduced universal HBV-vaccination and global coverage in infants has increased from around 30% in the year 2000 to over 80% in 2015. However, among migrants born before routine implementation of HBV-vaccination, the proportion of people living with chronic HBV-infection remains high [2]. Given that migrants are disproportionately affected by chronic viral hepatitis, both expansion of HBV and HCV screening programmes to increase early diagnose and improving access to effective treatment are important to reduce the burden of disease. Our results can guide implementation of cost-effective screening strategies targeting foreign-born migrants.

APPENDIX

Method

1. Screening procedure

Migrants who participate in HBV screening will be tested for hepatitis B surface antigen (HBsAg). In case patients have a positive HBsAg test they are referred to specialist care for assessment of the severity of liver disease and eligibility for antiviral treatment according to clinical practice guidelines [48]. This assessment includes additional ultrasonography by fibroscan and laboratory tests such as HBeAg, HBV-DNA, and ALT levels [49]. Patients for whom antiviral therapy is currently not indicated are followed up by their GP and monitored yearly. Those with CHB are offered treatment with Tenofovir disoproxil fumerate (245 mg a day) and quarterly monitoring in specialist care [50]. The treatment was assumed to be 96% effective after four years of treatment [51].

Migrants who participate in HCV screening are tested for anti-HCV. In case of positive test results patients are referred to a clinician; an ultrasonography including fibroscan and an additional PCR are performed to confirm a chronic infection and assess the virus genotype [48]. Although several treatment combinations with direct acting antivirals (DAAs) exist [52], we assumed the regimen of Ledipasvir/Sofosbuvir (12 weeks) [53] to be the treatment of choice. This treatment is reimbursed in the Netherlands and 97% effective for most genotypes [54].

2. Costs

Clinical management costs for inactive chronic HBV infection and for CHB patients were calculated using assumed resource use based on clinical guidelines [5] and, following Dutch guidelines for economic evaluations [17], multiplying those with Dutch references prices as presented in Table 1. Treatment costs were obtained from an official Dutch site on drug prices (www.medicijnkosten.nl). CHC treatment costs for sofosbuvir/ledipasvir were taken from a Health Technology Assessment report of the National Healthcare Institute [55]. Other healthcare costs were based on a Dutch cost-effectiveness analysis of HBV vaccination for MSM [56] and an economic evaluation targeted at injecting drug users, also performed in the Netherlands [30]. We assume similar healthcare costs for HCC and liver transplant for both HBV and HCV as the clinical symptoms and treatment options are similar, irrespective of the original infection. For more details see Table S5.

Productivity costs

Loss of productivity for CHB and CHC patients, up to 65 years of age was retrieved from Scalone et al. [32]. In this study, all patients were on surveillance or treatment for chronic viral hepatitis, cirrhosis or HCC, or on post-treatment follow-up after liver transplantation. The sick leave length was multiplied by the average hourly wage adjusted for the employment rate in several age groups of migrants originating from non-western countries (Table 1) [17].

Screening costs

The costs of the screening programme included laboratory test costs obtained from the Dutch Healthcare Authority [29], follow-up costs for an ultrasonography including fibroscan, and consulting clinicians based on reference prices from the National Health Care Institute [17].

Programme costs

We did not have access to detailed cost figures of the different ways to implement screening programmes for migrants. Therefore, we took the average cost figure of costs of migrant screening from a study that describes different forms of migrant screening in Europe [28]. Overall programme costs were set at €37 per person approached and included educating general practitioner (GPs), practice nurses, and Municipal Health Service (MHSs) staff, sending invitational letters to migrants, providing information in different languages on websites and in leaflets based on mean costs of three combined HBV/HCV screening projects targeted at migrants: workplace-based outreach screening, opportunistic screening, and community outreach screening [28].

3. Design of a screening programme

Several examples of Dutch community based screening pilots exist to design a screening programme [13, 14, 25]. Moreover, other suggestions are presented in literature to improve the participation rate in a healthcare setting. GPs and practice nurses can offer general testing for HBV and HCV to migrants from medium- or high-prevalence countries who are registered at the general practice [57-60]. At first, registered foreign-born migrants can be invited for free testing by mail. Testing is also possible on an opportunistic, individual basis when a patient consults the GP or practice nurse for other health problems or when the patient is newly registered with the general practice. Language barriers in migrant groups at increased risk can be addressed by providing translated information or information in audio or visual formats, for example via leaflets and special websites. Posters and leaflet displays in the practice waiting rooms can help to raise awareness among minority groups

at increased risk. GPs, practice nurses and other healthcare workers can attend an e-learning on testing and treating foreign-born migrants with HBV and HCV [61]. Finally, a screening programme can be integrated in a variety of healthcare facilities [62].

Table S1. HBV and HCV disease states

Disease State	Description
Delayed clearance	Persistent absence of HBsAg (or HCV RNA), the patient is no longer considered to have chronic infection; no viral treatment is indicated [63, 64]. We did not include this state in the HCV model.
Inactive chronic infection (HBV only)	Asymptomatic infection in which Hepatitis B virus is not actively replicating, with low ALT levels, no viral treatment is indicated [63-65].
Chronic infection	The virus is actively replicating in the liver, but patients often experience no symptoms of infection [63, 64]. If aware of disease, antiviral treatment reduces liver damage and prevents appearance of further sequelae. In case of HCV infection the virus can be cleared through direct-acting antivirals [52].
Compensated cirrhosis	Liver damage is present, but the patient often has no clinical symptoms [63, 64]. If aware of disease, antiviral treatment keeps infection under control and prevents further sequelae. In case of HCV infection the virus can be cleared through direct-acting antivirals [52].
Decompensated cirrhosis	Significant scarring of the liver has occurred and the patient has severe and possibly life-threatening symptoms [63, 64]. Yearly treatment is indicated; sometimes a patient will undergo a liver transplant. In case of HCV infection the virus can be cleared through direct-acting antivirals [39]
Hepatocellular carcinoma	Cancer of the liver [63-65]. Yearly treatment is indicated; sometimes a patient will undergo a liver transplant.
Liver transplant	The liver of the patient with chronic infection is replaced with a donor liver by surgery [63, 64].
HBV-related death/HCV-related death	Death from any cause related to chronic infection and sequelae.
Death from background causes	Death from any cause not related to chronic infection and sequelae.

Note: transmission rates between the different HBV and HCV disease states are presented in Table S2; Background mortality for causes of death other than HBV and HCV disease was calculated using age-specific Dutch population averages retrieved from Statistics Netherlands [39]

Table S2. Overview of annual transition rates for progression following screening and natural progression of HBV and HCV

		Natural course	Following screening	Source
Hepatitis B				
From	**To**			
Inactive chronic HBV	Delayed clearance	0.00425		[64, 66]
infection	CHB	0.02		[66, 67]
	HCC	0.003		[66, 67]
CHB	Inactive chronic infection	0	0.3	[37, 64, 66-68]
	Delayed clearance	0	0.008	[64]
	Compensated cirrhosis	0.038	0.0045	[18, 64, 66, 67]
	HCC	0.01	0.002	[18, 64, 66, 67]
	HBV-related death	0.00002	0	[37]
Compensated cirrhosis	Inactive chronic infection	0	0.165	[18]
	Decompensated cirrhosis	0.039	0.02	[69-72]
	HCC	0.034	0.016	[18, 64, 66, 67, 71]
	HBV-related death	0.049	0.024	[18, 67, 71]
Decompensated cirrhosis	HCC	0.06	0.06	[66, 67, 71]
	Liver transplant	0.2	0.06	[66, 67, 71]
	HBV-related death	0.26	0.26	[64]
HCC	Liver transplant	0.15	0.15	[66, 67, 71]
	HBV-related death	0.35	0.35	[66, 67, 71]
Liver transplant	HBV-related death	0.064	0.064	[73]
Hepatitis C				
From	**To**			
CHC	Compensated cirrhosis (aged 40)	0.009		[74]
	Compensated cirrhosis (aged 50)	0.016		[74]
Compensated cirrhosis	Decompensated cirrhosis	0.044	0.003	[75, 76]
	HCC	0.043	0.013	[75, 77]
Decompensated cirrhosis	HCC	0.035	0.035	[77]
	Liver transplant	0.022	0.022	[78]
	HCV-related death	0.28	0.13	[77, 79]
HCC	Liver transplant	0.017	0.017	[80]
HCC	HCV-related death	0.43	0.43	[79]
Liver transplant	HCV-related death	0.064	0.064	[73]

HCC=hepatocellular carcinoma, CHB=chronic hepatitis B infection, CHC=chronic hepatitis C infection, HBV=hepatitis B virus, HCV=hepatitis C virus

Table S3. Population size and chronic HBV prevalence among foreign- born migrants in the Netherlands per country of birth (2016 01-01)

Country	Population in NL	Point Prevalence (HBsAg)	Low Estimate	High estimate	Estimated average number of adults living with chronic HBV	Source
Afghanistan	31998	2.67%	0.94%	4.40%	855	[13]
Albania	1502	7.80%	7.56%	8.03%	117	[20]
Algeria	3829	2.92%	2.50%	3.33%	112	[20]
Angola	4803	12.49%	11.09%	13.88%	600	[20]
Argentina	2946	0.77%	0.77%	0.78%	23	[20]
Armenia	675	0.00%	0.00%	0.00%	-	[20]
Australia	5112	0.37%	0.36%	0.38%	19	[20]
Austria	5371	1.34%	0.81%	1.86%	72	[20]
Azerbaijan	717	3.10%	1.71%	4.49%	22	[20]
Bangladesh	933	3.10%	2.99%	3.21%	29	[20]
Bosnia and Herzegovina	684	1.13%	0.91%	1.35%	8	[20]
Brazil	13715	0.65%	0.65%	0.66%	89	[20]
Bulgaria	19742	4.00%	3.19%	4.81%	790	[20]
Burundi	2029	9.85%	5.97%	13.73%	200	[20]
Cambodia	686	4.08%	3.57%	4.59%	28	[20]
Cameroon	1639	12.25%	11.71%	12.78%	201	[20]
Canada	5306	0.00%	0.00%	0.00%	-	[20]
Cape Verde	11655	8.18%	4.26%	12.10%	953	[20]
China	45842	5.63%	4.25%	7.00%	2579	[12]
Colombia	8811	2.34%	1.86%	2.82%	206	[20]
Congo	845	11.02%	9.75%	12.29%	93	[20]
Congo (Democratic Republic)	4465	6.00%	5.68%	6.31%	268	[20]
Cuba	1257	1.66%	0.62%	2.70%	21	[20]
Cyprus	560	2.71%	2.38%	3.04%	15	[20]
Dominican Republic	8291	4.45%	2.65%	6.25%	369	[20]
Ecuador	2140	2.38%	1.08%	3.68%	51	[20]
Egypt	11936	0.95%	0.04%	1.85%	113	[14]
Eritrea	6492	2.50%	2.32%	2.67%	162	[20]
Estonia	930	0.00%	0.00%	0.00%	-	[20]

Country	Population in NL	Point Prevalence (HBsAg)	Low Estimate	High estimate	Estimated average number of adults living with chronic HBV	Source
Ethiopia	10961	6.04%	5.77%	6.31%	662	[20]
Former Dutch Antilles	79574	0.24%	0.00%	0.47%	187	[15]
Former Soviet Union	41123	3.83%	2.74%	4.91%	1573	[44]
Former Yu-guslavia	49784	3.98%	1.32%	6.64%	1981	[81]
Gambia	687	12.30%	11.50%	13.09%	84	[20]
Ghana	13338	5.55%	3.58%	7.52%	740	[82]
Greece	13240	0.97%	0.95%	1.00%	128	[20]
Guinea	2311	15.09%	14.16%	16.01%	349	[20]
Guyana	2245	1.32%	0.72%	1.91%	30	[81]
Hongkong	9617	8.98%	8.47%	9.48%	863	[44]
India	21848	1.46%	1.44%	1.47%	318	[20]
Indonesia	104480	1.51%	0.21%	2.81%	1578	[83]
Ireland	4770	0.03%	0.01%	0.07%	1	[20]
Israel	4743	0.96%	0.93%	0.99%	46	[20]
Italy	25242	2.52%	2.49%	2.54%	635	[20]
Ivory Coast	1049	9.42%	8.70%	10.14%	99	[20]
Jamaica	932	3.97%	2.65%	5.29%	37	[20]
Japan	5076	1.02%	1.01%	1.02%	52	[20]
Jordan	856	1.87%	1.68%	2.06%	16	[20]
Kenya	2046	5.17%	4.86%	5.48%	106	[20]
Kuwait	1217	0.80%	0.66%	0.97%	10	[20]
Latvia	3273	1.39%	1.10%	1.67%	45	[81]
Lebanon	3057	1.22%	1.10%	1.34%	37	[10]
Liberia	1575	17.63%	15.70%	19.55%	278	[10]
Libya	1063	2.16%	2.05%	2.27%	23	[10]
Lithuania	4563	1.71%	1.55%	1.86%	78	[10]
Luxemburg	747	0.00%	0.00%	0.00%	-	-
Morocco	166727	0.54%	0.01%	1.07%	900	[15]
Mozambique	564	8.38%	7.55%	9.21%	47	[20]
Myanmar	1061	3.40%	3.26%	3.54%	36	[20]

Country	Population in NL	Point Prevalence (HBsAg)	Low Estimate	High estimate	Estimated average number of adults living with chronic HBV	Source
Nepal	1475	0.82%	0.80%	0.84%	12	[20]
New Zealand	1877	4.11%	4.04%	4.18%	77	[20]
Nigeria	6016	9.76%	9.59%	9.93%	587	[20]
Pakistan	11395	2.76%	2.73%	2.79%	315	[20]
Peru	3503	2.11%	1.90%	2.32%	74	[20]
Philippines	11737	4.63%	4.53%	4.73%	543	[20]
Poland	107919	0.42%	0.42%	0.43%	453	[20]
Portugal	15681	1.05%	0.78%	1.31%	164	[20]
Romania	16936	5.62%	5.50%	5.73%	951	[20]
Russia	2279	2.74%	2.64%	2.83%	62	[20]
Rwanda	983	7.60%	3.82%	11.37%	75	[20]
Saudi Arabia	1615	3.18%	3.12%	3.24%	51	[20]
Senegal	894	11.06%	10.72%	11.40%	99	[20]
Serbia	721	0.48%	0.43%	0.55%	3	[20]
Sierra-Leone	3731	8.86%	5.99%	11.73%	331	[20]
Singapore	2530	4.10%	3.87%	4.33%	104	[20]
Somalia	22189	14.81%	13.77%	15.84%	3285	[20]
South Africa	8857	6.70%	6.56%	6.83%	593	[20]
South Korea	3497	4.37%	4.36%	4.37%	153	[20]
Spain	21806	0.34%	0.32%	0.37%	74	[20]
Sri Lanka	6755	2.61%	1.90%	3.31%	176	[20]
Singapore	2530	4.10%	3.87%	4.33%	104	[20]
Somalia	22189	14.81%	13.77%	15.84%	3285	[20]
South Africa	8857	6.70%	6.56%	6.83%	593	[20]
South Korea	3497	4.37%	4.36%	4.37%	153	[20]
Spain	21806	0.34%	0.32%	0.37%	74	[20]
Sri Lanka	6755	2.61%	1.90%	3.31%	176	[20]
Sudan	4342	9.79%	9.03%	10.54%	425	[20]
Surinam	176284	1.02%	0.51%	1.53%	1798	[83]
Switzerland	4660	0.18%	0.10%	0.33%	8	[20]
Syria	28254	2.67%	2.17%	3.17%	754	[20]
Taiwan	2384	12.25%	11.70%	12.80%	292	[81]
Tanzania	919	7.19%	6.59%	7.79%	66	[20]

Country	Population in NL	Point Prevalence (HBsAg)	Low Estimate	High estimate	Estimated average number of adults living with chronic HBV	Source
Thailand	12118	6.42%	6.37%	6.47%	778	[20]
Togo	1108	11.52%	7.45%	15.59%	128	[20]
Trinidad and Tobago	502	0.00%	0.00%	0.00%	-	-
Tunisia	4317	6.18%	5.95%	6.40%	267	[20]
Turkey	188450	3.96%	2.62%	5.30%	7463	[15]
Uganda	1426	9.21%	8.65%	9.77%	131	[20]
Ukraine	1169	1.50%	1.10%	1.89%	17	[20]
United Arab Emirates	547	0.70%	0.41%	1.20%	4	[20]
Uruguay	589	0.00%	0.00%	0.00%	-	[20]
USA	20775	0.27%	0.24%	0.30%	56	[20]
Vietnam	12539	7.72%	5.86%	9.58%	968	[13]
Zambia	593	6.10%	5.38%	6.82%	36	[20]
Zimbabwe	997	14.38%	13.43%	15.32%	143	[20]

- = *data not available*

Table S4. Population size and chronic HCV prevalence among foreign- born migrants in the Netherlands per country of birth (2016 01-01)

Country	population in NL	Point Prevalence (HCV-RNA)	Low Estimate	High estimate	Estimated average number of adults living with chronic HCV	Source
Afghanistan	31998	0.65%	0.00%	1.29%	206	[13]
Albania	1502	0.90%	0.80%	1.00%	14	[21]
Algeria	3829	1.00%	0.30%	1.70%	38	[21]
Angola	4803	3.50%	0.10%	6.90%	168	[21]
Argentina	2946	0.75%	0.30%	1.20%	22	[21]
Armenia	675	3.35%	2.80%	3.90%	23	[21]
Australia	5112	0.85%	0.70%	1.00%	43	[21]
Austria	5371	0.20%	0.10%	0.40%	11	[21]
Azerbaijan	717	1.70%	1.30%	2.10%	12	[21]
Bangladesh	933	0.95%	0.20%	1.70%	9	[84]
Bosnia and Herzegovina	684	0.90%	0.80%	1.00%	6	[21]
Brazil	13715	0.75%	0.60%	0.90%	103	[21]
Bulgaria	19742	1.15%	0.70%	1.60%	227	[21]
Burundi	2029	2.40%	0.80%	4.00%	49	[21]
Cambodia	686	1.30%	0.90%	1.70%	9	[21]
Cameroon	1639	0.65%	0.50%	0.80%	11	[21]
Canada	5306	0.55%	0.40%	0.70%	29	[21]
Cape Verde	11655	1.25%	1.10%	1.40%	146	[21]
China	45842	0.28%	0.06%	0.50%	128	[85]
Colombia	8811	0.75%	0.60%	0.90%	66	[21]
Congo	845	3.50%	0.10%	6.90%	30	[21]
Congo (Democratic Republic)	4465	3.50%	0.10%	6.90%	156	[21]
Cuba	1257	0.30%	0.10%	0.70%	4	[21]
Cyprus	560	0.00%	0.00%	0.00%	-	-
Dominican Republic	8291	0.70%	0.40%	1.00%	58	[21]
Ecuador	2140	0.45%	0.30%	0.60%	10	[21]
Egypt	11936	1.66%	0.43%	2.89%	198	[14]
Eritrea	6492	0.55%	0.40%	0.70%	36	[21]
Estonia	930	1.25%	0.90%	1.60%	12	[21]
Ethiopia	10961	0.55%	0.40%	0.70%	60	[21]

Country	population in NL	Point Prevalence (HCV-RNA)	Low Estimate	High estimate	Estimated average number of adults living with chronic HCV	Source
Former Dutch Antilles	79574	0.60%	0.40%	0.80%	477	[21]
Former Soviet Union	41123	2.75%	2.10%	3.40%	1131	[21]
Former Yuguslavia	49784	0.90%	0.80%	1.00%	448	[21]
Gambia	687	0.90%	0.50%	1.30%	6	[21]
Ghana	13338	0.38%	0.00%	0.76%	51	[21]
Greece	13240	1.10%	0.70%	1.50%	146	[21]
Guinea	2311	1.25%	1.10%	1.40%	29	[21]
Guyana	2245	0.60%	0.40%	0.80%	13	[21]
Hongkong	9617	0.00%	0.00%	0.00%	-	-
India	21848	0.60%	0.40%	0.80%	131	[21]
Indonesia	104480	0.50%	0.20%	0.80%	522	[21]
Ireland	4770	0.65%	0.40%	0.90%	31	[21]
Israel	4743	1.00%	0.70%	1.30%	47	[21]
Italy	25242	1.70%	0.70%	2.70%	429	[21]
Ivory Coast	1049	1.25%	1.10%	1.40%	13	[21]
Jamaica	932	0.60%	0.40%	0.80%	6	[21]
Japan	5076	0.55%	0.30%	0.80%	28	[21]
Jordan	856	0.30%	0.10%	0.40%	3	[21]
Kenia	2046	0.20%	0.10%	0.30%	4	[21]
Kuwait	1217	1.65%	1.40%	1.90%	20	[21]
Latvia	3273	2.00%	1.40%	2.60%	65	[21]
Lebanon	3057	0.20%	0.10%	0.40%	6	[21]
Liberia	1575	1.25%	1.10%	1.40%	20	[21]
Libya	1063	0.60%	0.50%	0.70%	6	[21]
Lithuania	4563	1.00%	0.70%	1.30%	46	[21]
Luxembourg	747	0.80%	0.60%	1.00%	6	[21]
Malaysia	3017	1.05%	0.80%	1.30%	32	[21]
Morocco	166727	0.84%	0.00%	1.68%	1401	[15]
Mozambique	564	0.55%	0.40%	0.70%	3	[21]
Myanmar	1061	0.65%	0.50%	0.80%	7	[21]
Nepal	1475	1.00%	0.70%	1.30%	15	[21]
New Zealand	1877	0.95%	0.60%	1.30%	18	[21]
Nigeria	6016	1.20%	1.00%	1.40%	72	[21]

Country	population in NL	Point Prevalence (HCV-RNA)	Low Estimate	High estimate	Estimated average number of adults living with chronic HCV	Source
Pakistan	11395	3.35%	2.80%	3.90%	382	[21]
Peru	3503	0.45%	0.30%	0.60%	16	[21]
Philippines	11737	0.45%	0.30%	0.60%	53	[21]
Poland	107919	0.50%	0.40%	0.60%	540	[21]
Portugal	15681	0.90%	0.70%	1.10%	141	[21]
Romania	16936	2.20%	1.80%	2.60%	373	[21]
Russia	2279	2.90%	2.30%	3.50%	66	[21]
Rwanda	983	0.55%	0.40%	0.70%	5	[21]
Saudi Arabia	1615	0.00%	0.00%	0.00%	-	-
Rwanda	983	0.55%	0.40%	0.70%	5	[21]
Saudi Arabia	1615	0.00%	0.00%	0.00%	-	-
Senegal	894	1.25%	1.10%	1.40%	11	[21]
Serbia	721	0.90%	0.80%	1.00%	6	[21]
Sierra-Leone	3731	1.25%	1.10%	1.40%	47	[21]
Singapore	2530	0.50%	0.30%	0.70%	13	[21]
Somalia	22189	0.55%	0.40%	0.70%	122	[21]
South Africa	8857	0.65%	0.40%	0.90%	58	[21]
South Korea	3497	0.40%	0.30%	0.50%	14	[21]
Spain	21806	0.75%	0.30%	1.20%	164	[21]
Sri Lanka	6755	0.65%	0.50%	0.80%	44	[21]
Sudan	4342	0.55%	0.40%	0.70%	24	[21]
Surinam	176284	1.67%	0.00%	3.33%	2935	[15]
Switzerland	4660	0.85%	0.60%	1.10%	40	[21]
Syria	28254	2.40%	1.30%	3.50%	678	[21]
Taiwan	2384	2.50%	1.30%	3.70%	60	[21]
Tanzania	919	0.55%	0.40%	0.70%	5	[21]
Thailand	12118	0.55%	0.40%	0.70%	67	[21]
Togo	1108	1.25%	1.10%	1.40%	14	[21]
Trinidad and Tobago	502	0.60%	0.40%	0.80%	3	[21]
Tunisia	4317	0.65%	0.20%	1.10%	28	[21]
Turkey	188450	0.03%	0.00%	0.06%	57	[15]
Uganda	1426	0.55%	0.40%	0.70%	8	[21]
Ukraine	1169	2.75%	2.10%	3.40%	32	[21]

Country	population in NL	Point Prevalence (HCV-RNA)	Low Estimate	High estimate	Estimated average number of adults living with chronic HCV	Source
United Arab Emirates	547	1.05%	0.50%	1.60%	6	[21]
Uruguay	589	0.60%	0.30%	0.90%	4	[21]
USA	20775	0.95%	0.70%	1.20%	197	[21]
Vietnam	12539	2.25%	0.14%	4.35%	282	[13]
Zambia	593	0.55%	0.40%	0.70%	3	[21]
Zimbabwe	997	0.65%	0.40%	0.90%	6	[21]

- = *data not available*

Table S5. HBV and HCV treatment costs

Hepatitis B	**Euro 2016**	**Source/Notes**
Inactive chronic infection, annual costs	€ 224	own calculations, annual follow-up costs at general practice (visit (n=1) and laboratory tests, ALAT, DNA amplification once a year)
Chronic HBV (CHB), annual costs	€ 5,386	own calculations, annual costs (4 outpatient visits, laboratory tests (routine laboratory testing, serological tests, 4 times a year) and treatment with tenofovir)
Compensated cirrhosis, annual costs	€ 6,670	Mangen [56]
Decompensated cirrhosis, annual costs	€ 28,170	van Santen [30]
HCC, annual costs	€ 21,592	van Santen [30]
Liver transplantation	€ 264,446	Mangen, costs liver transplantation including 10 year follow-up costs [56]
Hepatitis C		
Chronic HCV (CHC), annual costs	€ 211	van Santen [30]
Compensated cirrhosis, annual costs	€ 437	van Santen [30]
Costs including treatment		
Chronic HCV (CHC), Compensated cirrhosis, Decompensated cirrhosis	€ 48,044	once only costs based on 12-weeks treatment with ledipasvir/sofosbuvir including outpatient visits (n=7), routine laboratory testing and additional diagnostics (radiology, ECG)
HCC, annual costs	€ 21,592	van Santen [30]
Liver transplantation	€ 264,446	Mangen, costs liver transplantation including 10 year follow-up costs [56]
Monitoring costs after successful treatment		
Chronic HCV, annual costs	€ 205	van Santen [30]
Compensated cirrhosis, annual costs	€ 501	van Santen [30]
Decompensated cirrhosis, annual costs	€ 501	van Santen [30]

Table S6. Results sensitivity and scenario analysis

	Hepatitis B		Hepatitis C	
	ICER (costs €/QALY)	**Relative change compared to main analysis (%)**	**ICER (costs €/QALY)**	**Relative change compared to main analysis (%)**
Main analysis	6,233		5,803	
Discount rate 3%	10,426	67	6,838	18
Participation 20%	6,897	11	6,679	15
Participation 40%	5,902	-5	5,365	-8
Corrected background mortality	5,801	-7	5,619	-3
Without including productivity losses	6,404	3	6,527	12
Without including utility losses for a chronic HBV/ HCV disease state	7,519	21	12,605	117
50% increase of screening costs and 60% of persons will seek treatment when tested positive	7,691	23%	7,682	32%
Participation 10% and 60% of persons will seek treatment when tested positive	10,346	66%	11,187	93%

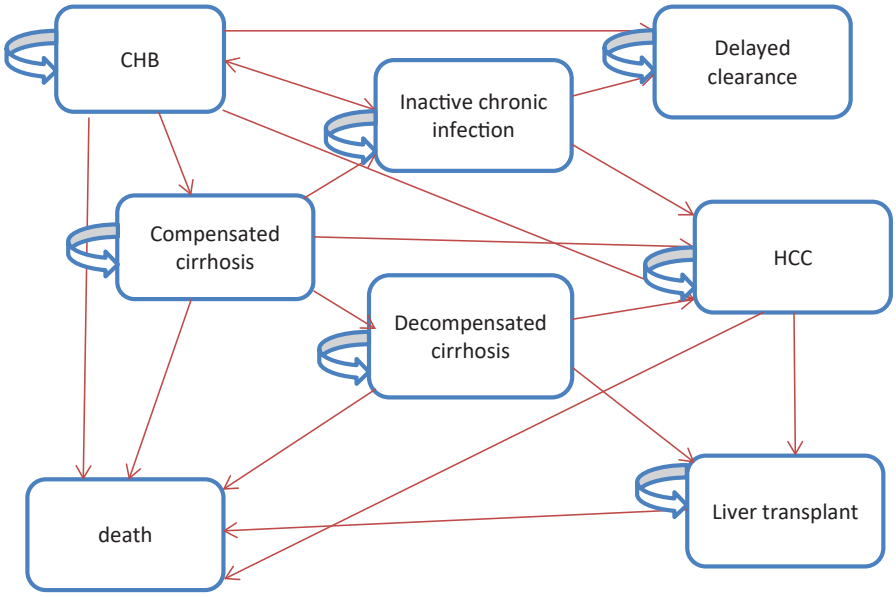

Figure S1. Markov model for chronic HBV infection
CHB=chronic hepatitis B, HCC=hepatocellular carcinoma, adapted from Jazwa et al [37]. From each health state other causes of mortality are possible (not shown)

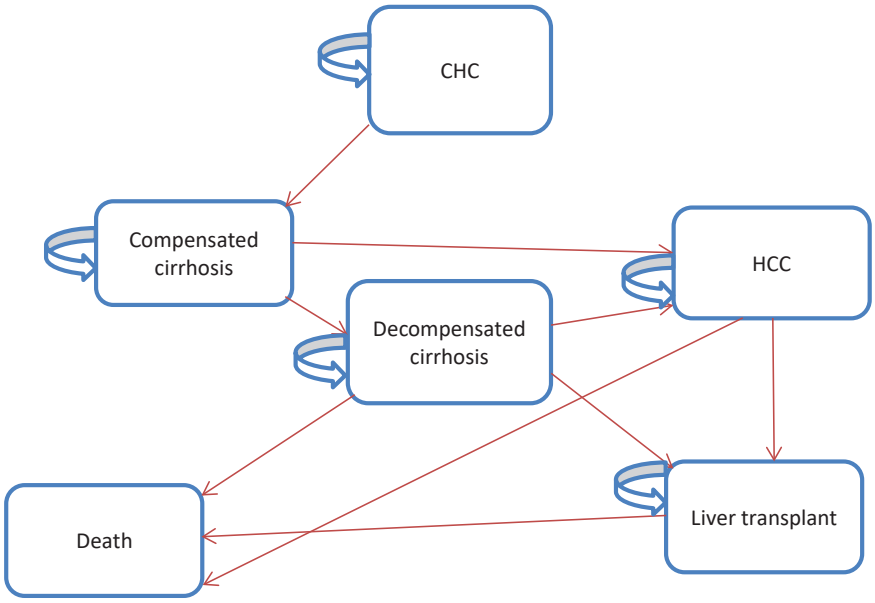

Figure S2. Markov model for chronic HCV infection
CHC=chronic hepatitis C, HCC=hepatocellular carcinoma. From each health state other causes of mortality are possible (not shown)

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CHAPTER 12

General discussion

GENERAL DISCUSSION

Infectious diseases, especially when they present as an outbreak or remain at an increased level of endemicity, pose an important threat to public health. Implemented collaborative disease surveillance, guidance for the management of infectious diseases, and a range of preventive intervention efforts have resulted in reductions of outbreaks of infectious diseases in the last years.

Unlike devastating epidemics in history when plague, smallpox, influenza, and cholera epidemics resulted in high number of deaths, current outbreaks in developed countries are characterised by rather low mortality rates due to high quality of care [1]. However, the SARS epidemic and more recently the Ebola epidemic, highlighted our ongoing vulnerability to natural pathogens without appropriate treatment [2]. Followed by large media attention, control of these outbreaks was achieved through ancient methods: strict isolation of cases and quarantine of their contacts.

Consistent with the nature of infectious diseases dynamics, outbreaks of infectious diseases still occur, making additional interventions and policies necessary. Information on cost-of-illness is key in the planning of preventive health policies targeted at infectious diseases. When compared to full economic evaluations in the field of infectious diseases, the number of costing studies on infectious diseases outbreaks is relatively small [3]. The first objective of this thesis was to gain insight into the societal costs of infectious diseases outbreaks. In this thesis, costs of four recent Dutch outbreaks with different routes of transmission (foodborne, airborne, nosocomial, and through body fluids) and which all resulted in large media attention are described in part 1.

Implementing new interventions can be helpful to reduce the disease burden of infectious diseases and future outbreaks. Cost-effectiveness is regularly mentioned as the 'fourth hurdle' that a health intervention has to take in order to be eligible for funding, after having proven safety, quality, and effectiveness. The second objective of this thesis was to evaluate the cost-effectiveness of particular interventions in infectious disease control. These evaluations are described in part 2.

In the following paragraphs, the main research findings regarding these two objectives are described. Per objective, the methodological considerations regarding the studies and the implications for policy and research are discussed. Finally, the chapter ends with concluding remarks.

PART 1

1.1. Main findings

1.1.1. Salmonella outbreak due to smoked salmon

In chapter 2, the cost-of-illness, including reported and unreported cases, of an extensive food-related outbreak of *Salmonella* Thompson due to consumption of contaminated smoked salmon is evaluated [4]. Healthcare costs, patient costs, production losses and outbreak control costs were assessed. Total outbreak costs were estimated at €7.5 million and an estimated 21,000 cases were involved in the outbreak [4]. The majority of cases do not necessarily consult a general practitioner but are a few days absent from work to recover from disease. Therefore, productivity losses were the main cost driver with 66% of total outbreak costs (Figure 1). However, more than 2000 cases were estimated to experience complications such as reactive arthritis and irritable bowel syndrome, and an estimated 25 cases deceased because of the infection, corresponding with around 500 DALYs lost [5].

1.1.2. Measles outbreak among orthodox Protestants

The societal costs of the large 2013-2014 measles outbreak are described in chapter 3 [6]. Total costs were assessed at €3.9 million of which outbreak control costs were the primary cost (54%) (Figure 2). In this outbreak, Municipal Health Services (MHSs) related costs were highest due to greater demand of expert advice, response to extensive media attention, registration and follow-up of notified cases, and more surveillance activities than usual. In sum, 2,700 measles cases were reported; the outbreak concerned mostly children aged 5–14 years. Around 180 persons were hospitalised and one child died as a result of complications of infection. Considering underreporting, the true number of cases was probably around 30,000 [7]. Van den Hof et al. assessed underreporting of hospitalised measles cases in a previous outbreak in 2000 [8]. When taking underreporting of only hospitalised cases into account following estimates of van den Hof et al, total outbreak costs were probably €0.8 million higher.

1.1.3. Klebsiella pneumoniae hospital outbreak

Total cost of a nosocomial outbreak caused by NDM-1–containing *Klebsiella pneumoniae* described in chapter 4, was approximately €654,000 [9]. The outbreak took place in a Dutch peripheral hospital; 29 patients acquired this multiresistant strain during October-December 2015. The source of infection remained unknown. The closure of beds had the highest (34%) impact on costs, followed by staff time targeted at infection prevention measures (Figure 3).

1.1.4. Threat of Ebola outbreak

In chapter 5 response and preparedness costs of the threat of Ebola Virus Disease (EVD) borne by the Dutch health system were described [10]. Although the number of cases was relatively low (13 possible cases were clinically evaluated and one confirmed case was admitted to hospital), the estimated costs were high: estimated at €12.6 million. The main cost categories were personal protective equipment expenditures and preparedness activities of personnel, especially those associated with the ambulance services and hospitals. Costs of response activities with respect to suspected EVD cases were much lower (Figure 4).

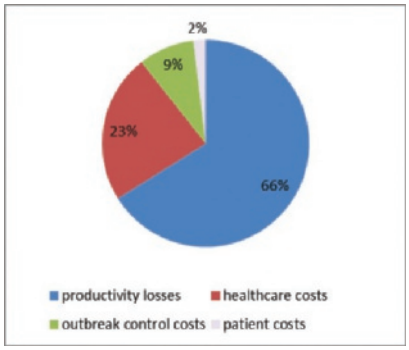

Fig 1 Costs S. Thompson outbreak (societal perspective)

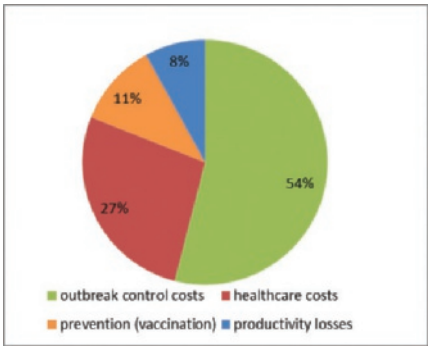

Fig 2 Costs measles outbreak (societal perspective)

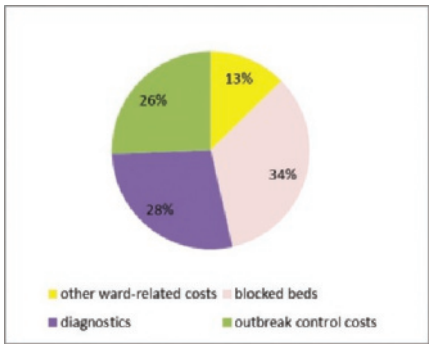

Fig 3 Costs NDM outbreak (hospital perspective)

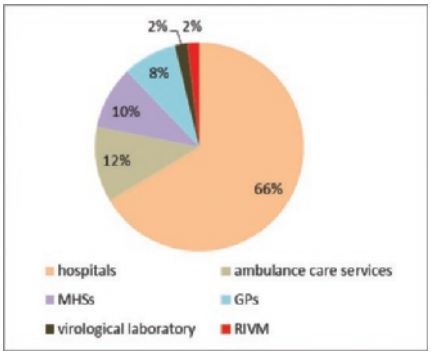

Fig 4 Costs Ebola outbreak (societal perspective)

Figures 1 to 4 present the importance of the varied cost items included in the cost calculations. In the *Salmonella* Thompson outbreak, productivity losses were most important. The main cost category in the measles outbreak was the outbreak control

costs. Blocked beds during the *Klebsiella pneumoniae* outbreak led to highest costs. Finally, most costs were incurred by hospitals in the response and preparedness for Ebola. Figure 5 shows total costs per outbreak.

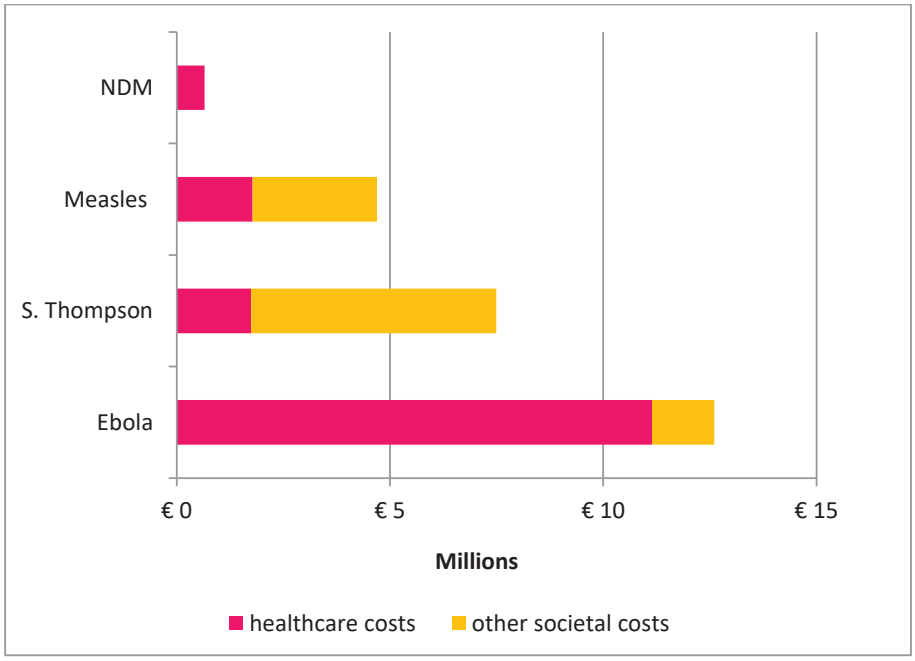

Fig 5 total costs * million per outbreak

1.2. Methodological and policy considerations

In the four studies described, healthcare costs, productivity losses, patient costs, and outbreak control costs could be assessed in a proper way. Other costs, such as basic preparedness costs, costs incurred in foreign countries, costs of retail businesses, costs after the defined outbreak period, and costs of additional outbreak-related research could not be included. These cost items are described below.

1.2.1. Costs of additional outbreak-related research and evaluations

All outbreaks led to increased interest to prevent this specific infection and to other research and evaluations of which costs were not included in total outbreak costs. For instance, with respect to the *S.* Thompson outbreak, the Dutch Safety Board performed a nationwide evaluation [11]. Following the measles outbreak, adherence to recommendations on measles preventive measures in hospitals [12], communication [13], and epidemiology [7] were examined. Further typing of the NDM-positive isolates in the hospital outbreak was performed [14] and in the case of the

Ebola outbreak, preparedness was also explored qualitatively [15, 16]. Quantification of such longer-term infection outbreak related costs at least requires a clear view on the time horizon of the outbreak and on the boundaries between the specific outbreak related activities and ongoing scientific research with a renewed interest in a particular infectious disease due to its outbreak.

1.2.2. Underestimation of other cost items

Other cost items could not be included in the calculations as well. During the measles and *S.* Thompson outbreak, costs made outside the Netherlands, neither for foreign control authorities, nor for infected persons were taken into account due to data restrictions. In the studies included in the thesis, only complications during the outbreak period were examined. Long-term complications of salmonellosis and measles were not taken into account. For example *Salmonella* gastro-enteritis during childhood increases the risk for irritable bowel syndrome later in life [17] and subacute sclerosing panencephalitis rarely occurs but with very severe and lethal complications a few years after the acute phase of measles [18]. Regarding the *S.* Thompson outbreak, economic losses for retail businesses could not be incorporated. Both the Dutch fish company concerned and supermarket chains incurred high costs after setting the production on hold and recalling contaminated smoked salmon from supermarkets for public health purposes. Due to a decline in consumers' trust in the safety of smoked salmon there could be potential economic losses due to loss of business. In addition, an unknown number of NDM-positive patients were discharged to a nursing home leading to other infection control measures and costs that were not taken into account. Finally, only the organisations that spent substantial time, effort, and costs targeted at Ebola preparedness and response, were included in the study. Many other organisations such as the Ministry of Volksgezondheid, Welzijn en Sport (VWS), the Inspectorate of Health, Non-Governmental Organisations working in the Netherlands, and umbrella organisations of hospitals, GPs, MHSs, and GHOR organisations spent also time on Ebola preparedness. To a lesser extent and beyond the healthcare domain, EVD preparedness costs were experienced by public transportation, waste management, and funeral businesses.

1.2.3. Costs of basic preparedness infrastructure

An adequate infectious diseases response to outbreaks demands a general outbreak infrastructure, with guidance, agreements and contracts between (healthcare) organizations, disaster care plans, and experience with routine infectious disease control and small-scale outbreaks [19]. In the Netherlands, the RIVM-Centre for Infectious Disease Control forms a strong public health foundation together with municipal health services and other healthcare organisations to perform infectious

disease surveillance, laboratory detection, and epidemiologic investigation. To achieve such a basic infectious diseases outbreak system, continuous investments have to be made to maintain routine control, expertise, and general preparedness activities. This basic preparedness infrastructure with associated costs is also not included in these studies.

1.2.4. Magnitude of the non-included costs

About the extent of the above mentioned cost items not included in the studies: costs made outside the Netherlands, costs that arose after the outbreak period, costs of organisations that were only indirectly involved, or costs for general preparedness activities can only be speculated; they will definitely comprise millions of Euros. We know that in the months after the *S.* Thompson outbreak, supermarket chains alone stated a decrease in salmon sale valued at €10 million. Costs for all retail businesses and the food production sector are likely to have been several times this figure.

1.2.5. Variation in costs

The papers describe the large variation in costs between the different organisations involved in outbreak control. It can be helpful to depict the variation in costs incurred within each type of organisation as well. With respect to the measles and *Salmonella* outbreak, only average costs per type of organisation were presented. However, due to experiences with measles and foodborne outbreaks in the past, organisations such as MHSs and GPs took a similar, more standard approach therefore reducing variety in costs. Regarding these outbreaks, fluctuations in costs merely stem from the number of cases affected to be dealt with in the organisation. The threat of an Ebola outbreak was completely new for most organisations. In the estimates of the Ebola outbreak costs, variation between similar organisations (anonymously) was included in the uncertainty analysis. The NDM-outbreak only concerned one hospital; therefore variation in costs was not relevant.

1.2.6. Time horizon

The outbreaks are also affected by a 'time horizon' in which healthcare professionals with diverse backgrounds need to work together quickly to identify cases, perform laboratory diagnostics and trace contacts [20]. At the start of an outbreak, preparedness and response activities have to be set up and internal guidelines have to be updated and implemented. Since this requires taking action before all the facts are known and investigations are completed, acting on incomplete information is sometimes needed. None of the costing studies comprised the fluctuation of costs over time, which can be helpful for large ongoing outbreaks such as the Ebola outbreak. Only in the case of the NDM- outbreak the cost study was carried out within six months

after the termination of this outbreak, in all other cases more than a year had passed, making it more difficult to recall and collect all relevant information. To reduce recall bias cost evaluations should be performed shortly after the outbreak.

1.3. Implications for policy and research

All these outbreaks showed that close collaboration between laboratories, public health institutes, healthcare organisations, and, if relevant, industry and food safety institutes, is essential to contain outbreaks rapidly in order to reduce the burden of disease as well as societal costs. First of all, cross-sectoral surveillance between the animal and public health sector [21] and a notifiable infectious disease reporting system are important, including risk assessment and early warning as is established in the Netherlands [22]. Second, timeliness within this system is vital for an effective response. Third, an infectious diseases control system requires surveillance, assessment and communication instruments to increase alertness and to initiate outbreak control [23, 24]. Finally, efforts are needed to achieve a high level of protection for infectious diseases, for example by increasing the vaccination coverage.

1.3.1. Faster detection of Salmonella outbreak

Although smoked salmon is a very uncommon cause of foodborne outbreaks, the S. Thompson outbreak was rapidly detected after an observed increase in salmonellosis diagnoses reported by laboratories. With results of a case-control study the source of infection could be identified. Still, more than 20,000 cases were affected by the outbreak [25]. Food quality assurance systems have been developed to take into account the complete food production chain, from primary production to consumer [26]. According to the Dutch Safety Board an enhanced incident management system for food manufacturers and retailers would have helped to detect the vehicle of infection and track and trace contaminated products more early [11]. In such a proactive safety assessment system for food manufacturers potential threats of food safety of unknown origin can be monitored and real-time information exchange among both public and private parties can be provided. In this way, problems around food safety can be addressed adequately and public and private parties can learn from each other. The establishment of such an incident management system or ameliorations of existing systems require investments; therefore, it has to be assessed whether further food safety measures can be implemented in a cost-effective way.

1.3.2. Strategies to increase vaccination coverage

The second outbreak described in this thesis concerned measles among orthodox Protestant citizens. The Dutch National Immunisation Program (NIP) in general is highly effective, also reducing mortality through indirect protection as was shown in

a historical analysis [27]. For measles, the vaccination uptake in the Netherlands is around 93% but in orthodox Protestant communities it is only around 60%. Despite a slow increase in vaccination coverage among Dutch orthodox Protestants observed over time, future measles outbreaks in these communities are to be expected as these people live close together [7, 28]. There is a risk of spread and ongoing transmission in areas with susceptible populations and vaccination coverage below 95%. In the last few years, many European countries have faced measles outbreaks even though WHO and ECDC have the goal to eliminate measles [29]. Lo et al. confirmed in a published modelling study that even minor reductions in childhood vaccination, based on personal vaccine hesitancy, will have significant public health and economic consequences [30]. While the vaccination coverage among orthodox Protestants has slightly increased, participation in the NIP in the general population has slightly declined for the past few years [31]. Besides religious beliefs [32] many of the arguments against vaccination focus on areas of distrust in medical science [33]. Parents who refuse vaccinations suppose that vaccines are unsafe because of contaminants brought into the body via vaccination leading to harmful side effects. Other arguments are based on misinformation regarding the immune system and vaccine response, suggesting that vaccines devastate the immune system, and that natural immunity is better than immunity induced by vaccines [33]. Vaccine hesitancy should be addressed in policy dialogues at the national level in order to influence and modify personal distrust of childhood vaccination. According to media reports, measles vaccination will possibly be made mandatory in Italy and France since these countries experience large numbers of measles cases [34, 35]. However, it is unclear whether this rigorous measure would lead to a higher uptake.

Successful strategies to improve childhood vaccination rates in the general population have been described such as the implementation of a reminder/recall system, the introduction of caregiver home visits and education to empower informed decision-making [36]. Decision aids and counseling by child vaccine providers could improve the knowledge of decliners and support informed decision-making [37, 38]. Decision aids can be used as an alternative to the standard information provision and make decisions explicit by providing information about vaccination options and the associated benefits and harms. Lehmann et al. demonstrated that parents who received a decision aid with respect to childhood immunization showed an increased probability to vaccination at the appropriate time, had a decreased perception of vaccination risks and were more satisfied with their decision. However, it is debatable whether these strategies would influence parents who have religious motives to refrain from vaccination.

During the measles epidemic in 2013-2014, vaccination was additionally offered to 6-14-month-olds in municipalities with low vaccination coverage with the purpose to avoid infections in this specific risk group. These infants proved to have a lower risk of measles than unvaccinated infants in a study of the effectiveness of the early measles vaccination [39].
The measles outbreak evaluated in this thesis posed considerable logistical challenges for MHS staff, especially due to registration and follow-up of legally notifiable cases. To reduce this MHS workload and costs in a future outbreak, for the majority of measles cases who usually recover within a few days or weeks, only general information could be collected for surveillance purposes. For measles cases with complications, such as hospitalised cases, detailed information should continue to be collected.

1.3.3. Investment in prevention activities to avoid hospital outbreaks

The third study was related to antimicrobial resistance of which outbreaks in healthcare settings continue to evolve; they pose significant challenges to healthcare workers and negatively impact patient care [40]. When infections can no longer be treated by first-line antibiotics, more expensive medicines must be used. A longer duration of illness and treatment, often in hospitals, and aggressive prevention measures increase healthcare costs [41]. The NDM-1 outbreak at Jeroen Bosch Hospital (JBZ) in 's-Hertogenbosch, described in this thesis, demonstrates that even small outbreaks of antibiotic-resistant Gram-negative bacteria (only 29 patients were involved) result in substantial costs to an organisation. High costs were incurred by the JBZ hospital while from a public health view adequate control of the outbreak also benefits public interest. Therefore, it would be essential to continue hospital investment in prevention activities and organise financial compensation when hospitals experience major outbreaks for which they generally have no responsibility. In addition, the current weekly reports of the Netherlands Early Warning Committee in which infectious diseases causing a potential threat to Dutch public health are assessed and distributed among public health experts, is an important instrument to contain antimicrobial resistance outbreaks in a timely manner [42].

1.3.4. Efficiency improvement in controlling outbreaks of highly contagious viruses

The last outbreak described in this thesis applied to Ebola. It does not happen frequently that many organisations, from both curative and public health sectors have to be prepared for the introduction of a highly contagious and lethal infectious disease as Ebola. In the past, this occurred during SARS epidemic (2002/2003) and the 2009 influenza pandemic. The Ebola costing study raised suggestions to improve efficiency in working methods. For next outbreaks of this magnitude, national

standard guidelines will be useful regarding donning and doffing procedures, the necessary materials, and personal protective equipment [16]. In order to relieve possible shortages of materials, it may be helpful to form a temporary national supply chain [43]. The study also revealed that ambulance care services and hospitals experienced far more costs for preparedness activities than for response activities. The costs of response activities (transportations of suspected EVD cases) of ambulance services were 0.94% of total costs for ambulance services. The costs of response activities (admissions of suspected cases) of academic hospitals were 18.82% of total academic hospital costs. Given the small size of the Netherlands, it is important to discuss whether it is necessary that every ambulance care service and hospital ought to be prepared for an imported, possibly infected, case. Instead, a few selected organisations might fulfil this task for the whole country, while the rest could rely on more general preparedness [16]. Major increase in capacity and resources is therefore required only within these selected organisations. After the outbreak, the RIVM initiated working groups to restructure outbreak guidance and mutual work arrangements between ambulance services, hospitals, MHSs, and RIVM, which will be beneficial with respect to preparedness for upcoming outbreaks and their associated cost [16].

1.3.5. Structuring cost calculations

Estimation of outbreak costs can be challenging and time-consuming, and an organized approach is required to optimize accuracy. For the design, performance and assessment of cost-calculations in this thesis, the Dutch manual for performing economic evaluations was used and was adapted to assess outbreak costs [44]. The manual describes cost-concepts, steps to be taken, and contains practical information (standard costs and values) that can be applied in the cost calculations. Our experiences can be helpful to evaluate future outbreak costs. At first, the scope of the cost calculation has to be made. Besides the cost calculation of the NDM outbreak in which a hospital perspective was chosen, the aim was to include a wide range of social costs. At the start of the cost evaluation, also the boundaries of the outbreak time span are important. Second, relevant cost-categories are chosen mainly based on interviews with professionals. Within these cost-categories, measurable units/elements were identified such as personal protective clothing during the Ebola outbreak. This was followed by the measurement of resource use. The last step includes the monetary valuation of the units. In the bottom-up calculations as performed in the studies described, costs per organisation are determined by measuring time spent by staff, and use of materials and equipment; for example, by measuring the time professionals spent on (certain procedures) in the outbreak. Costs are then calculated by valuing the average time measured, using an estimate of the wage costs of the professional.

To facilitate future calculations of outbreak costs a standard calculation tool could be developed in which all relevant cost items as described above are included and can be collected in a prospective way.

1.3.6. Budget impact

Outbreaks have different financial consequences for the organisations and stakeholders involved. MHSs and RIVM take into account that they have to deal with future outbreaks and they made some financial reservations to control them however, often in a context of fixed staff time. Ambulance care services and hospitals do not consider upcoming outbreaks and they do not have specific resources for this purpose. For these organisations, adequate internal allocation of resources can be helpful to settle outbreak threats in future. The NDM-outbreak resulted in lowest outbreak cost but meant a high economic burden for the hospital concerned. To assess the financial consequences for these organisations, a budget impact analysis (BIA) can be performed [45, 46]. Usually, a BIA is performed in addition to a cost-effectiveness analysis in which a new intervention is adopted. In that case, a BIA evaluates whether the high-value intervention is affordable. With respect to outbreak costs, a BIA approach can be helpful to assess the costs per organisation, as described in this thesis. For example, the suggested incident management system in case of the *S.* Thompson outbreak will lead to high costs for food manufacturers that will most likely be passed on to consumers, but also may be hampering the international competitive position of Dutch food manufacturing companies. Additionally, it can be used for resource allocation for upcoming outbreaks and for new measures recommended after the outbreak took place.

1.3.7. Infectious diseases outbreak costs in relation to other public health incidents

With respect to other incidents that affect public health, costs of outbreaks are relatively low. For example, in 2017, laying-hen farms were confronted with fipronil found in eggs resulting in large economic consequences for the farms that used this agent. Costs incurred by laying-hen farms based on damage during the 'transport-ban period' (in which eggs were removed and destroyed) and the expenses of fipronil decontamination measures were assessed at €65 to €75 million, as of 22 September 2017 [47]. Direct costs for supermarkets were assessed at €7 to €8 million. In another example, regarding the pollution of soil in the Netherlands, repair costs are estimated at €300 million annually [48]. Although the amount of costs of these specific incidents were higher than the outbreak costs found in this thesis it is worthwhile to gain control over outbreak costs.

1.4. Concluding remarks

1.4.1. Outbreak costs are often underestimated

The papers in this thesis revealed that outbreaks are associated with a range of social costs and may have a large impact on the organizations involved, both in terms of staff resources and in terms of costs. It is important that outbreaks of a certain magnitude are evaluated to learn lessons for the future. For that reason, it would be helpful if organizations keep track of staff activities and financial expenses during outbreaks, which is crucial information for these cost evaluations. Cost evaluations should be performed preferably shortly after the outbreak to reduce recall bias. Due to data restrictions, social outbreak costs are almost definitely much higher in reality than found in the studies included in this thesis. In general, healthcare costs, productivity losses, patient costs, and outbreak control costs could be assessed adequately. Outbreak costs for trade and industry are not publicly accessible and therefore difficult to include in total costs. Compared to the other outbreaks in this thesis, the costs estimation of the *S.* Thompson outbreak is therefore possibly hampered by the largest underestimation.

1.4.2. Importance of cost evaluations

Cost evaluations of outbreaks are important. They give insight in expenditures of public funds and show where inefficiencies take place. They generate essential information for resource allocation at the start of future outbreaks. Last but not least they help in decision making about preventive interventions and justify the present structure targeted at prevention and control of infectious diseases both performed by public health institutes and healthcare organisations. Current policies for preventing infectious diseases outbreaks regarding the NIP, and a high quality of sanitation, food, and healthcare have reduced the burden of infectious disease and economic losses. New interventions appear, such as a new universal vaccination against influenza [49] and pre-exposure prophylaxis for HIV [50]. However, the competition between scientific progresses and the adaptation or the influx of new pathogens, continues and outbreaks will remain.

PART 2

2.1. Main findings

2.1.1. Possible introduction of hepatitis A vaccination

In chapter 6, the potential introduction of hepatitis A vaccination into the NIP is assessed using an evaluation model [51]. The increasing group of elderly lacking protection against hepatitis A could be an argument for including the vaccine into the NIP, or initiating a vaccination programme targeted at the elderly only. Both universal and targeted vaccination were not considered cost-effective interventions. The number of annual hepatitis A notifications was declining steadily in the past years. Although healthcare costs and productivity losses per patient were rising, this did not outweigh the annual costs of a vaccination programme estimated at €10 million for infants and €13 million for older people (with an additional €210 million for catch-up vaccination in the first year only). Targeted preventive measures such as vaccinating travellers and other high-risk groups and timely vaccination of close contacts of hepatitis A cases were considered an adequate alternative.

2.1.2. Diseases included in economic evaluations targeted at HPV vaccination

Chapter 7 presents a systematic review of HPV economic evaluations [52]. Most published HPV cost-effectiveness analyses have focused on the prevention of cervical disease as a main health outcome. In this review, the influence of non-cervical HPV-associated diseases on the incremental cost-effectiveness ratio (ICER) of pre-adolescent HPV vaccination was assessed. Eighteen studies were identified that included non-cervical diseases in the economic evaluation. When HPV-related diseases other than cervix carcinoma were taken into account, the ICERs became considerably more favorable. Compared to not including such other diseases, the mean ICERs were 2.85 times more favourable (95%CI 1.35-4.36) for girls only vs. no vaccination, and 3.89 times (95% CI -0.10-7.85) for gender neutral vs. girl only vaccination. The inclusion of non-cervical diseases in economic evaluations of HPV vaccination programs increases the likeliness of gender neutral vaccination to be cost-effective.

2.1.3. Evaluation of restricted STI testing policy on costs and QALYs

In chapter 8, a more restrictive STI testing policy is evaluated with regard to the number of infections missed, test costs and QALYs lost [53]. In 2015, this policy was introduced with syphilis and HIV tests only on indication for heterosexual clients up to 25 years of age, born in the Netherlands. The 2015 policy led to estimated savings of €1.1 million for the Netherlands, while missing approximately 3 HIV infections and 7 syphilis infections annually. Expressed in a cost-effectiveness ratio, the associated

savings were €435,000/QALY lost. We also described that STI testing could be improved in an efficient manner by offering syphilis and HIV tests for both first- and second-generation immigrants. Moreover, in case of a positive chlamydia or gonorrhoea diagnosis we demonstrated that an additional HIV test was recommended.

2.1.4. Social cost-benefit analysis of Interventions to prevent toxoplasmosis

The design of a Social Cost-Benefit Analysis (SCBA) targeted at toxoplasmosis is described in chapter 9 [54]. Toxoplasmosis causes an important disease burden in the Netherlands, with an estimated health loss of 1,900 Disability Adjusted Life Years and a cost-of-illness estimated at €44 million per year. Two interventions were explored to prevent toxoplasmosis: freezing of meat destined for undercooked consumption, and improving biosecurity in pig husbandries. Putting these interventions into practice would expectedly reduce the number of infections; however, the net benefits for society are unknown. In chapter 10, costs and benefits of these interventions for all relevant stakeholders are presented. The freezing meat intervention proved to be far more effective than the biosecurity intervention. Despite high freezing costs, freezing meat products steak tartare and mutton leg yielded net social benefits in both the minimum as maximum scenario, ranging from €3 million to €12 million for steak tartare and €6 million to €15 million for mutton leg. The biosecurity intervention would result in net costs in all scenarios ranging from €1 million to €2.5 million, due to high intervention costs. To reduce the burden of toxoplasmosis, freezing steak tartare and leg of mutton is to be considered. However, a discrete choice experiment (DCE) performed in this study revealed that consumers would prefer fresh meat instead of industrially frozen (and thawed) meat.

2.1.5. Cost-effectiveness hepatitis B and C screening foreign-born migrants

Chapter 11 describes results of the cost-effectiveness of screening foreign-born migrants originating from hepatitis B (HBV) and hepatitis C (HCV) endemic countries in the Netherlands. Combined HBV and HCV screening is the most cost-effective strategy for migrant groups with a high number of expected cases of HBV and HCV with ICERs ranging from €4,962/QALY gained for migrants originating from the Former Soviet Union and Vietnam to €9,375/QALY gained for Poland. Screening only for HBV is the most cost-effective option (€6,233/QALY gained) for migrants originating from Turkey. Considering the Dutch threshold value for cost-effectiveness, screening migrant groups for HBV has a cost-effectiveness level below €20,000/QALY at an HBV prevalence of 0.41%. HCV screening is cost-effective at a prevalence of 0.22%, taking the same reference value for cost-effectiveness into account. These findings are driven by the prevention of long-term disease sequelae such as cirrhosis, hepatocellular carcinoma and death due to disease. The largest number of complications due to

HBV-infection can be prevented by screening migrants born in Turkey, with an estimated number of 7,463 chronically infected cases in the Netherlands. The largest number of HCV complications can be averted by screening and treating migrants born in Surinam, with an estimated number of 2,935 chronically infected cases in the Netherlands.

2.2. Methodological and policy considerations

The papers in part 2 contain mixed methods research, each with their own advantages and pitfalls.

2.2.1. Hepatitis A, rise among MSM

In the hepatitis A paper, a description of the hepatitis A epidemiology, disease burden, and costs of potential vaccination programmes for the Netherlands was presented. Vaccination was not recommended because of the low number of annual cases, but monitoring the hepatitis A epidemiology was suggested as susceptibility of older age groups could increase and hepatitis A vaccination may be reassessed. After the study period, the number of hepatitis A cases further declined to around eighty cases annually in 2015 [55]. However, in 2016 and 2017 an unexpected large international outbreak among MSM took place, also affecting the Netherlands leading to 380 hepatitis A cases of which 280 cases are related to MSM (personal communication Ingrid Friesema, RIVM) [56, 57]. This specific risk group was not considered in the paper. To some extent, universal hepatitis A vaccination could have reduced the outbreak since there was some transmission outside the MSM risk group. Vaccination against hepatitis A was provided at reduced costs at own expenses and was administered in combination with hepatitis B vaccine for the MSM risk group.

The current hepatitis A vaccination schedule consists of two doses. Introduction of hepatitis A vaccination could become more feasible with single-dose vaccination. Single-dose vaccination has a beneficial cost-effectiveness profile and has been proven effective in outbreak control [58]. Moreover, single dose universal hepatitis A vaccination is already implemented in some low-income countries [59]. It resulted in sustained immunologic protection for up to 9 years after vaccination, confirming the success of the intervention [60]. For 2020, the Health Council has planned to assess introduction of universal or targeted hepatitis A vaccination for the Netherlands, taking single dose vaccination into account.

2.2.2. Few HPV studies in the review included all HPV-associated diseases

The review of economic evaluations of HPV vaccinations aimed at assessing the effect of including all known HPV-associated diseases in models that assess the cost-effectiveness of vaccination. However, few studies truly incorporated all known

HPV associated diseases: 11 out of 18 studies considered most but not all presently known HPV-associated diseases. Furthermore, 8 out of 18 studies did not include cross-protection in the model. Both aspects will negatively affect cost-effectiveness estimates, as there will be less vaccine preventable diseases included in the analysis [61-64].

Many studies included in the review were hampered by a lack of available national cancer data regarding incidence, and other national data on costs of treatment and utilities associated with cancer. This may have influenced the ICER which is based on differences on costs and effects (QALYs gained by vaccination). Moreover, most studies assumed that the incidence of HPV-associated cancers will be constant over time. For oropharyngeal, penile and anal cancer however, an increasing trend is observed [65-67]. In all but two studies targeted at boys, transmission among MSM was neglected [64, 68]. None of the economic evaluations included productivity losses, influencing the ICER negatively. Among the included studies, the efficacy of vaccination for women was in most cases above 95%, while in men no efficacy higher than 90% was included with a minimum of only 41%. Again, this aspect will affect the ICER negatively and makes it less likely to support implementation of boys' vaccination [69]. The cost-effectiveness estimates found in the review might even be more favourable due to higher vaccine prices used in the included studies compared to the actual prices that were realized in several vaccination programs [70]. Most of the included studies considered a three-dose scheme, while in the meantime the two-dose scheme has been licensed in several countries [71]. It has been suggested that even one dose might be enough to reach the same protection against infection [72, 73]. Finally, probably more HPV-associated diseases are to be considered in economic evaluations. For example, cancer of the oral cavity is classified as having a possible connection with HPV [74, 75]. As this cancer occurs frequently, even a small fraction that could be attributable to HPV would already lead to many cases that could be prevented by HPV vaccination. In summary, methodological choices, limitations and fast developments that were not reflected in economic evaluations seem to result in conservative estimates of the cost-effectiveness of HPV vaccination. It seems therefore plausible that vaccination of both girls and boys is a cost-effective policy option.

2.2.3. Willingness-to-accept in evaluation STI testing policy

The evaluation of the restricted STI testing policy for young heterosexuals was restricted by data limitations. Some well-known factors predicting STI risk are not recorded at STI clinics and are therefore not included in the study, such as having syphilis or HIV specific symptoms, having been notified for syphilis or HIV infection or having a partner born in an STI endemic country. In addition, based on the assessment of clients' STI risks at the clinic clinicians have the opportunity to perform additional

tests. Therefore, the real number of missed infections due to the new testing policy will be lower than conservatively estimated in our economic evaluation. The long-term transmission effect of the new testing policy was not included in the study. Treatment costs, nor costs and QALY losses due to transmission of undetected syphilis and HIV infection were included. Including these items would result in less favourable estimates of cost-effectiveness. The results in this analysis used data based on the epidemiological situation in 2011-2013, while afterwards the epidemiological situation may have changed. For example, in 2015 and 2016 small geographical clusters of heterosexual syphilis cases were observed (unpublished data). Finally, the new policy at STI clinics could lead to additional tests and associated costs in general practice, making our results less beneficial. Due to data restrictions this was ignored in our analysis.

The study on changing STI testing policies is relatively unique as economic evaluations with ICERs in the southwest quadrant are relatively rare. Here, it is important to realize that the results rely on the assumption that the maximum amount society is willing to invest to avoid one QALY lost, the Willingness-To-Pay (WTP), corresponds with the compensation for a QALY lost, the Willingness-To-Accept (WTA). However, as people are risk averse, it is generally accepted that the compensation for health losses will need to be higher than the WTP for health gains [76]. At an estimated cost-effectiveness ratio of €435,000 per QALY lost, the WTA to WTP ratio could be as high as 5.4, at a threshold value of 80.000 and 21 at a threshold of 20.000. These high WTA to WTP values suggest that the health loss that was observed as a result of limitation of testing facilities is acceptable to society. The often used Dutch WTP threshold of €20,000 per QALY gained was applied which is low compared to the US' threshold of $50,000 per QALY gained [77]. Using a higher threshold in the sensitivity analysis resulted in a lower net monetary benefit.

2.2.4. Assumptions in SCBA toxoplasmosis

The main limitation of the SCBA was the lack of effectiveness data applied to the biosecurity intervention. Currently, this intervention is evaluated in a pilot study conducted by Wageningen University. If the effectiveness in that project turns out to be more than 1% as assumed in our study, it would lead to more benefits for the biosecurity intervention. Due to other reasons, findings of the SCBA might be underestimated. Based on a French study, only productivity losses for caregivers were included, not for children born with complications from toxoplasmosis [78]. In contrast to the Netherlands, screening during pregnancy is implemented in France, with probably an altered population of congenital toxoplasma cases as a result. In our study, DALY estimations were based on fetal losses from only 24th week of gestation.

Moreover, productivity losses for fetal and neonatal deaths were excluded from the calculations based on Dutch SCBA guidance [79], which might be different from other cost-benefit analyses based on other guidelines [80].
Not considered in the SCBA was the fact that by freezing and unthawing meat, an additional step is introduced in the meat chain, with an increased risk of introducing additional hazard such as other microorganisms with a negative impact on human health. Therefore, the estimates might be overestimated to some extent. International trade/market distortion was ignored in our study, assuming that the interventions would be enforced by law in the European Union (at the least). However, if this assumption does not hold, the results are no longer valid since in the Netherlands about 75% of all meat is exported, mostly to EU countries [81].
Due to data restrictions, price elasticity of meat was based on old figures and was not specifically targeted at the specific meat products in the SCBA. If meat products would become too expensive for consumers they might shift to consuming other meat products with other attribution towards toxoplasmosis (and possibly other pathogens) not considered in this study [82, 83].

2.2.5. Uncertainty in the ICER regarding screening migrants for HBV and HCV

In our study, we did not explore the contribution of the statistical uncertainty around each parameter on the ICER using a probabilistic sensitivity analysis. Instead, we took a deterministic approach and explored which parameters were most influential in changing the ICER. We found that the ICER was mostly affected by treatment costs and utility losses of chronic HBV and HCV disease. The relatively high current market prices were already used in baseline and if we excluded utility losses for these disease states from the model (that is assuming perfect health for these conditions) screening remained cost-effective. Additionally, if we combined a low participation rate of only 10% with specialist care treatment of 60% of those who tested positive, screening migrant populations was cost-effective. Given that even with extreme assumptions of the most influential parameters the ICER was still cost-effective we are confident that our conclusions are robust.
The findings in this cost-effectiveness analysis are largely driven by the underlying seroprevalence estimates of chronic HBV and HCV infection in the specific migrant groups. These seroprevalence figures were based on migrant screening projects and prevalence studies performed in the Netherlands and if unavailable, were taken from literature [84-86]. Due to several bias mechanisms prevalence rates found in the Netherlands may be lower than in the country of origin. In addition, migrants are not only a very heterogeneous group between countries, but also within countries, where

migrant-groups from the same country can defer in social-economic status, language and culture. Therefore, our cost-effectiveness estimates should be interpreted as an indication.

Data were lacking for the proportion of migrants who have already been tested in the past. Therefore, we may have overestimated the number of people who can still benefit from screening. Additionally, we used an average age of 40 years, based on the average age that was observed in several Dutch hepatitis screening projects. When the average person screened is older, the cost-effectiveness will be less beneficial as less QALYs can be gained. A younger average age, would probably result in a more cost-effective programme, presuming the same prevalence.
In our study, we adopted a societal perspective and included productivity losses in the model based on estimates taken from the literature [87]. However, Scalone et al assessed productivity losses only for persons with a paid job while some persons lost their job due to disease. As a result productivity losses are probably underestimated in our study, influencing the ICER negatively.

2.2.6. CEA versus SCBA

SCBAs are not often conducted in the field of infectious diseases; an exploration of the optimal use of SCBAs versus cost-effectiveness analysis (CEA) is in place and will be described below.
CEA and BCA are both aimed at providing information for policy makers to stimulate evidence-based decision-making by providing evidence on the costs and consequences of investments [88]. For policy making, the information from economic evaluations is often combined with information on non-quantifiable effects, ethical issues, legal circumstances, and technical, budgetary, and political restrictions. Both evaluation methods focus on comparing the impacts of alternative interventions (often including the option of current policies or no action). In addition, they typically use the same approaches for estimating costs. Ideally, a CEA is just as an SCBA performed from a societal perspective taken all relevant costs and effects into account. However, in practice, often a less informative healthcare perspective is chosen, leaving for example productivity losses out of the calculations. The main difference is that in CEA, the costs of an investment are generally divided by a single outcome measure, often QALYs gained or DALYs averted. SCBAs consider all possible intervention outcomes, both health and non-health outcomes, and value them in monetary terms. A positive net benefit implies that the intervention has more benefits than costs, and the other way around. The net monetary outcome is an important issue in SCBAs. Besides, as in the market place, it is used as an easy and well-established means of exchange that permits comparison of unequal ingredients of the SCBA. In addition, the net benefit

calculated in the SCBA is not equal to money that can be freely spent, since the SCBA is an accumulation of financial Euros (such as savings because of less demand for special education, 'real money') and non-financial Euros (such as the monetary value of an increase in quality of life).
Designating values in monetary terms in SCBAs simulates the actual assessment often implicitly used in policy making. It answers the question: "How does societal welfare change as a consequence of implementing policy options?" If a government or other organisation chooses to allocate money on one initiative, it will have fewer resources available to assign money to other targets, including those that address the same or similar problems.

Taking all societal effects of an intervention into account, the SCBA seems more ambitious than the CEA as it considers welfare changes between stakeholders involved. However, SCBAs do not explicitly account for how changes in wellbeing are distributed in the population and among stakeholders [89]. For example the net benefits may be identical whether many people gain small benefits or a few people gain large benefits, and these differences might be valued differently by politicians. Second, SCBAs can be hampered by data restrictions and uncertainty about likely consequences as was the case in our SCBA regarding toxoplasmosis. Consequently, differences in net benefits of alternative options can be masked by differences in assumptions, potentially leading to broadly varying conclusions regarding the interest of a particular intervention.

2.2.7. Methodological differences between SCBAs internationally

To be useful for evidence-based decision-making, researchers must preferably use equal methods in economic evaluations to achieve comparable results. Otherwise, they should clearly explain the rationale for any differences in approach and the implications of these differences for decision-making. In addition to the Netherlands, several guidelines for SCBAs in other high-income countries exist, for example in Australia, UK, US, Canada, and France [79, 90-95]. In general, these guidelines reflect a similar view on SCBAs as their main purpose is to support decision-making. However, differences between these guidelines exist: for example the value of a statistical life ranges from $2.9 million to $9.3 million (in US$ 2014), a variety of non-health outcomes are included in these guidelines, and discount rates range from 2.5% to 8%. Strzepek et al recently described a guidance to assess the broad effects of health and environmental interventions to support cost-benefit analyses [96]. He includes overall GDP growth, productivity, market outputs, and distribution of income among populations.

2.3. Implications for policy and research

2.3.1. More evidence is needed for a single dose hepatitis A vaccination

The Dutch policy to monitor hepatitis A cases, to trace and vaccinate contacts, and identify risk groups for hepatitis A appears sufficient to control the number of infections. Besides a large outbreak among MSM, the number of hepatitis A cases did not increase in the last years, not even in the elderly. WHO recommends universal vaccination for intermediate endemic countries, and vaccination of only risk groups in low endemic countries such as the Netherlands [97]. Additionally to MSM, groups at increased risk of hepatitis A include travellers to areas of intermediate or high endemicity and patients with chronic liver disease who are at increased risk for fulminant hepatitis A [98]. This is already current practice in the Netherlands. As evidence on long term effectiveness is limited, it is too early to replace the two-dose vaccination scheme with an economically more favourable single-dose vaccination. Further research on the vaccine doses needed to achieve long-term protection against hepatitis A infection is required [99].

2.3.2. Including all HPV-associated diseases supports boys' vaccination

Future HPV cost-effectiveness analyses targeted at new programs, settings, or vaccines such as the nonavalent vaccine, should consider all known HPV-associated diseases and in consequence, the complete QALY gains of HPV vaccination [100]. With respect to the already existing HPV vaccination program in the Netherlands, our review implies that the cost-effectiveness might be considerably more favourable than estimated at the time of introduction of the vaccine, as the QALYs gained by vaccination were only related to cervical cancer. Further studies on immunogenicity and effectiveness of HPV vaccination for both men and women should enable better assumptions on long-term efficacy. Recently, Donken et al demonstrated that the effectiveness against vaccine type infections, six years after introduction of HPV vaccination in the Netherlands, was very high (97.7%) [101]. Additional information on utilities, survival and etiological fractions of non-cervical cancers would be helpful to unravel the overall cost-effectiveness profile of HPV vaccination.

In addition, the inclusion of all recognized HPV-associated diseases could support policymakers to extend the target group of HPV-vaccination to males; especially when considering the reduced vaccine prices and simplified dosing strategies. Furthermore, specific programs for groups at increased risk, for example MSM, could be explored as girls' vaccination will not significantly influence the burden of anal cancer in men, which is primarily existent in MSM [100, 102-104]. Finally, more efforts are needed to increase the HPV-vaccination coverage in girls [31, 105].

2.3.3. Efficiency STI testing policy

In several countries, the necessity to decrease or at least curb public expenditures has led to restricted budgets in healthcare. To accommodate these budget cuts in the best possible way, it becomes increasingly important to evaluate and increase the cost-effectiveness of interventions in the health sector. This may entail reconsidering, and even suspending, current treatment procedures. The evaluation of a reduced STI prevention programme implemented by the Dutch government, as well as alternative reduced testing schemes was performed against this background.

We found that the implemented testing policy at STI clinics seemed to be an adequate decision; only leading to a modest decline in HIV and syphilis infections diagnosed, while generating substantial test cost savings for society. We suggested a few ameliorations of the testing policy, such as offering syphilis and HIV tests to second-generation immigrants and those who tested previously positive for chlamydia and gonorrhoea. For the future, it is important to monitor the effects of the restricted testing policy. Finally, efficiently finding those with undetected HIV and syphilis infection beyond the setting of the STI clinics is of importance. Smartphone-enabled, internet-based, and other STI self-testing devices, linked with online clinical care pathways for treatment, partner notification, and disease surveillance, are possibilities to increase testing among risk groups that underutilise existing services in a cost effective way [106-108].

With the growth of diagnostic tests and new treatments in healthcare during the last decades, overuse and misuse of medical and diagnostic procedures have raised concerns [109]. According to Emanuel and Fuchs, overutilisation can take 2 practices: higher volumes, such as more consultations, hospitalisations, tests, procedures, and prescriptions than are appropriate *or* more costly professionals, tests, procedures, and prescriptions than are appropriate [110]. At first, attention should be paid to the use of diagnostic procedures and therapies that have no evident benefit, which was the case in STI, testing in young heterosexual cases in the Netherlands. The purpose to reduce STI testing costs shows resemblance with the “Choosing Wisely” campaign, initiated in 2012 in the USA, and followed by many other countries aiming to stimulate physicians and patients to discuss the likely overuse of healthcare. The main goal was to improve patients’ health by averting risks inherent in diagnostic and therapeutic interventions. Also infectious diseases issues were identified, related to treatment, diagnostics, and prevention [111]. Reduction of costs seemed to be the spin-off of this initiative and was achieved through improvements in service quality and efficiency, including the reduction of ineffective, overused, or inappropriate procedures. The case in the STI testing policy can serve as an example for other infectious diseases

such as the unnecessary testing or use of antibiotics in upper respiratory tract infections [111]. A restrained prescription of antibiotics is beneficial to avoid antibiotic resistance however, it may extend the duration of disease.

2.3.4. Freezing meat is to be considered to prevent toxoplasmosis

Surprisingly, the DCE performed in this study revealed that consumers are not intending to buy frozen (and thawed) meat. For that purpose, informing consumers seems crucial to persuade them to buy toxoplasma-safe meat. The exploration of other interventions such as improving education of pregnant women, sheep vaccination, high pressure processing (HPP), gamma radiation, and cat vaccination using the SCBA method is worthwhile. As scientific evidence on effectivity of prenatal education for the prevention of congenital toxoplasmosis is scarce, further RCTs on this topic are required [112]. Despite a number of vaccination experiments targeted at limiting acute infections and eliminating tissue cysts in the intermediate hosts such as sheep, these vaccinations are not licensed yet for this purpose [113]. Currently, a cat vaccination is also not available. High pressure meat treatment is effective but will lead to additional costs and often results in discoloration of meat making it less attractive to consumers [114]. Gamma ray irradiation also has the potential to effectively increase food safety [115]. However, this technology is very controversial among consumers leading to reluctance to purchase irradiated products [116]. Here, proper and extensive information campaigns may be needed.

2.3.5. Combined screening migrant groups on HBV and HCV is recommended

WHO launched a global viral hepatitis strategy aimed at reducing mortality by 65% by the year 2030. To reach this goal, increased strategies are needed to scale-up testing and treatment [117]. Implementation of targeted HBV and HCV screening programmes to increase early diagnosis and treatment is important to reduce the burden of chronic hepatitis B and C among migrants. For most migrant populations in the Netherlands offering combined HBV and HCV screening proved to be cost-effective.

In our study, we assumed a modest participation rate of 30% as baseline. Several interventions at low cost can improve engagement and compliance along the chronic viral hepatitis care continuum [118, 119]. As in most general practices, only a few patients will be eligible for screening, a close collaboration between GPs, MHS and community-based organisations is recommended in which MHSs can take the lead in coordinating the screening programme [120-123]. Several examples of Dutch community based screening pilots exist to design a screening programme [120, 122, 124].

2.3.6. Considering differences between SCBA and CEA in the Netherlands

In the Netherlands, based on two different guidelines, important methodological differences between SCBAs and CEA exist that should be taken into account in the process of decision-making [44, 79, 125]. First of all, the value of a QALY differs. In CEA, the suggested value of a QALY ranges from €20,000 to €80,000, whereas in SCBAs the value of a QALY is assessed at €50,000 [79, 126]. To address time preferences in SCBAs the discount rate is defined at 3%, while in CEA performed in the Netherlands the discount rate for costs and effects is 4% and 1.5%, respectively. In case evaluating a preventive intervention with effects only occurring after a number of years, CEAs will calculate more favourable results than SCBAs. Therefore, discounting procedures can strongly influence results from economic evaluations and it is subject to debate. In most countries an equal discount rate for costs and health effects are applied in economic modelling, also in CEA [127]. The choice between uniform and differential discounting depends on the assumption whether the value of health effects is expected to change over time [127]. Following Brouwer et al. this growth needs to be accounted for in economic evaluations [128]. Using monetary values this can be done by using a growing value for health. When using non-monetary values, such as QALYs, the growth can be accounted for by lowering the discount rate for effects relative to that of costs. Claxton et al. also states that benefits from better health will increase compared to benefits from increased consumption hence, the consumption value of health will also increase [129]. Contrary to Brouwer et al., Claxton et al. showed that with a fixed budget for healthcare, decisions based on ICERs, and a constant threshold for ICERs, discounting costs and health gains at a differential rate would be incorrect.

Another important issue is the assessment of productivity losses, in an SCBA the human capital method is designated, while in CEA the friction cost method is to be used. The human capital method estimates productivity losses as the sum of wages during the time of absence, whereas the friction cost method only considers productivity costs until the worker is substituted [130]. Following the human capital method, generally a longer period of productivity losses will be taken into account, often resulting in economically more favourable results in SCBAs than in CEAs. Both methods have a hidden assumption. In the human capital method, calculating the sum of wages during absence, may overestimate the value of the productivity losses due to the disease [130]. Any individual is susceptible to death or disability due to a range of diseases, and to unemployment. The second hidden assumption relates to the friction cost method: any vacancy created by a worker's disability will be directly filled in by an unemployed person, which might not be the case [130]. If a vacancy is covered by an already employed person looking for a better job, a vacancy chain could start leading to several friction costs. Targoutzidis' has suggested adjustments

of these methods. With respect to the human capital method, he proposes a depreciation of productivity with risks of disability, death, and unemployment. The friction cost method could be adjusted with the expected length of the vacancy chains, which is of course depending on the unemployment rate. After amendments of the two methods, estimates for productivity losses will come together and it can serve as a solution to the great cleavage in results between these two methods.

2.4. Concluding remarks

The results of the papers in part two of this thesis can be used for policy making in the field of infectious diseases. With respect to hepatitis A it confirms the absence of the need of introducing hepatitis A vaccination into the NIP. For HPV it may stimulate introduction of gender neutral vaccination. In the study regarding STI, the already implemented testing policy was evaluated, leading to discussions of ameliorations to reduce missed infections and improve efficiency of testing. The SCBA targeted at toxoplasmosis resulted in a viable policy option to reduce the burden of disease. The results of our cost-effectiveness analysis can guide implementation of HBV and HCV screening strategies targeting foreign-born migrants. As migrants are disproportionately affected by chronic viral hepatitis, both expansion of HBV and HCV screening programmes to increase early diagnose and improving access to effective treatment are important to reduce the burden of disease.

Methods and assumptions with respect to the value of a QALY, assessing productivity, and discounting differ between CEAs and SCBAs. Consensus is needed on these methods and assumptions to allow for the comparison of results across CEAs and SCBAs internationally, but above all within the Netherlands first. To achieve consensus, discussion of these items between (health) economists in the Netherlands is essential, for example facilitated by the Health Care Institute.

SCBAs and CEA research in the field of infectious diseases

Whether an SCBA or CEA is the method of choice depends on the nature of the problem to be addressed, the decision-making context, and the needs of decision-makers and other stakeholders [88]. An SCBA provides information on the highest net present value of an intervention, CEA present the option with the lowest cost per outcome unit (mostly QALYs gained). CEA is the leading evaluation method in the health sector. In general, performing an SCBA is more labour- and data-intensive. An SCBA is particularly important to apply if the problem concerned and its solution in the form of a new intervention, affect more sectors of society. This is for example the case when the economics of interventions to control zoonosis are to be evaluated

and the influence on the human and animal health sector need to be integrated for decision makers in both sectors and it is the methodology to apply in a One Health approach [131].

5. OVERVIEW OF MAIN RECOMMENDATIONS FOR POLICY AND RESEARCH

The studies in this thesis revealed recommendations for research and policy. The most important ones are described, in short, below.

5.1. Research

1. When major outbreaks occur, cost evaluations should be performed more often. These are important to inform and optimize outbreak control in future outbreaks. Cost evaluations should be performed shortly after the outbreak to reduce recall bias;
2. To facilitate future calculations of outbreak costs a standard calculation tool could be developed in which all relevant cost items as described in this thesis are included and can be collected standardized in a prospective way;
3. Future HPV economic evaluations should take all known HPV-associated diseases into account and in consequence the complete QALY gains of HPV vaccination;
4. The case in the STI testing policy can serve as an example for evaluations targeted at new policies for other infectious diseases in which restricted testing or treatment is recommended, for instance with respect to the use of antibiotics in upper respiratory tract infections;
5. Consensus is needed on methods and assumptions regarding discounting, the value of a QALY, and assessment of productivity losses, both used in CEAs and SCBAs, to allow for the comparison of results across studies applying different methods. To achieve consensus, discussion of these items between (health) economists in the Netherlands is necessary. An SCBA is recommended if the problem under study and possible interventions affect more sectors of society. It is the preferred methodology to apply in a One Health approach when the influence of interventions on both the human and animal health sector needs to be integrated for decision makers in both sectors.

5.2. Policy

1. Continuation of hospital investment in infection prevention activities is of importance, as well as transparency and exchange of information in case of possible hospital outbreaks. Financial compensation when hospitals experience major outbreaks for which they have no responsibility should be considered;
2. There is a need for national guidelines for upcoming outbreaks caused by highly virulent and lethal pathogens with respect to donning and doffing procedures, the necessary materials, and personal protective equipment. It may be helpful to form a temporary national supply chain to prevent possible shortage of materials. Given the small size of the Netherlands a few selected ambulance care services and hospitals might take responsibility for care and treatment of patients for the whole country, while the remainder of organisations could rely on more general preparedness;
3. Offering syphilis and HIV tests to first- *and* second-generation immigrants and those who tested previously positive for chlamydia and gonorrhoea is recommended. Monitoring the effects of the restricted testing policy is important. Finally, efficiently finding those with undetected HIV and syphilis infection beyond the setting of the STI clinics is key;
4. Freezing high-risk meat products is to be considered to prevent toxoplasmosis. Informing consumers seems crucial to persuade them to buy toxoplasma-safe meat;
5. Implementation of targeted HBV and HCV screening programmes to increase early diagnosis and treatment is important to reduce the burden of chronic hepatitis B and C among migrants. For most migrant populations in the Netherlands with a high expected number of chronically infected cases, offering combined HBV and HCV screening is recommended.

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CHAPTER 13

Summary

SUMMARY

In the Netherlands, as in other Western countries, infectious diseases outbreaks regularly occur, mostly foodborne and respiratory outbreaks. These outbreaks can have a large impact on society regarding the burden of disease and induce financial costs. These costs concern, amongst others, medical costs, productivity losses, patient costs, business losses, and cost to control the outbreaks. As outbreaks are poorly predictable and initiate substantial control efforts to contain them, healthcare organizations should be well prepared to address sudden increases in infectious diseases. Cost assessments can be helpful in learning to address infectious disease outbreaks. Here we summarize the results of cost-evaluations of four outbreaks that took place in the past years, including preparedness and response activities of public health authorities (Part 1, Chapters 2-5). Disease surveillance, laboratory detection, and epidemiologic investigation are necessary elements in an infectious diseases infrastructure. In addition, preventive strategies, such as vaccination programmes, adequate treatments, screening initiatives, and health education programmes are key to protect the general population from infectious diseases. Part 2 of this thesis focuses on economic evaluations. Economic evaluations often contribute to the development of new national policies targeted at infectious diseases and guide in well-informed decision making for new interventions. It is an important source of information about costs and consequences of new interventions for policy makers.We present results of evaluations of cost-effectiveness of several interventions in infectious disease control (Part 2, Chapters 6-11). In the introductory **Chapter 1** the research questions as well as the outline of this dissertation is described.

PART 1

Chapter 2 presents the societal costs of the most extensive food-related outbreak of *Salmonella* ever recorded in the Netherlands. Smoked salmon contaminated with *Salmonella* Thompson during processing caused the outbreak. More than 1000 cases of salmonellosis were laboratory confirmed and reported to RIVM of which twenty percent of cases was hospitalised and four cases died because of infection. Using the Dutch foodborne disease burden model, the real number of cases was expected to be much higher, around 21,000 cases. Total outbreak costs, including healthcare costs, productivity losses, patient costs, and outbreak control were estimated at €7.5 million. Productivity losses were the main cost driver in this outbreak. We concluded

that early warning and strengthening cooperation between food industry, health authorities, and laboratories is vital for rapid detection and control of foodborne outbreaks, in order to reduce disease and economic burden.

Chapter 3 describes a similar study to the one reported in Chapter 2, this time with respect to a large nationwide measles outbreak. The measles outbreak took place in 2013 and 2014 in orthodox Protestant communities. Vaccination rates for mumps, measles and rubella are lower in these communities than in the general population. During the epidemic 2,700 measles cases were reported, however, the real number was expected to be tenfold higher. Without considering underestimation, total outbreak costs were around €3.9 million. As this outbreak mostly affected children, productivity losses were less important than in the *Salmonella* outbreak, instead outbreak control costs was the central cost item. We provided suggestions to decrease the workload of MHSs' professionals in recording most measles cases in less detail in future outbreaks.

Chapter 4 presents the costs of Ebola preparedness and response of the Dutch health system in 2014 and 2015. Only 13 possible cases were clinically evaluated and one confirmed case was admitted to hospital. The estimated total costs were high at €12.6 million. To reduce future outbreak costs and increase efficiency allocating only one ambulance service for transportation and a few hospitals for treatment of possible patients with a highly infectious disease was proposed.

Chapter 5 focuses on the costs of a hospital outbreak with a multidrug-resistant, New Delhi-metallo-β-lactamase–positive (NDM) *Klebsiella pneumoniae* strain in 2015-2016. After detection of this strain on a surgical ward of a peripheral hospital, 6 other wards showed uncontrolled transmission with this pathogen. 29 patients proved to be colonized. We calculated hospital outbreak costs based on information retrieved from the hospital (for example the number of blocked beds, laboratory tests, cleaning costs) and interviews with staff with respect to the time spent on outbreak control activities. Total outbreak costs incurred by the hospital were estimated at €654,000. Closure of beds and staff time targeted at infection prevention were the most important cost items. Investment in prevention activities to avoid hospital outbreaks remains important as well as financial compensation for hospitals that experience large outbreaks.

PART 2

In **Chapter 6** potential introduction of hepatitis A vaccination into the National Immunisation Programme is assessed since future cohorts of non-vaccinated elderly will lack natural protection against disease. Potential benefits and drawbacks of implementing hepatitis A vaccine were evaluated using a vaccine evaluation scheme.

As the number of annual hepatitis A notifications is declining, the cost-of-illness due to hepatitis A is rather low (around €650,000 per year) and annual costs for mass-vaccination would be around €10 million for infants and €13 million for the elderly, initiating a vaccination program would most likely not be cost-effective. Instead, targeted preventive measures such as vaccinating travellers and other high-risk groups and timely vaccination of close contacts of hepatitis A patients are acceptable.
In **Chapter 7** the consequences of a more restrictive testing policy for sexually transmitted infections (STI) is evaluated. Since 2015, younger, heterosexual clients without having risks for an STI were no longer standard tested on syphilis and HIV. Surveillance data from 2011- 2013 were used, with still extensive testing for all, to calculate effects of the new testing policy on test costs, number of infections missed, costs per Quality Adjusted Life Year (QALY) lost, and the net monetary benefit. The new testing policy led to estimated savings of €1.1 million, whereas three HIV infections and seven syphilis infections would be missed per year. Savings were €435,000/QALY lost. We found that offering syphilis and HIV tests for both first- and second-generation immigrants and offering an HIV test in case of positive chlamydia or gonorrhoea diagnosis would improve efficiency of the testing policy.
Chapter 8 presents results of a systematic review of economic evaluations of Human Papilloma Virus (HPV) vaccination. In this review, we evaluated the influence of non-cervical HPV-associated diseases on the incremental cost-effectiveness ratio (ICER) of preadolescent HPV vaccination. The cost-effectiveness of vaccination is expected to be underestimated if not all HPV-associated diseases are taken into account. We identified 18 studies that included non-cervical diseases in the cost-effectiveness model of HPV-vaccination. The ICERs became considerably more favourable when HPV-related diseases other than cervix carcinoma were considered in the model: compared to only including cervix carcinoma, the mean ICERs were 2.85 times more favourable (95%CI 1.35-4.36) for girls only vs. no vaccination, and 3.89 times (95% CI -0.10-7.85) for gender neutral vs. girls only vaccination. Including all known HPV-associated diseases in economic evaluations makes gender neutral vaccination more likely as the ICER falls beneath accepted cost-effectiveness reference values (€20,000/QALY).
The design of a Social Cost-Benefit Analysis (SCBA) of preventive interventions for toxoplasmosis is presented in **Chapter 9,** which includes freezing meat intended for raw or undercooked consumption, and improving biosecurity in pig farms**.** In **Chapter 10** the results of this SCBA are given and the net value of two potential interventions for the Dutch society is estimated. Costs and benefits of the two interventions were compared with the current practice of education, especially during pregnancy. Freezing high risk meat products was more effective than the biosecurity intervention. Freezing steak tartare and mutton leg generated net social benefits, ranging from €3

million to €12 million annually for steak tartare and €6 million to €15 million annually for mutton leg. The biosecurity intervention would result in net costs to society in all scenarios. To reduce the burden of toxoplasmosis and its associated costs freezing steak tartare and leg of mutton before selling them to consumers is to be considered. In **Chapter 11** results of an economic evaluation of hepatitis B (HBV) and hepatitis C (HCV) screening of foreign-born migrants are described. Screening migrant groups living in the Netherlands and originating from HBV and HCV endemic countries with a seroprevalence of at least 0.41% for HBsAg and 0.22% for HCV-RNA is expected to be cost-effective. For most migrant groups with a high expected number of chronic infection offering combined HBV and HCV screening proved to be the most cost-effective strategy. For migrants originating from Turkey, screening only for HBV is the most cost-effective intervention. For all migrant groups, the ICERs lie well below the accepted reference value for cost-effectiveness of €20,000/QALY in the Netherlands. The results and methodological considerations of the studies in this thesis are integrated and discussed in **Chapter 12**.

Overview of main recommendations for policy and research

The studies in this thesis revealed recommendations for research and policy. The most important ones are described, in short, below.

Research

1. When major outbreaks occur, cost evaluations should be performed more often. These are important to inform and optimize outbreak control in future outbreaks. Cost evaluations should be performed shortly after the outbreak to reduce recall bias;
2. To facilitate future calculations of outbreak costs a standard calculation tool could be developed in which all relevant cost items as described in this thesis are included and can be collected standardized in a prospective way;
3. Future HPV economic evaluations should take all known HPV-associated diseases into account and in consequence the complete QALY gains of HPV vaccination;
4. The case in the STI testing policy can serve as an example for evaluations targeted at new policies for other infectious diseases in which restricted testing or treatment is recommended, for instance with respect to the use of antibiotics in upper respiratory tract infections;
5. Consensus is needed on methods and assumptions regarding discounting, the value of a QALY, and assessment of productivity losses, both used in CEAs and SCBAs, to allow for the comparison of results across studies applying different methods. To achieve consensus, discussion of these items between (health) economists in the Netherlands is necessary. An SCBA is recommended if the

problem under study and possible interventions affect more sectors of society. It is the preferred methodology to apply in a One Health approach when the influence of interventions on both the human and animal health sector needs to be integrated for decision makers in both sectors.

Policy

1. Continuation of hospital investment in infection prevention activities is of importance, as well as transparency and exchange of information in case of possible hospital outbreaks. Financial compensation when hospitals experience major outbreaks for which they have no responsibility should be considered;
2. There is a need for national guidelines for upcoming outbreaks caused by highly virulent and lethal pathogens with respect to donning and doffing procedures, the necessary materials, and personal protective equipment. It may be helpful to form a temporary national supply chain to prevent possible shortage of materials. Given the small size of the Netherlands a few selected ambulance care services and hospitals might take responsibility for care and treatment of patients for the whole country, while the remainder of organisations could rely on more general preparedness;
3. Offering syphilis and HIV tests to first- *and* second-generation immigrants and those who tested previously positive for chlamydia and gonorrhoea is recommended. Monitoring the effects of the restricted testing policy is important. Finally, efficiently finding those with undetected HIV and syphilis infection beyond the setting of the STI clinics is key;
4. Freezing high-risk meat products is to be considered to prevent toxoplasmosis. Informing consumers seems crucial to persuade them to buy toxoplasma-safe meat;
5. Implementation of targeted HBV and HCV screening programmes to increase early diagnosis and treatment is important to reduce the burden of chronic hepatitis B and C among migrants. For most migrant populations in the Netherlands with a high expected number of chronically infected cases, offering combined HBV and HCV screening is recommended.

CHAPTER 14

Samenvatting

SAMENVATTING

Net als in andere westerse landen, komen in Nederland infectieziekte-uitbraken regelmatig voor, meestal gaat het daarbij om voedselgerelateerde en respiratoire uitbraken. Deze uitbraken kunnen een grote impact hebben op de samenleving wat betreft ziektelast en brengen ook kosten met zich mee. Deze kosten kunnen onder andere medische kosten, productiviteitsverliezen, kosten voor patiënten zelf, kosten voor het bedrijfsleven en kosten om de uitbraak te bestrijden zijn. Omdat uitbraken moeilijk te voorspellen zijn en veel inspanning vragen om ze te bestrijden is het van belang dat zorgorganisaties goed voorbereid zijn om in te spelen op plotselinge toenames van infectieziekten. Kostenevaluaties kunnen helpen om te leren van de aanpak van infectieziekte-uitbraken.
We vatten hier de resultaten samen van kostenevaluaties van vier uitbraken die in de afgelopen jaren hebben plaatsgevonden, hierin nemen we ook de voorbereidings- en bestrijdingskosten van volksgezondheidsorganisaties mee (Deel 1, Hoofdstukken 2-5). Surveillance van infectieziekten, signalering via laboratoria en epidemiologisch onderzoek zijn belangrijke basiselementen in een systeem van infectieziektebestrijding. Daarnaast zijn preventieve interventies, zoals vaccinatieprogramma's, adequate behandeling, initiatieven voor screening en voorlichtingsprogramma's essentieel om de algemene bevolking te beschermen tegen infectieziekten. Deel 2 van dit proefschrift richt zich op economische evaluaties. Economische evaluaties dragen vaak bij aan de ontwikkeling van nieuw beleid gericht op infectieziekten en aan het maken van onderbouwde keuzes voor het al dan niet inzetten van interventies. Het is voor beleidsmakers een belangrijke bron van informatie over kosten en consequenties van nieuwe interventies. We presenteren de resultaten van evaluaties van kosteneffectiviteit van verschillende interventies voor de bestrijding van infectieziekten (Deel 2, Hoofdstukken 6-11). In het inleidende **Hoofdstuk 1** worden de onderzoeksvragen en de opzet van het manuscript beschreven.

DEEL 1

Hoofdstuk 2 presenteert de maatschappelijke kosten van de grootste voedselgerelateerde uitbraak door *Salmonella* die ooit geregistreerd werd in Nederland. De uitbraak werd veroorzaakt door gerookte zalm die tijdens de voedselbereiding besmet werd met *Salmonella* Thompson. Meer dan 1000 gevallen werden bevestigd door een positieve laboratoriumtest en werden gerapporteerd aan het RIVM. Twintig procent van alle gevallen werd in een ziekenhuis opgenomen en vier mensen overleden vanwege deze infectie. Aan de hand van het Nederlandse

ziektelastmodel van voedselgerelateerde ziekten werd geschat dat het werkelijk aantal gevallen veel hoger was, ongeveer 21.000. De totale uitbraakkosten, inclusief medische kosten, productiviteitsverliezen, patiëntkosten en kosten voor de bestrijding van de uitbraak werden geschat op €7,5 miljoen. Productieverliezen waren de belangrijkste kostenpost in deze uitbraak. We concludeerden dat vroege opsporing en versterkte samenwerking tussen voedselindustrie, volksgezondheidsorganisaties en laboratoria essentieel is voor een snelle detectie en bestrijding van voedselgerelateerde uitbraken. Hiermee kunnen ziektelast en kosten worden teruggebracht.

Hoofdstuk 3 beschrijft een vergelijkbare studie als in hoofdstuk 2 maar dit keer met betrekking tot een landelijke uitbraak van mazelen. De mazelen uitbraak vond plaats in 2013 en 2014 in de gemeenschap van bevindelijk gereformeerden. De vaccinatiegraad voor bof, mazelen en rodehond is in deze gemeenschap lager dan in de algemene bevolking. Tijdens de epidemie werden 2.700 gevallen van mazelen gerapporteerd. Naar verwachting was echter het werkelijke aantal gevallen tien keer zo hoog. De totale uitbraakkosten met betrekking tot deze gerapporteerde gevallen waren ongeveer €3,9 miljoen. Omdat deze uitbraak voornamelijk schoolgaande kinderen betrof waren productiviteitsverliezen minder belangrijk dan bij de *Salmonella* uitbraak. In plaats daarvan waren de kosten van de bestrijding van de uitbraak de belangrijkste kostenpost. We hebben enkele suggesties gegeven om de werklast van GGD-werknemers in toekomstige uitbraken te verminderen, zoals het achterwege laten van registratie van detailinformatie bij het merendeel van de aangiften.

Hoofdstuk 4 laat de kosten zien van de voorbereiding op en de bestrijding van Ebola voor de Nederlandse gezondheidszorg in 2014 en 2015. Slechts 13 mogelijke gevallen werden klinisch onderzocht in een ziekenhuis en één patiënt werd met een bevestigde infectie in het ziekenhuis opgenomen. De geschatte totale kosten waren hoog en bedroegen €12,6 miljoen. Om de kosten van toekomstige uitbraken te verminderen en de efficiëntie te verhogen was de aanbeveling om slechts één ambulancedienst aan te wijzen voor het transport van een patiënt met een zeer besmettelijke infectieziekte en een paar ziekenhuizen voor de behandeling van mogelijke patiënten.

Hoofdstuk 5 richt zich op de kosten van een ziekenhuisuitbraak veroorzaakt door een multiresistente New Delhi-metallo-β-lactamase–positieve (NDM) *Klebsiella pneumoniae* stam in 2015-2016. Na detectie van deze stam op een chirurgische afdeling van een regionaal ziekenhuis werd op zes andere afdelingen ongecontroleerde verspreiding van deze ziekteverwekker gevonden. 29 patiënten bleken gekoloniseerd te zijn met deze bacterie. Wij berekenden de kosten van deze ziekenhuisuitbraak, gebaseerd op informatie van het ziekenhuis (zoals het aantal gesloten bedden, laboratoriumtests en schoonmaakkosten) en interviews met het personeel over de tijd die gemoeid was met bestrijdingsactiviteiten. De totale uitbraakkosten voor het ziekenhuis werden geschat op €654,000. Het sluiten van bedden en de inzet van personeel voor infectiepreventie

waren de belangrijkste kostensoorten. Het blijft belangrijk om te investeren in preventiemaatregelen om ziekenhuisuitbraken te voorkomen. Daarnaast is financiële compensatie van belang voor ziekenhuizen die te maken krijgen met grote uitbraken.

DEEL 2

Vanwege de afname van natuurlijke afweer tegen hepatitis A bij toekomstige cohorten ouderen werd in **Hoofdstuk 6** mogelijke opname van het hepatitis A vaccin in het rijksvaccinatieprogramma beoordeeld. De mogelijke voor- en nadelen van implementatie van het hepatitis A vaccin werden geëvalueerd aan de hand van een vaccinatie-evaluatie schema. Omdat het aantal jaarlijkse hepatitis A aangiften afneemt, de kosten van ziekten laag zijn (ongeveer €650.000 per jaar) en de jaarlijkse kosten van grootschalige vaccinatie ongeveer €10 miljoen voor zuigelingen en €13 miljoen voor ouderen zullen zijn, zal introductie van een vaccinatieprogramma waarschijnlijk niet kosteneffectief zijn. In plaats daarvan zullen gerichte preventieve maatregelen zoals vaccinatie van reizigers en andere hoog-risicogroepen en tijdige vaccinatie van contacten van hepatitis A patiënten een acceptabel alternatief zijn.

In **Hoofdstuk 7** worden de gevolgen van een meer restrictief testbeleid voor seksueel overdraagbare aandoeningen (soa) geëvalueerd. Sinds 2015 worden jonge heteroseksuele cliënten, die geen andere risicofactoren hebben voor een soa, niet langer standaard getest op syfilis en HIV. Surveillance data over 2011 tot en met 2013 werden gebruikt, waarin iedereen nog uitgebreid getest werd, om de effecten te berekenen van het nieuwe testbeleid op testkosten, het aantal gemiste infecties, de kosten per verloren Quality Adjusted Life Year (QALY) en de netto financiële baten. Het nieuwe testbeleid leidde tot geschatte besparingen van €1,1 miljoen en drie gemiste HIV en zeven gemiste syfilis infecties per jaar. De besparingen waren €435.000 per verloren QALY. De efficiëntie van het testbeleid zou vergroot worden door een HIV en syfilis test aan te bieden aan zowel eerste- als tweedegeneratie migranten en door een HIV test aan te bieden bij een positieve chlamydia of gonorroe test.

Hoofdstuk 8 toont de resultaten van een systematische literatuurverkenning van economische evaluaties van Humaan Papilloma Virus (HPV) vaccinatie. In deze literatuurverkenning evalueerden we de invloed van andere ziekten dan enkel cervix carcinoom die geassocieerd zijn met HPV, op de Incrementele Kosteneffectiviteitsratio (ICER) van vaccinatie aan jongeren. Naar verwachting wordt de kosteneffectiviteit van vaccinatie onderschat als niet alle ziekten die gerelateerd zijn aan HPV worden meegenomen. We vonden 18 studies die andere ziekten dan cervix carcinoom in het economische model van HPV vaccinatie meenamen. ICERs werden aanzienlijk gunstiger als andere ziekten werden betrokken in het model: de gemiddelde ICERs werden een factor 2,85 (95% BI 1,35-4,36) gunstiger voor vaccinatie van meisjes

vergeleken met geen vaccinatie en een factor 3,89 (95% BI 0,10-7,89) voor meisjes èn jongens vaccinatie vergeleken met vaccinatie voor alleen meisjes. De inclusie van alle bekende HPV gerelateerde zieken in economische evaluaties maken vaccinatie van zowel jongens als meisjes meer acceptabel omdat de ICER lager uitkomt dan de voor vaccinatie gehanteerde drempelwaarde voor kosteneffectiviteit (€20.000/QALY).

De opzet van een Maatschappelijke Kosten-Baten Analyse (MKBA) voor preventieve interventies voor toxoplasmose wordt gepresenteerd in **Hoofdstuk 9.** Deze interventies betreffen invriezen van vlees dat rauw of halfgaar gegeten wordt en het verbeteren van de hygiëne op varkensbedrijven.

In **Hoofdstuk 10** worden de resultaten van deze MKBA gegeven en een schatting van de netto baten van de mogelijke interventies voor de Nederlandse samenleving. De kosten en baten van de twee interventies werden vergeleken met de huidige praktijk van voorlichting die zich voornamelijk richt op zwangeren. Het invriezen van risicovolle vleesproducten was veel effectiever dan de hygiëne interventie. Het invriezen van filet americain en schapenbout leidde tot netto baten, uiteenlopend van jaarlijks €3 tot €12 miljoen voor filet americain en €6 tot €15 miljoen voor schapenbout. De hygiëne interventie zou in alle scenario's leiden tot kosten voor de samenleving. Om de ziektelast van toxoplasmose en de kosten voor de samenleving terug te dringen is het te overwegen om filet americain en schapenbout voor verkoop aan de consument eerst in te vriezen.

In **Hoofdstuk 11** worden de resultaten beschreven van een kosteneffectiviteitsanalyse van hepatitis B (HBV) en hepatitis C (HCV) screening van eerste generatie migranten. Screening van migrantengroepen die in Nederland leven en afkomstig zijn uit HBV en HCV endemische landen met een seroprevalentie van tenminste 0,41% voor HBsAg en 0,22% voor HCV-RNA is naar verwachting kosteneffectief. Voor de meeste migrantengroepen met een hoog aantal verwachte chronische infecties is het aanbieden van een gecombineerde screening de meest kosteneffectieve strategie. Voor migranten afkomstig uit Turkije, screening van enkel HBV is de meest kosteneffectieve interventie. Voor de migrantengroepen is de ICER ruim beneden de geaccepteerde drempelwaarde van kosteneffectiviteit in Nederland van €20.000 per QALY.

De resultaten en methodologische overwegingen naar aanleiding van de onderzoeken in dit proefschrift worden geïntegreerd en bediscussieerd in **Hoofdstuk 12.** In dit hoofdstuk worden aanbeveling voor beleid en onderzoek, gebaseerd op dit proefschrift, samengevat.

Overzicht van de belangrijkste aanbevelingen voor onderzoek en beleid

De studies in dit proefschrift hebben aanbevelingen opgeleverd voor onderzoek en beleid. De belangrijkste hiervan worden in het kort, hieronder, beschreven.

Onderzoek

1. Bij het optreden van grote uitbraken zouden vaker kostenevaluaties moeten worden uitgevoerd. Deze geven belangrijke informatie en kunnen leiden tot verbeterde bestrijding bij toekomstige uitbraken. Om recall bias te verminderen is het van belang om deze kostenevaluaties kort na de uitbraak uit te voeren.
2. Een standaard rekenhulpmiddel kan worden ontwikkeld om toekomstige kostenschattingen van uitbraken te faciliteren. Hierin zijn alle relevante kostensoorten zoals beschreven in dit proefschrift opgenomen, waardoor deze op een gestandaardiseerde en prospectieve wijze kunnen worden verzameld;
3. Toekomstige economische evaluaties van HPV vaccinatie zouden alle bekende HPV-gerelateerde ziekten mee moeten nemen en daarmee de complete QALY winst van HPV vaccinatie;
4. De studie naar het soatestbeleid kan dienen als een voorbeeld voor evaluaties van nieuw beleid waarin minder testen of behandelen wordt aanbevolen zoals in het geval van antibioticagebruik bij bovenste luchtweginfecties;
5. Consensus is nodig over methoden en aannames in zowel kea's en MKBA's met betrekking tot discontering, de waarde van een QALY en het bepalen van productieverliezen waarmee een goede vergelijking van resultaten tussen studies met verschillende methoden mogelijk is. Een discussie tussen gezondheidseconomen is noodzakelijk om deze consensus te bereiken. Een MKBA wordt aanbevolen als de onderzoeksvraag en mogelijke interventies verschillende domeinen in de samenleving raken. Deze methode heeft de voorkeur in een One Health Approach als de invloed van interventies in zowel de humane als diergezondheidssector geïntegreerd moeten worden voor beleidsmakers in beide sectoren.

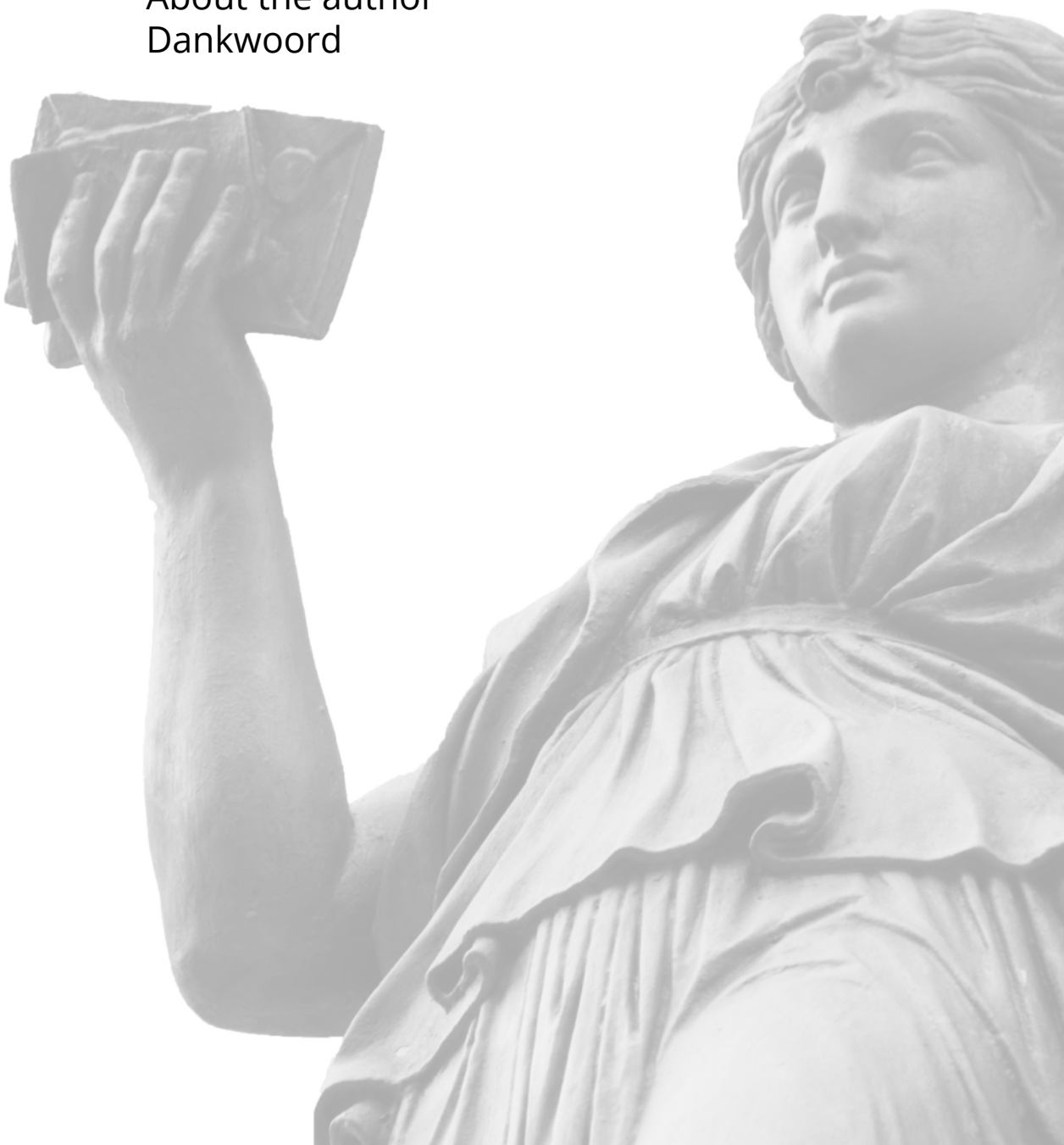
Beleid

1. Investeringen van ziekenhuizen in activiteiten voor infectiepreventie blijven belangrijk, evenals transparantie en informatie-uitwisseling bij mogelijke ziekenhuisuitbraken. Financiële compensatie als ziekenhuizen te maken krijgen met grote uitbraken waar ze zelf geen schuld aan hebben is te overwegen;

2. Landelijke richtlijnen voor omkleedprocedures, noodzakelijke materialen en persoonlijke beschermende maatregelen zijn van belang voor toekomstige uitbraken van zeer besmettelijke en dodelijke pathogenen. Een tijdelijke landelijke voorraad kan behulpzaam zijn om mogelijke tekorten aan materialen te voorkomen. Vanwege de kleine omvang van Nederland zouden een klein aantal ambulancediensten en ziekenhuizen voor het hele land zorg kunnen dragen voor de zorg en behandeling van patiënten, terwijl de rest van de organisaties kunnen volstaan met algemene preventiemaatregelen;
3. Het is aanbevolen om syfilis en HIV testen aan te bieden aan eerste en tweede generatie immigranten en aan mensen die een positieve chlamydia en/of gonorroe test hebben. Het is belangrijk om de effecten van het beperktere soatestbeleid te monitoren. Tot slot is het noodzakelijk om op een efficiënte manier HIV en syfilis infecties op te sporen buiten de organisatie van soacentra;
4. Om toxoplasmose te voorkomen is het invriezen van risicovolle vleesproducten te overwegen. Informatie voor consumenten lijkt essentieel om ze over te halen toxoplasmavrij vlees te kopen;
5. Implementatie van gerichte hepatitis B en C screening programma's voor tijdige diagnose en behandeling is belangrijk om de ziektelast aan chronische hepatitis B en C onder migranten terug te dringen. Voor de meeste migrantengroepen in Nederland met een hoog verwacht aantal chronische infecties is gecombineerde hepatitis B en C screening aanbevolen.

CHAPTER 15

About the author
Dankwoord



ABOUT THE AUTHOR

Anita Suijkerbuijk was born on the 20th of July 1965 in Etten-Leur, the Netherlands. After finishing secondary education (athenaeum) at Katholieke Scholengemeenschap Etten-Leur she studied a higher professional education in nursing from 1983 – 1987 at Hogeschool Breda. Thereafter, she worked for several years as a nurse in the psychiatric hospital Sinaï in Amersfoort and as a public health nurse at the Municipal Health Service Gooi en Vechtstreek. She completed a postgraduate degree course for public health nurses in 1989 and a course for professional innovation in 1993. Between 1993 and 2008, she worked as a public health nurse at the centre of epidemiology and surveillance (EPI) at RIVM. In 2008, she obtained her Master's Degree Evidence Based Practice at the University of Amsterdam, the Netherlands, with distinction. Subsequently, she worked as an epidemiologist at the EPI department. In 2011, she started working in the field of health economy at the Centre of Nutrition, Prevention and Health Services at RIVM. She participated in several additional courses: Methodology in health economic evaluation at Julius Center for Health Sciences and Primary Care and in house courses of health economy, social cost-benefit analyses, and behavioral economics. She lives together with Ben Roelands and together they have three children Niek (23), Tim (21), and Mara (20).

DANKWOORD

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CHAPTER 16

List of publications

LIST OF PUBLICATIONS

Consequences of restricted STI testing for young heterosexuals in the Netherlands on test costs and QALY losses. *Suijkerbuijk AWM, Over EAB, van Aar F, Götz HM, van Benthem BHB, Lugnér AK.* Health Policy. 2018 Feb;122(2):198-203.

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