# Broadening the perspective in economic evaluations of infectious diseases

*Klas Kellerborg*

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# Broadening the Perspective in Economic Evaluations of Infectious Diseases

## Verbreden van het perspectief in economische evaluaties van infectieziekten

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Klas Martin Kellerborg
born in Västerled, Stockholm, Sweden.

Erasmus University Rotterdam

## Doctoral Committee:

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# CHAPTER 1

## General introduction

## Background

In the last century, life expectancy has increased substantially and, as a consequence, we are now living longer than ever before (Cutler et al., 2006). This increase in life expectancy is related to various interventions ranging from the early improvements in sanitation in urban areas, vaccination campaigns to prevent infectious diseases, to improved treatments for cardiovascular disease such as statins (Cutler et al., 2006). Outbreaks of severe infectious diseases, which for a long period were relatively common, have decreased significantly due to higher vaccination rates or, as in the case of smallpox, have even been eradicated (Fenner et al., 1988). However, although the most important causes of death have shifted to non-communicable diseases, in some poorer parts of the world communicable diseases remain the most important cause of death (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). Furthermore, with the global increase in population density, urbanization, and global travel and trade, the chance of widespread outbreaks of high-threat infectious diseases has increased (Smith et al., 2014), as evidenced by recent examples of outbreaks of Ebola, Zika, Lassa fever, and of course COVID-19. Furthermore, there are examples of endemic diseases, for instance, the measles, that have the potential to threaten health and lives, of which the incidence has more recently increased due to decreasing vaccination rates (CDC, 2019). To combat these threats, improvements in disease surveillance, public health campaigns, and medical technologies are needed, which can be very costly. These interventions must compete with other spending opportunities for finite (healthcare) resources, and hence decisions need to be made regarding whether or not they can be funded, reimbursed, and implemented. The pressure on the budgets is increasing, with increasing technological possibilities, higher demands, and the aging of the population, while healthcare expenditures continue to increase. In 2018, healthcare spending constituted on average almost nine percent of GDP in OECD countries, implying an increase of almost one percentage point during the last 15 years (OECD, 2019a).

As the proportion of GDP that is spent on health care increased and these increases are predicted to continue in the future (OECD, 2019b), there are worries about the rate of return ('value for money') of additional investments in medical care (Chandra and Skinner, 2012). Improvements in health are made (Gheorghe et al., 2014) and healthcare expenditures continue to increase, however, the pace of gains in terms of increases in life-expectancy has decreased (Cardona and Bishai, 2018), suggesting that the marginal benefits of additional health spending may be decreasing (van Baal et al., 2013b). In many countries, health care and public health interventions are to a large extent collectively financed. Therefore, decisions need to be made regarding which health-improving interventions are to be funded from public resources. When evaluating the options available the most popular form of economic evaluation is a so-called cost-effectiveness analysis (CEA) or cost-utility analysis (CUA) in which

costs are expressed in monetary terms but health gains in terms of Quality Adjusted Life Years (QALYs) (Drummond et al., 2015). Such QALYs comprise both length and quality of life. Cost-effectiveness analyses have become a more prominent tool in certain jurisdictions in informing decision-makers about the costs and consequences of funding or implementing certain health policies or medical technologies (Drummond et al., 2015). The results of economic evaluations are typically one element of information in the total decision-making process regarding funding some new technology, next to broader considerations related to the health system and societal goals, including for instance considerations related to equity, ethics, organizational or cultural issues, etcetera. It has been recognized that economic evaluations do not capture all aspects relevant to reach a final decision regarding funding a technology (Hutton et al., 2008; Nielsen et al., 2011). Next to broader considerations than those captured in an economic evaluation, important questions and debates remain regarding the methodology of performing these economic evaluations (Meltzer and Smith, 2011).

To name one important example of such a debate, the issue of which costs and effects should be included in an economic evaluation of health technology remains controversial. The answer to the question of which cost categories should be included in an economic evaluation to a large extent depends on the perspective chosen for the evaluation (Drummond et al., 2015; Meltzer and Smith, 2011). Two important perspectives taken are the health care perspective and the societal perspective. Adopting a healthcare perspective implies that only costs that occur within the healthcare sector (or fall on the health budget) should be accounted for and only health effects are relevant benefits. The implicit assumption underlying this perspective is that economic evaluations aid a health care decision-maker with a finite health care budget to maximize the health gained from that budget. Adopting a societal perspective implies that all costs and benefits flowing from an intervention should be included in the analyses, no matter where they fall or in whom (and what form) they occur. The implicit assumption here is that the health care decision maker ultimately wishes to contribute to the maximization of social welfare through funding health technologies. The healthcare perspective is prescribed in countries such as Wales and England (NICE, 2013), while in other countries, such as the Netherlands, the US, and Sweden, adopting a societal perspective is recommended (Eldessouki and Dix Smith, 2012). However, in practice, even studies claiming to take the same perspective can importantly differ in terms of the costs included in the evaluation. This partly reflects differences in national guidelines that prescribe the same perspective but nonetheless differ in their specific recommendations as to which cost-categories to include (van Lier et al., 2018). The differences are even larger when also considering *how* the different cost-categories are included (Pike and Grosse, 2018). These differences can reflect a theoretical or practical lack of consensus on whether and how to include certain cost-categories. To make optimal use of economic evaluations, such issues should ideally be resolved. This increases the consistency and comparability between and potentially confidence in

the results of economic evaluations. This is important for the application of economic evaluations in general, but also specifically in the context of performing economic evaluations in challenging contexts, such as that of infectious disease outbreaks, where economic evaluations have been conducted less frequently (Drake et al., 2016), and currently appear to lack consistency in terms of used methods (Rennert-May et al., 2018). Applying economic evaluation in these important fields brings up new questions regarding how the costs and benefits of interventions should best be captured.

## The societal perspective and infectious diseases

In evaluating the costs and benefits of interventions targeted at (outbreaks of) infectious diseases, including pandemic outbreaks, adopting a broad perspective and long time-horizon appears to be most relevant for several reasons. First, many strategies for the prevention of and response to infectious disease outbreaks are not necessarily initiated or financed from the health care sector. Interventions such as improved hygiene or sanitation, disease surveillance, contact tracing, and border control can fall outside the (direct) healthcare system and budget and motivate a broad perspective that fully captures all relevant costs. Second, the consequences of outbreaks can affect many more sectors than only the health care sector. In extreme cases, it can affect the full functioning of a society, which school closures, quarantine of affected individuals, major losses of production, and so on. In establishing, for instance, the benefits of preventing an outbreak, such broad consequences must be included in the evaluation in order to be able to make a realistic trade-off of costs and benefits. Third, in contrast to some other diseases, such as oncology, people who survive the acute phase of the illness often have no further health consequences from the illness and live their lives similar to those who were not infected after the disease is cured. Often treatment duration and treatment costs are relatively low. Of course, the effect of saving the life of a young person is that a stream of future health is gained. Besides the health gains, this may lead to benefits such as increased production. However, when an intervention or technology averts a premature death and adds life-years, during these years not only benefits but also costs will be incurred. Hence, the effects of an effective intervention include positive elements (benefits) such as productivity gains during the added life-years, but negative ones (costs) in the form of consumption of medical and non-medical goods and services. These costs are often referred to as ‘survivor costs’ or ‘future costs’.

Future costs can be divided into three distinct categories (de Vries et al., 2018):

(i) Related medical costs. These are costs that are directly related to the illness or disability at which the intervention was targeted. A child that has been infected with, but recovered from, pneumococcal meningitis may be at risk of experiencing long-term health consequences due to that disease such as hearing loss. An example of future related medical costs in this instance would be the costs of a hearing aid.

(ii) Unrelated medical costs. These are costs that result from the consumption of medical goods in the added life-years but are not directly related to the initial illness. For instance, using the previous example, the same child lives until old age after surviving the infection but then is affected by an age-related illness, such as dementia. The care costs related to dementia would be categorized as unrelated medical costs.

(iii) Non-medical costs, or future consumption costs. These can be seen as the costs of consumption of all other goods and services during the added life-years. So, the costs of housing, food, and clothing during added life years would for instance fall in this category. These costs are sometimes netted against the productivity gains of the individual during added life-years to calculate 'net consumption costs'. Since this consumption implies using scarce resources, it represents real opportunity costs to society.

The inclusion of future costs in economic evaluation is still a topic of much debate (de Vries et al., 2018). Which of the three cost categories should be included in an economic evaluation is partially determined by the perspective chosen in the evaluation. For evaluations conducted from the healthcare perspective, only costs that fall within the healthcare budget should be considered. Therefore, the non-medical consumption of individuals, whether in normal life years or in life-years gained, should not be included. However, future (related and unrelated) medical costs may still be of relevance. For economic evaluations performed from the societal perspective, all future costs are at least theoretically relevant and hence in principle should be included in the analysis. However, national guidelines recommending the societal perspective nonetheless differ in their recommendations regarding the inclusion of these costs. While both types of future medical costs are more commonly recommended for inclusion, future non-medical consumption is only recommended for inclusion by the US Panel on Cost-Effectiveness in Health and Medicine (Sanders et al., 2016). Future related medical costs are the least controversial, probably because these costs are a direct consequence of the intervention evaluated, and typically included in economic evaluations. Although there were arguments early on regarding the inclusion of future unrelated medical costs (Drummond et al., 2015; Weinstein et al., 1980), their inclusion remained much more controversial. One of the main arguments in favor of their inclusion is that the added quality and length of life (which assume common care use) are already included in economic evaluations and therefore, using the argument of symmetry, so should the costs that facilitate these improvements.

The consensus regarding future non-medical consumption has been to not include it in economic evaluations, even though they represent real societal costs. However, the debate is ongoing and importantly revolves around the argument of symmetry. More specifically, an unresolved issue is whether the utility gained from future consumption is adequately captured in the QALY measure (de Vries et al., 2018; Meltzer, 1997a; Nyman, 2011). If these utility benefits are not captured, that could be an argument to also leave out consumption costs (or to argue for broader outcome measures). Due to the theoretical debates surrounding the inclusion of future costs and the fact that most guidelines for a long time did not discuss or recommend the inclusion of future costs, empirical studies estimating these costs and assessing the impact of their inclusion in economic evaluations are scarce. This means, especially for economic evaluations in contexts such as (outbreaks of) infectious diseases, that the estimation of these costs as well the impact of their inclusion requires further attention.

## Aim of this thesis

This thesis aims to contribute to applying a full societal perspective in economic evaluations[1] within the field of infectious diseases. The different chapters will explore the current practice of conducting economic evaluations of interventions in the context of infectious diseases, to establish shortcomings in the inclusion and estimation of broader societal benefits and costs. We focus on the inclusion of future costs as these are particularly relevant in this context and are currently much debated. If all future costs are to be included in economic evaluations, and guidelines would increasingly prescribe their inclusion, then the methods of estimating these costs must be sound and the implications of their inclusion need to be clear. The included studies in this thesis will attempt to address current methodological issues in the estimation of these costs and aim to facilitate the standardization of their inclusion. This may indirectly contribute to future guidelines recommending their inclusion. While there is more consensus regarding the inclusion of future medical costs than regarding that of future non-medical costs, there is a lack of ready-to-use estimates in both areas. To date, internationally there has not been much research on standardizing the estimation of future medical costs across diseases. The few available figures (e.g van Baal et al., 2011) require updating, to better reflect the current situation. For future non-medical consumption, the available estimates have not accounted for issues such as household size, cohort effects, and period effects (Kruse et al., 2012; Manns et al., 2003a; Meltzer, 1997a; Meltzer et al., 2000a), which nonetheless can be highly relevant.

1 From here on the terms economic evaluation, cost-utility analysis and cost-effectiveness analysis will be used interchangeably and will refer to economic evaluations using the QALY as outcome measure, although these terms are not necessarily synonyms.

The insights gained from studying the aforementioned methodological issues will be applied to economic evaluations of infectious disease interventions; an area in which economic evaluations are relatively new and numerous methodological challenges exist (Drake et al., 2016). By doing so, this thesis will also address the issue of modeling infectious diseases and the costs and consequences of interventions in that area. The insights from this thesis will especially contribute to the understanding of the role of future costs in economic evaluations, and the methods for and implications of their inclusion in economic evaluations aimed at informing reimbursement decisions.

The main research questions addressed in this thesis are:

1. What is the current practice of inclusion of costs and benefits in economic evaluations of interventions aimed at infectious diseases?
2. How can the current methods for the estimation and inclusion of broader costs in economic evaluations of infectious disease interventions be improved?
3. What are the implications of broadening the perspective of economic evaluations of infectious disease interventions?

## Structure of this thesis

These three research questions will be addressed in the different chapters of this thesis. The structure of the thesis is as follows.

First, Chapter 2 aims to review the published literature and answer the first research question regarding current practices of inclusion of costs and benefits in economic evaluations of infectious diseases. Specifically, the study reported in this chapter investigates published literature on economic evaluations of interventions for some of the prominent infectious disease threats of modern times. This chapter also highlights existing knowledge gaps and provides an indication of important areas for improving economic evaluations. The inclusion of future costs is such an area.

Chapter 3 will explore the costs associated with extreme outbreaks and begin to answer what the implications of the inclusion of future costs in economic evaluations are, focusing on productivity gains in a low-income setting. This chapter presents an evaluation that is conducted in line with current practice (as observed in Chapter 2). This increases our understanding of the limited operationalization of the societal perspective in many current economic evaluations and the consequences thereof.

Chapters 4 and 5 will be specifically devoted to the estimation and practical inclusion of future costs. The aim of chapter 4 is to improve on the methods used to estimate future non-medical consumption to address the question of how these costs can be reliably estimated. Second, building on previously published studies, it provides estimates for future costs in the Dutch context, allowing their standardized inclusion in economic evaluations.

Chapters 6 and 7 focus on the inclusion of future costs and highlight the (joint and separate) impact of different elements of future costs on outcomes when included in economic evaluations. More specifically, Chapter 6 will consider the distributional consequences of including future non-medical consumption, and Chapter 7 highlights the impact of these estimates by including future costs in a case-study of adult pneumococcal conjugate vaccination.

Finally, Chapter 8 will discuss the above studies in relation to the general research questions and aim of this thesis. This Chapter will also highlight some policy implications and areas for future research.

As a final remark, we note that the different chapters are all based on separate publications. While this may have resulted in some repetition of arguments in the different chapters, it also allows reading them independently.

# 1

# CHAPTER 2

## Costs and benefits of interventions aimed at major infectious disease threats: Lessons from the literature

## Abstract

Pandemics and major outbreaks have the potential to cause large health losses and major economic costs. In order to prioritize preventive and responsive interventions it is important to understand the costs and health losses interventions may prevent. We review the literature, investigating the type of studies performed, the costs and benefits included, and the methods employed against perceived major outbreak threats. We searched PubMed and SCOPUS for studies concerning the outbreaks of SARS in 2003, H5N1 in 2003, H1N1 in 2009, Cholera in Haiti in 2010, MERS-CoV in 2013, H7N9 in 2013, and Ebola in West-Africa in 2014. We screened titles and abstracts of papers, and subsequently examined remaining full-text papers. Data were extracted according to a pre-constructed protocol. We included 34 studies of which the majority evaluated interventions related to the H1N1 outbreak in a high-income setting. Most interventions concerned pharmaceuticals. Included costs and benefits, as well as the methods applied, varied substantially between studies. Most studies used a short time horizon and did not include future costs and benefits. We found substantial variation in the included elements and methods used. Policymakers need to be aware of this and the bias towards high-income countries and pharmaceutical interventions, which hampers generalizability. More standardization of included elements, methodology, and reporting would improve economic evaluations and their usefulness for policy.

## Introduction

Historically, infectious disease outbreaks have proven to be potentially devastating. A prominent example is the Spanish influenza which may have claimed as many as 50 million lives (Johnson and Mueller, 2002). The number of outbreaks of infectious diseases has been increasing since 1980, as has the number of unique pathogens (Smith et al., 2014). In order to prevent and effectively combat outbreaks, reporting agreements such as those arranged in the International Health Regulations (IHR) between national governments and international organizations, were established (*International Health Regulations, (2005), 2nd ed*, 2008). The current IHR require the countries which ratified them to develop a minimum capacity of core functions related to surveillance and response (*International Health Regulations, (2005), 2nd ed*, 2008). However, with new threats emerging and given the fragile health systems in many parts of the world, outbreaks still have the potential to occur with potentially severe consequences in multiple countries. Therefore, there is a continuous pressure to improve available detection and response systems, and to increase the possibilities of preventing new threats from doing too much harm.

A recent example that illustrates the relevance of outbreak containment, is the Ebola outbreak of 2014. The response to this outbreak received important criticisms, and, as a consequence, the World Health Organization reformed, improving its response to infectious threats (Lough, 2015). Aside from international organizations and non-governmental organizations, under the IHR nations are obliged to have at least a minimum threat handling capacity. However, countries are usually faced with limited healthcare budgets, which require prioritization of what to fund and in which disease areas to invest. Funding of detection and response facilities in case of an outbreak also needs to compete for available resources. Preferably, decisions on how to optimally allocate scarce health care resources are informed by sound estimates of potential costs and benefits of various policy scenarios. Assessing the cost-effectiveness of different prevention and treatment strategies is of utmost importance in order to ensure value for money and optimal health and welfare from the available budgets (Drummond et al., 2015). However, obtaining sound estimates of both costs and effects of intervention strategies, compared to a relevant comparator (such as the current situation or doing nothing) is not a straightforward task, and one that is full of methodological challenges.

To comprehensively capture the costs and benefits related to an intervention, numerous issues need to be considered, including the costs of the intervention itself, the incurred and avoided health losses, and the incurred and avoided treatment costs. A full analysis may also include elements such as production losses due to illness and premature death from the disease, or even broader economic impacts such as those due to reduced trade and tourism. Clearly, some of these elements may be more difficult to estimate and quantify. Importantly, in applied cost-effectiveness analyses, the decision regarding

which costs to include, depends on the perspective chosen. The societal perspective aims to capture all relevant costs and effects, regardless of where, when or on whom in society they fall (Gold et al., 1996). Narrower perspectives, such as the patient's perspective or a healthcare perspective are sometimes used, which limits the scope of the evaluation. Especially for interventions targeted at preventing outbreaks, which can have rather broad impacts, adopting a societal perspective seems warranted (Drummond et al., 2008). Indeed, the impact of outbreaks is not confined to the healthcare sector and interventions to prevent or mitigate these outbreaks are often not confined to healthcare interventions (or funding). Note that when evaluating pandemics not only a broad range of cost categories in various sectors of the economy need to be considered but also the fact that a pandemic may trigger non-marginal changes in the health care sector and possibly the entire economy. Non-marginal changes in the health-sector may occur when outbreaks cause capacity problems and displace a large portion of usual care within health care and outside the health-care sector entire industries might be threatened. This suggests that the usual micro-economic perspective which is taken in economic evaluations is insufficient and a more macro-economic perspective might be more appropiate (Beutels et al., 2008; Keogh-Brown et al., 2010).

Simulation models are often used to estimate the consequences of preventing or mitigating disease outbreaks (Anderson and May, 1992). Modeling of infectious diseases is typically done using either so-called static or dynamic transmission models (Vynnycky and White, 2010). Static models, such as decision trees and Markov models, assume that the probability of infection between individuals is constant over time. Dynamic models allow for the force of infection to be varied, and can include possible herd immunity effects (Pitman et al., 2012). Dynamic models are often considered to be more complex, but may be preferred to static models because they are able to take into account a varying transmission rate, which is highly relevant in this context (Vynnycky and White, 2010). Both types of models offer the ability to model different scenarios and interventions, and costs and benefits can be estimated using these models by linking them to events and/or states distinguished in the model (Vynnycky and White, 2010).

An important challenge in infectious disease modeling is to account for behavioral responses that occur when under the threat of an infection (Drake et al., 2012; Funk et al., 2015). Whether or not individuals themselves take action in the face of an outbreak (threat), may introduce bias in the evaluation of a policy to mitigate an outbreak (Philipson, 1999). For instance, when the actual severity and the perceived severity of an illness diverge, this may complicate forecasts of the impact of interventions. Apart from the challenges in modeling the disease itself, there is also room for improvement in other parts of infectious outbreak policy evaluation. Previous research indicated that outbreak evaluations are often biased towards high-income settings and that little research is done in low-income regions (Drake et al., 2012). High-income and low-income countries may

face a different set of challenges, including different resource and capacity constraints, different threats and different living environments. Such differences need to be accounted for in evaluations and when attempting to translate results of interventions across settings. Furthermore, it should be acknowledged that an intervention, like setting up a surveillance system or response protocol, targeted at one specific disease may strengthen the health care system more generally. This means that the effects of such a measure could go beyond preventing and mitigating one particular type of outbreak. Such "policy spill-over effects" are rarely included (Morton et al., 2016).



The aim of this study is to review cost-effectiveness studies of major outbreak threats, based on WHO publications (World Health Organization, 2017). The focus of this review will be on investigating the methodological approaches used to estimate costs and (health) benefits, with the aim of improving our understanding of how evaluations of interventions related to outbreaks are currently conducted. This is key, because if decisions are to be based on available evidence, the evidence itself should preferably be comparable, valid and broad enough for policymakers to consider all relevant elements in the decision-making process.

## Methods

To determine how costs and benefits in economic evaluations of interventions aimed at (potential) outbreaks are estimated, we first compiled a list of major outbreak threats of the 21st century. We based this on publications of the WHO which were produced for the meeting ''Anticipating Emerging Infectious Disease Epidemics' (World Health Organization, 2017). The aim of selecting diseases based on this list was not to capture the most severe diseases or those that, in retrospect, turned out to be found the most costly outbreaks, rather we aimed to collect a broad sample of diseases that have the potential of causing large-scale health and economic damage. Future major outbreaks may have similar characteristics to their predecessors, implying that policy decisions regarding preventing or countering them will (need to) be based on similar information as found in the economic evaluations included here. In this review, we extracted information on study outcomes and methods, using a pre-determined protocol.

### *Data*

We searched PubMed and SCOPUS in April 2018 for the following major outbreaks in the 21st century; SARS in 2003, H5N1 in 2003, H1N1 in 2009, Cholera in Haiti in 2010, MERS-CoV in 2013, H7N9 in 2013 and the West African Ebola outbreak in 2014. For this search, we constructed three blocks, which we used in combination and all terms were searched for in title and/or abstract. The full syntax for both Pubmed and SCOPUS is available in Appendix 1. The first block was the list of the relevant diseases in various combinations: Middle East respiratory syndrome coronavirus OR SARS OR

H5N1OR H1N1 OR Cholera OR MERS-CoV OR H7N9 OR Ebola. The second block defined the study type: economic OR cost* OR costing. The third block complemented the second: benefits OR effectiveness OR cost-effectiveness OR cost-benefit OR cost-utility. Lastly, filters were applied to include studies from 2003 and onwards and exclude studies with only animal subjects. We only considered articles published from 2003, given that we focused on the outbreaks of 2003 and later. We assumed that no articles had been published on the relevant outbreaks before their occurrence.

### *Study selection*

We performed two screening rounds. In the first round, we screened articles based on title and abstract. In the second round, we screened full-text articles. Studies reviewed in full-text, but subsequently excluded, are shown with a justification for their exclusion in Appendix 2. We included peer-reviewed studies that conducted a quantitative economic evaluation of any form (cost-minimization, cost-effectiveness, cost-utility, or cost-benefit evaluations) with one or more comparators, and evaluated one or more interventions within the context of the outbreaks previously mentioned. We included studies based on actual reported case data but also included studies using measures of how infectious a disease is based on observations to model the outbreak, for example force of infection. We excluded review papers and only included studies written in English.

### *Data extraction and analysis*

The in-depth reviewing of the selected studies focused on characteristics of the study setting (target disease, country, interventions evaluated), issues related to modeling, and, finally, the included costs and health gains. We will elaborate on the latter two.

We extracted information about what type of model (dynamic or static) was used in the included studies, and how the studies dealt with uncertainty around estimates. Some models, such as microsimulations, are stochastic by definition while other models may employ various types of sensitivity analyses. Sensitivity analyses may be used to test uncertainties, but also to test different assumptions of the transmission model and the economic model. Such analyses may involve varying assumptions and parameters related to the specific setting of a study, which can inform the generalizability of the results to other settings, for instance other drug prices or intervention efficacies (Ginsberg, 2013). Thus, we also extracted information about the setting of the included studies and grouped these settings according to the World Bank Country and Lending Groups (World Bank, n.d.).

We divided costs into two categories: (i) costs that occur within the healthcare sector and (ii) costs that occur outside of the healthcare sector. For both categories, we further divided the costs into short-term costs and future costs. We defined short-term cost as the costs that occur during the outbreak, and the future costs as those that occur when

life is extended. Short term costs within the healthcare sector are for example staff, equipment, and current treatment costs. Future costs within the healthcare sector include both future consumption of healthcare related to the specific disease being targeted but also future utilization of healthcare due to other diseases in life years gained (van Baal et al., 2016).

Short term costs outside the healthcare sector are costs that arise for example for the patient or the caregiver of a patient. These costs can be for transportation, time off from work to undergo treatment in a healthcare facility, or out-of-pocket expenses. Future costs outside the healthcare sector include productivity losses due to disability and premature mortality. Productivity losses are often estimated by methods such as the Human capital approach or the Friction cost method. The human capital approach quantifies the remaining productivity that would have occurred during all life-years lost (Brouwer WBF, Rutten FFH, 2001). The friction cost method quantifies the time required to replace a worker by someone else, like a formerly unemployed person (Koopmanschap et al., 1995).

There is currently an ongoing debate on which future costs to include in health economic evaluations (van Baal et al., 2017). This particularly relates to costs in gained life years (i.e., those years that patients would not have lived without the intervention, but do with). If the aim is to comprehensively capture all impacts of an intervention, future costs and benefits, related to consumption and production, cannot be excluded from an analysis (Meltzer, 1997a; van Baal et al., 2016).

For all cost categories distinguished we extracted information regarding the measurement and valuation of these costs and categorized them according to a micro-costing or a gross-costing approach. Micro-costing refers to the approach of costs estimation where the unit cost is multiplied by the used quantity of the referred unit, gross-costing, on the other hand, is when a budget is divided into sectors of usage (Barnett, 2009). Micro-costing is considered a more precise estimation of cost but may be more demanding in term of data availability, and the sum may even exceed the total budget (Barnett, 2009). Gross costing is less data demanding but may misclassify costs between sectors. Finally, we checked whether studies took account of more disruptive effects on the health care sector and the wider economics to account for non-marginal impacts of a pandemic.

To fully account for all the relevant effects the time horizon should be long enough to capture all costs and benefits of the intervention. Therefore, we extracted this information from the included articles. Additionally, we extracted information about discounting of cost and health effects. Discounting is common in economic evaluations as the effects that occur in the present are valued higher than similar effects occurring in the future. The WHO-CHOICE uses an annual discount rate of 3% for both health effects and costs, but national guidelines may recommend different rate(s) (Baltussen et al., 2004).

## Results

The literature search resulted in 298 records, of which 76 met the inclusion criteria and were assessed in full-text. Of the 76 records, 34 were considered eligible for inclusion in our study. The 42 excluded records were excluded due to: not conducting any form of economic evaluation (10 records), methodology paper (6 records), not based on relevant outbreaks (4 records), effectiveness study (3 records), not in English (3 records), studying animal subjects (3 records), not quantifying the impact of an intervention against outbreak (3 records), reviews (2 records), not comparing intervention against baseline (1 record), being a preliminary study to an already included study (1 record), budget impact analysis (1 record), not able to access (5 records).

As shown in Table 1, H1N1 was the most frequently studied outbreak, with 29 of the included studies. Few studies compared more than two interventions. Pharmaceutical interventions (vaccinations and antivirals) were studied in 23 included studies. Vaccinations were most commonly studied, followed by school closure. Evaluated non-pharmaceutical interventions mostly consisted of strategies aimed at decreasing contact between infected and susceptible individuals. Only four studies compared pharmaceutical interventions with non-pharmaceutical interventions.

Of the included studies, 17 were cost-effectiveness analyses (Andradottir et al., 2011; Brouwers et al., 2009; Carias et al., 2016; Dan et al., 2009; Gupta et al., 2005; Halder et al., 2011; Jamotte et al., 2016; Kelso et al., 2013; Lee et al., 2011a; Li et al., 2013; Mota et al., 2011; Nishiura et al., 2014; Pershad and Waters, 2012; Tsuzuki et al., 2018; Wong et al., 2016a; Yoo et al., 2015). Cost-utility analyses were performed in 13 studies (Araz et al., 2012; Beigi et al., 2009; Giglio et al., 2012; Hibbert et al., 2007; Khazeni et al., 2014, 2009b, 2009a; Lee et al., 2011b; McGarry et al., 2013; Prosser et al., 2011; Sander et al., 2010; Xue et al., 2012; You et al., 2012), and four studies performed cost-benefit analyses (Basurto-Davila et al., 2017; Brown et al., 2011; Mamma and Spandidos, 2013; Wang et al., 2012). 29 studies were conducted in a high-income setting, 4 were conducted in an 'upper-middle' income setting and only one was conducted in a low-income setting. Of the high-income studies, a majority (i.e. 16 out of 29) were situated in the US.

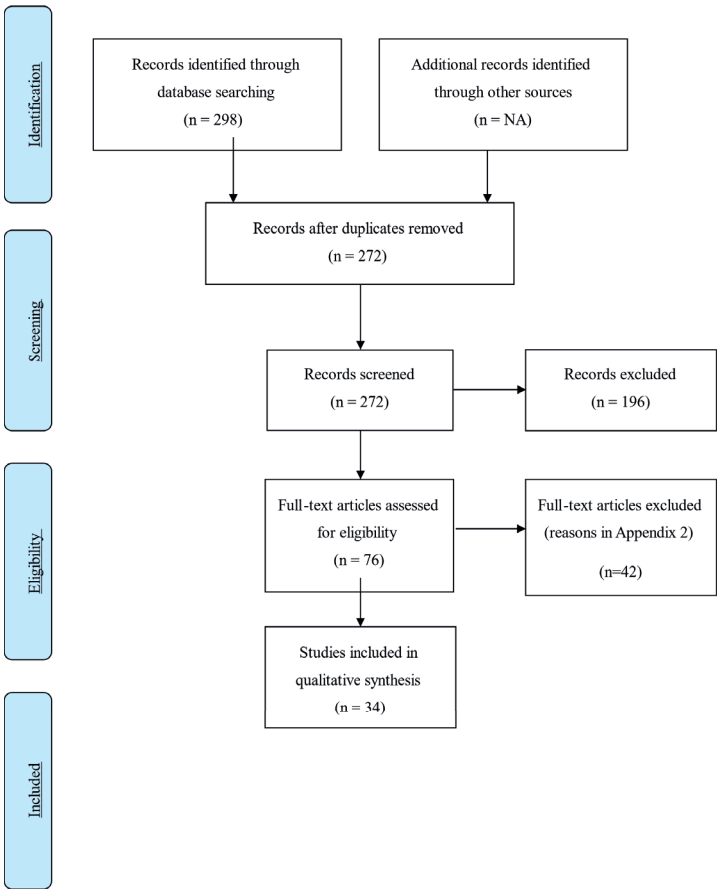


*Figure 1: Schematic flowchart of study selection process*

A dynamic model was used in 19 studies, while 11 studies used a static model. Four studies, all evaluating interventions against H1N1, did not use a transmission model and instead used trial data. One study evaluated the impact of individuals taking own initiative to have less contact with others, thereby aiming to reduce the risk of contracting the disease, in a sensitivity analysis (Khazeni et al., 2014).

Of all included studies, 30 conducted at least some sort of sensitivity analysis by varying parameter values. A univariate analysis was conducted in 19 studies, a probabilistic in 10 studies and a multivariate sensitivity analysis in one study (Dan et al., 2009). For dynamic models, in which probabilistic sensitivity analysis is inherently difficult due to the parameters in the model being highly inter-dependent, univariate sensitivity analyses on key or all parameters were performed. Only 11 out of the 34 included studies discounted both costs and health benefits.

| Outbreak | Frequency* | %* |
|---|---|---|
| H1N1 | 29 | 85% |
| H5N1 | 3 | 9% |
| SARS | 3 | 9% |
| Ebola | 1 | 3% |
| H7N9 | 1 | 3% |
| **Intervention** | **Frequency*** | **%*** |
| Vaccination | 16 | 47% |
| School closure | 8 | 24% |
| Antivirals | 6 | 18% |
| Quarantine | 2 | 6% |
| Personal Protective Equipment | 2 | 6% |
| Social distancing | 2 | 6% |
| Screening | 1 | 3% |
| Whole response program | 1 | 3% |
| Sick leave policies | 1 | 3% |
| Non-specified non-pharmaceutical | 1 | 3% |
| Other pharmaceutical | 1 | 3% |
| **Setting**** | **Frequency** | **%** |
| High income | 29 | 85% |
| Upper middle income | 4 | 12% |
| Low income | 1 | 3% |

* Sum of frequencies and/or percentages larger than number of studies included as some studies evaluated more than one outbreak/intervention. ** Classified accordingly to the World Bank's classification of Countries and Lending Groups (World Bank, 2016.)

Nine studies did not mention the perspective used, however, several of those studies did include costs outside the healthcare perspective suggesting the use of a societal perspective. Fourteen studies used a societal perspective and six studies a healthcare perspective. Four studies assessed the costs and benefits from both a healthcare perspective and the societal perspective. One study used a patient perspective (Lee et al., 2011a). Of the studies stating a lifetime horizon, two included some types of future costs (Khazeni et al., 2014; McGarry et al., 2013).

Among the cost-effectiveness studies the outcome measure varied greatly: five used cases averted as outcome measure, four estimated the reduced attack rates, two assessed life years lost (Nishiura et al., 2014; Tsuzuki et al., 2018). The remaining studies all used different outcome measures, including: deaths averted (Dan et al., 2009), averted admissions (Carias et al., 2016), care quality indicators (such as turn-around time and emergency department recidivism) (Pershad and Waters, 2012), proportion vaccinated (Yoo et al., 2015), or days of sick leave per 100 healthcare workers (Mota et al., 2011). All but two studies included treatment costs within the healthcare sector. Both of the studies that did not include these costs assessed the cost-effectiveness of school closures (Araz et al., 2012; Nishiura et al., 2014). Other included health care costs were administration costs (19 studies), equipment (two studies) (Basurto-Davila et al., 2017; Carias et al., 2016), co-payments (one study) (Andradottir et al., 2011), and costs due to days of sick leave of health care workers (one study) (Mota et al., 2011). One study mentioned healthcare costs but subsequently did not define the costs explicitly (Dan et al., 2009). Only one study included future non-related healthcare costs (Khazeni et al., 2014). With respect to costs outside the healthcare sector, 24 studies included productivity losses due to short-term absenteeism, transportation (two studies) (Jamotte et al., 2016; Xue et al., 2012), administration (one study) (Li et al., 2013), treatment (one study) (Jamotte et al., 2016), presenteeism (one study) (Hibbert et al., 2007),and energy savings (one study) (Xue et al., 2012).

Ten studies included some form of future costs. Eight of these included future productivity losses, one included non-related medical costs (Khazeni et al., 2014) and one included related medical costs (McGarry et al., 2013). No study included more than one type of future costs. The studies that included productivity losses all used the human capital approach, basing calculations on wages and remaining life expectancy. One study included future related medical costs in the form of lifetime disability caused by the illness (McGarry et al., 2013). Another study included future non-related medical consumption by age based on insurance data in the US (Khazeni et al., 2014). Four of the ten studies including future costs did not discount these costs.

When possible, we assessed the most likely costing method used, based on the (sometimes limited) information provided in the manuscripts. We refrained from labeling the costing method in two studies as the data used for costing was not described. The most common method found was micro-costing, which was used in 27 of the studies. Mixed costing methods using both micro and gross costing were the second most frequently used, while gross-costing was third. None of the studies took into account macro-economic effects of a pandemic.

Table 2. Overview of included articles.

| Author | Type | Setting | Outbreak | Intervention | Results summary | Mdel type | Uncertainty |
|---|---|---|---|---|---|---|---|
| Basurto-Davila (Basurto-Davila et al., 2017) | CBA | US | H1N1 | Vaccination | Vaccination averted 4,600 influenza cases and was cost saving | Dynamic | Probabilistic |
| Brown (Brown et al., 2011) | CBA | US | H1N1 | School closure | Cost per averted case with a 8 week school closure varied between 14,000 and 25,000 depending on the infection rate | Dynamic | Univariate |
| Mamma (Mamma and Spandidos, 2013) | CBA | Greece | H1N1 | Vaccination | Depending on participation rate, % symptomatic the net cost per case averted ranged from -36.67 to 35.42 EUROs | Static | Univariate |
| Wang (Wang et al., 2012) | CBA | China | H1N1 | Combination of preventive measures, testing and treatment based on polices enacted in Hubei Province | The estimated benefits of the Hubei response program were more than five times the estimated costs. | Static/ mathemat-ical | - |
| Tracht (Tracht et al., 2012) | CEA* | US | H1N1 | PPE | 10%, 25% and 50% use of facemasks in the population could reduce costs by 478, 570, 573 billion USD respectively and decrease the number of cases | Dynamic | Univariate |
| Lee2 (Lee et al., 2011a) | CEA* | US | H1N1 | Vaccination | The cost per case averted varied between 14 and 2,387 USD f depending on vaccine cost and vaccination time. | Static | Probabilistic |
| Andradóttir (Andradottir et al., 2011) | CEA* | US | H1N1 | vaccination, antiviral, school closure, social distancing | Many scenarios consisting of combinations of interventions are presented. Most scenarios resulted in lower attack rates and cost savings. | Dynamic | Univariate |
| Brouwers (Brouwers et al., 2009) | CEA | Sweden | H1N1 | Vaccination | A vaccination rate of 60% of the population was the most cost-effective saving 2.5 billion SEK | Dynamic | Univariate |

| Perspective stated | Time horizon stated | Costs | | | | | Health outcome | Discount rate (%) |
|---|---|---|---|---|---|---|---|---|
| | | Within HC | | Outside HC | | Costing method | | |
| | | Short term | Future | Short term | Future | | | |
| Societal | NR | T,ADM,EQ | Not included | AB | FNM | Micro-costing | Cases averted | 3 |
| Societal | NR | T | Not included | AB | FNM | Mixed | Cases averted | 3 |
| NR | NR | T | Not included | AB | Not included | Micro-costing | Cases averted | NR |
| NR | NR | T,ADM | Not included | AB | FNM | Micro-costing | Cases averted | NR |
| NR | NR | T,ADM | Not included | AB | FNM | Micro-costing | Cases averted | NR |
| Patient | NR | T | Not included | AB | Not included | Micro-costing | Cases averted | 3 |
| NR | NR | T, CP | Not included | AB | FNM | Micro-costing | Attack rates | NR |
| Societal | NR | T,ADM | Not included | AB | Not included | Mixed | Cases averted | NR |

| Author | Type | Setting | Outbreak | Intervention | Results summary | Mdel type | Uncertainty |
|---|---|---|---|---|---|---|---|
| Carias (Carias et al., 2016) | CEA | west Africa | Ebola | Other pharmaceutical | Administration of malaria treatment to Ebola admitted patients dominated no malaria treatment resulting in fewer cases and cost savings | Dynamic | Probabilistic |
| Dan (Dan et al., 2009) | CEA | Singapore | SARS, H1N1, 1918 Spanish influenza | PPE | Protective measures aimed at only infected patients was the most cost-effective intervention at 23,300 USD per death averted | Dynamic | Multivariate |
| Halder (Halder et al., 2011) | CEA | Australia | H1N1 | school closure, antiviral | Limited school closure in combination with antiviral treatment was the most cost-effective with 632-777 USD per case averted | Dynamic | Univariate |
| Jamotte (Jamotte et al., 2016) | CEA* | Australia | H1N1 | Vaccination | Quadrivalent, compared trivalent, vaccines were cost-saving and averted almost 70,000 cases per year | Static | univariate |
| Kelso (Kelso et al., 2013) | CEA* | Australia | H5N1 | school closure, antiviral, workforce reduction, social distancing | A combination of antiviral treatment and prophylaxis, extended school closure, social distancing was most effective and was cost-saving compared to no intervention | Dynamic | Univariate |
| Li (Li et al., 2013) | CEA | China | H1N1 | Quarantine | Mandatory quarantine in the H1N1 epidemic in China had a cost of 22 USD per case averted which was not considered to be cost-effective** | Dynamic | - |
| Nishiura (Nishiura et al., 2014) | CEA | Japan | H1N1 | School closure | School closure was not found to be cost-effective with an ICER ranging from approximately 1.5E+07 to 1E+11 Yen per Life Year | Dynamic | Univariate |

| Perspective stated | Time horizon stated | Costs | | | | | Health outcome | Discount rate (%) |
|---|---|---|---|---|---|---|---|---|
| | | Within HC | | Outside HC | | Costing method | | |
| | | Short term | Future | Short term | Future | | | |
| Healthcare | 1-year | T,ADM,EQ | Not included | Not included | Not included | Micro-costing | Admissions averted | 0 |
| Healthcare | NR | T, UNDEF | Not included | Not included | Not included | not described | Deaths averted | NR |
| Societal | NR | T,ADM | Not included | AB | FNM | Micro-costing | Attack rate reduction, cases averted | 3 |
| Societal & healthcare | NR | T,ADM | Not included | AB, TR,T | Not included | Micro-costing | Cases averted | NR |
| Societal | Lifetime | T | Not included | AB | Not included | Micro-costing | Attack rates | 3 |
| NR | NR | T | Not included | ADM | Not included | Not described | Cases averted | NR |
| Societal | NR | Not included | Not included | AB | Not included | Micro-costing | Years of life saved | NR |

| Author | Type | Setting | Outbreak | Intervention | Results summary | Mdel type | Uncertainty |
|---|---|---|---|---|---|---|---|
| Pershad (Pershad and Waters, 2012) | CEA | US | H1N1 | Screening | Pre-screening in tents compared to no use of tents resulted in 637 USD per percentage point decrease in hospital elopement rate | Trial data | Univariate |
| Tsuzuki (Tsuzuki et al., 2018) | CEA | Japan | H1N1 | Vaccination | Quadrivalent, compared trivalent, vaccines were cost-saving and averted 528 cases per 100,000 | Dynamic | Probabilistic |
| Wong (Wong et al., 2016b) | CEA | Hong Kong | H1N1 | School closure | Individual school closure at the lowest case threshold was the most cost-effective with 1,145 USD per case averted | Dynamic | Probabilistic |
| Yoo (Yoo et al., 2015) | CEA | US | H1N1 | Vaccination | School located season influenza vaccination resulted in a 12% higher vaccination rate with 36 USD per vaccination | Trial data | Probabilistic |
| Mota (Mota et al., 2011) | CEA | Brazil | H1N1 | Sick leave policies among health care workers | 2-day sick leave with reassessment proved to be cheaper and more effective than a 7-day sick leave policy with 609 USD per health care worker on leave | Trial data | - |
| Gupta (Gupta et al., 2005) | CEA* | Canada | SARS | Quarantine | Compared to care as usual and isolation of infected patients, quarantine of infected patients and contacts was cost saving and reduced transmission | Static | - |
| Araz (Araz et al., 2012) | CUA | US | H1N1 | School closure | In the H1N1 scenario school closure had an ICER between 56,100 to 334,800 USD per QALY gained depending on closure length and transmission intensity | Dynamic | Univariate |

| Perspective stated | Time horizon stated | Costs | | | | Costing method | Health outcome | Discount rate (%) |
|---|---|---|---|---|---|---|---|---|
| | | Within HC | | Outside HC | | | | |
| | | Short term | Future | Short term | Future | | | |
| Healthcare | NR | T,ADM | Not included | Not included | Not included | Micro-costing | Health care quality indicators | NR |
| Societal & healthcare | NR | T,ADM | Not included | AB | FNM | Micro-costing | Years of life saved | 2 |
| NR | NR | T | Not included | AB | Not included | Micro-costing | Attack rates | NR |
| Societal | NR | T,ADM | Not included | AB | Not included | Micro-costing | Proportion vaccinated | NR |
| NR | NR | T,AB | Not included | Not included | Not included | Mixed | Days of sick leave averted per 100 health care workers | NR |
| NR | NR | T,ADM | Not included | AB | FNM | Mixed | Cases averted | NR |
| Societal | NR | Not included | Not included | AB | Not included | Micro-costing | QALY | 3 |

| Author | Type | Setting | Outbreak | Intervention | Results summary | Mdel type | Uncertainty |
|---|---|---|---|---|---|---|---|
| Beigi (Beigi et al., 2009) | CUA | US | H1N1 | Vaccination | Single dose vaccination in high prevalence scenarios dominated the no vaccination option with decreasing cost effectiveness with lower prevalence and increased doses | Static | Probabilistic |
| Giglio (Giglio et al., 2012) | CUA | Argentina | H1N1 | Vaccination | Vaccination of 6 months old to 5 years old was the most cost-effective with 717 USD per QALY gained | Static | Univariate |
| Hibbert (Hibbert et al., 2007) | CUA | US | H1N1 | Vaccination | Vaccination of children dominated the no vaccination strategy** | Trial data | Univariate |
| Khazeni (Khazeni et al., 2014) | CUA | US | H7N9, H5N1 | Vaccination | Vaccination at 4 months compared to 6 months was cost-effective with 10,689 USD per QALY gained | Dynamic | Univariate |
| Khazeni2 (Khazeni et al., 2009b) | CUA | US | H5N1 | Non defined non-pharmaceutical interventions, Vaccination, Antiviral, | Non-pharmaceutical interventions, vaccination and antivirals in quantities similar to current US stockpiles resulted in 8,907 USD per QALY gained compared to no intervention | Dynamic | Univariate |
| Khazeni3 (Khazeni et al., 2009a) | CUA | US | H1N1 | Vaccination | Vaccination in the US population against the H1N1 pandemic in October instead of November would be cost-saving and an additional gain of 9,200 QALYs | Dynamic | Univariate |

| Perspective stated | Time horizon stated | Costs | | | | Costing method | Health outcome | Discount rate (%) |
|---|---|---|---|---|---|---|---|---|
| | | Within HC | | Outside HC | | | | |
| | | Short term | Future | Short term | Future | | | |
| Societal & healthcare | NR | T | Not included | AB | Not included | Micro-costing | QALY | 3 |
| NR | NR | T,ADM | Not included | Not included | Not included | Micro-costing | QALY | 3 |
| Societal | 1-year | T,ADM | Not included | AB, PR | Not included | Micro-costing | QALY | 0 |
| Societal | Lifetime | T | FNRM | AB | Not included | Micro-costing | QALY | 3 |
| Societal | Lifetime | T,ADM | Not included | AB | Not included | Micro-costing | QALY | 3 |
| Societal | Lifetime | T,ADM | Not included | AB | Not included | Micro-costing | QALY | 3 |

| Author | Type | Setting | Outbreak | Intervention | Results summary | Mdel type | Uncertainty |
|---|---|---|---|---|---|---|---|
| Lee (Lee et al., 2011b) | CUA | US | H1N1 | Antivirals | Initialization of antiviral treatment after PCR confirmed test was the most cost-effective with a difference of 67 USD per QALY to the second most cost-effective strategy and increasing with cost of antivirals | Static | Probabilistic |
| McGarry (McGarry et al., 2013) | CUA | US | H1N1 | Vaccination | PCV13 vaccination compared to PCV7 vaccination was cost saving and would have prevented 3,700 deaths in a H1N1 scenario | Static/ mathemat-ical | Univariate |
| Sander (Sander et al., 2010) | CUA | Canada | H1N1 | Vaccination | The vaccination program against the H1N1 in Ontario was cost-effective with an ICER of 9,140 per QALY gained | Dynamic | Probabilistic |
| Xue (Xue et al., 2012) | CUA | Norway | H1N1 | School closure | When simulating a pandemic similar to H1N1 school closure as single intervention would not have been cost-effective with an ICER ranging from 136 427 - 2 192 323 USD per QALY | Dynamic | Univariate |
| You (You et al., 2012) | CUA | Hong Kong | H1N1 | Antivirals | Initialization of antiviral treatment based on empirical assessment alone dominated PCR guided treatment and a combination of both | Static | Probabilistic |
| Prosser (Prosser et al., 2011) | CUA | US | H1N1 | Vaccination | Vaccination prior to the H1N1 outbreak was found cost-saving for high-risk groups. For non-risk groups the ICER varied from 5,000-18,000 USD per QALY | Static | Univariate |

Cost abbreviations: CBA= Cost-Benefit Analysis, CEA= Cost-Effectiveness Analysis, CUA= Cost-Utility Analysis, T= treatment, A= administrative, EQ= equipment, AB= absenteeism, PR= presenteeism, TR= travel expenses, CP= co-payments, ES= energy savings,, FRM= future related medical costs, FUM= future unrelated medical costs, FNM= future non-medical costs, NR= not reported. Treatment costs may include the cost of vaccination if applicable, Absenteeism may

| Perspective stated | Time horizon stated | Costs | | | | Costing method | Health outcome | Discount rate (%) |
|---|---|---|---|---|---|---|---|---|
| | | Within HC | | Outside HC | | | | |
| | | Short term | Future | Short term | Future | | | |
| Societal & healthcare | NR | T,ADM | Not included | AB | Not included | Micro-costing | QALY | 3 |
| Healthcare | Lifetime | T | FRM | Not included | Not included | Mixed | QALY | 3 |
| Healthcare | Lifetime | T,ADM | Not included | Not included | Not included | Micro-costing | QALY | 5 |
| Societal | NR | T | Not included | AB, ES,TR | Not included | Micro-costing | QALY | 4 |
| Healthcare | NR | T,ADM | Not included | Not included | Not included | Micro-costing | QALY | 3 |
| Societal | 1-year | T,ADM | Not included | Not included | Not included | Micro-costing | QALY | 3 |

include the estimated opportunity loss for students not attending school during school closures and the opportunity cost lost from educational professionals during school closure. *= Type of study determined by author as this was not explicitly mentioned in the study, **= ICERs not presented in article but calculated by author.

## Discussion

This study identified a substantial number of studies evaluating intervention strategies for important recent major outbreaks in terms of costs and benefits. We found a strong focus on the H1N1 outbreak and a clear bias towards high-income settings. We also found a discrepancy between pharmaceutical and non-pharmaceutical interventions being evaluated. The majority of the studies adopted a societal perspective but its operationalization varied substantially between studies, also in terms of which costs were included in the evaluation. Furthermore, although many studies modeled future health gains, the inclusion of future costs was limited. Also, none of the included studies included non-marginal effects that outbreaks might have on the health care sector and the wider economy.

In this study, we presented an overview of economic evaluations in multiple settings without restrictions to certain interventions. This allowed us to create an overview of the methods used in these economic evaluations of strategies to prevent or mitigate the consequences of major outbreaks. Our focus was on the economic aspects, rendering a comprehensive appraisal of the disease and transmission models used beyond the scope of this study. Still, we emphasize the need for high-quality transmission models in producing reliable economic estimations. In our search of the literature we did not find any studies that took into account more disruptive non-marginal effects of pandemics on the health care sector and the wider economy. This suggests that there is a gap between the research on the ex-post evaluation of a pandemic taking a macro-economic perspective and ex-post economic evaluations that estimate the impact of specific interventions.

Some limitations of our study need mentioning. First, our search strategy was broad, but may have missed specific studies. It seems unlikely this would have changed our results. Indeed, we believe that the included studies are relevant and form a sample large enough to base our conclusions on. Second, we searched for economic evaluations in relation to specific outbreaks. in particular, the sample of studies included in this review represents outbreaks that were identified as being potentially large threats. Other criteria could have been used for selecting outbreaks and interventions, which would have resulted in a different sample of studies. We cannot generalize to economic evaluations of interventions targeted at other outbreaks. For, example, outbreaks that may have or have had an even larger impact on health and society than the ones included here, may have been evaluated more extensively, potentially leading to different conclusions. Third, included articles were primarily screened by one researcher (KK). Having a second reviewer for all studies would have been more appropriate. Fourth, we encountered some difficulties in extracting the methods used and assumptions made in some studies. Given the level of information provided in those studies, we cannot rule out that some studies or methods were misclassified in this review. A more

detailed presentation of the included elements, methods used and the data sources would facilitate the interpretation of the results and add to the transparency as well as the ability to replicate and compare studies.



To the best of our knowledge, there are no previous studies with a similar scope as ours. Previous reviews often applied a narrower scope by either restricting the search for a specific disease or to a specific setting. Pérez Velasco et al (Perez Velasco et al., 2012), reviewed the strategies against influenza pandemics. Consistent with our results they found an overrepresentation of pharmaceutical interventions in high-income countries. Pérez Velasco et al also assessed the quality of the included articles in their study, but focused less on variation in methods. A systematic review by Drake et al (Drake et al., 2016), focusing on dynamic transmission economic evaluations of infectious disease interventions in low- and middle-income countries, highlighted the lack of reporting parameter values. This was also the case in our review. Drake et al. emphasized the lack in highlighting the uncertainty surrounding cost estimates in modelling studies. In our sample we found a vast majority of studies using secondary cost data, with a large number of the studies performing a sensitivity analysis of the cost data. Specifically, many studies addressed uncertainty regarding parameters influencing prices or volumes either using uncertainty applied as a proportion of the mean price estimate or uncertainty regarding the mean cost estimates directly obtained. The number of parameters varied in the sensitivity analyses ranged substantially, from all too just a few. A possible explanation for this difference with the findings from the study by Drake et al, is that in our sample the studies mostly originated from high-income settings where the availability of data might be better. Drake et al (Drake et al., 2016) proposed a value of information (VOI) framework to address the indicated shortcomings. This was also suggested by Pérez Velasco et al. (Perez Velasco et al., 2012). VOI analysis may provide insights about potential beneficial areas to conduct further investigation. In addition, other topics could be addressed such as capacity constraints of the healthcare providers, especially in extra resource constrained or vulnerable settings (van Baal et al., 2018). A major outbreak with a large number of cases will require large efforts in any setting, which may affect the provision of other healthcare service when resources are diverted.

Our results show that there are large differences in the methods used to estimate the costs and benefits of different interventions. These differences can only very partially be explained by differences in the perspective adopted in the studies, as we found large differences within perspectives as well. Therefore, we conclude that there is a need to standardize which costs to include in economic evaluations in this context. Differences in the inclusion of costs will lead to difficulties comparing studies and their results. Moreover, excluding certain cost categories might create biases in results of economic evaluations and can be done strategically. By ignoring real costs, one also risks unwanted or unexpected effects when the intervention is actually implemented.

Another recommendation is to adopt a lifetime time horizon and to include all relevant benefits and costs during that period. This also implies that future costs need to be included in the evaluation. If life is prolonged due to an intervention, the life years gained can result in additional contributions to society (e.g. productivity) but may also result in additional costs, such as healthcare consumption and other consumption. Using long time horizons also increases the importance of discounting, which was not performed in all studies including costs beyond the outbreak duration. Not discounting future costs and effects may lead to biases in the results of an economic evaluation and its influence may be profound (Westra et al., 2012). As no global standards exist on which costs to include and which rates to use for discounting costs and effects and whether these should be identical presentation of results with and without discounting (at varying rates) and with and without future costs would be a practical approach (Attema et al., 2018; Claxton et al., 2011).

The lack of evaluations from non-high-income countries and regions creates difficulties in generalizing the results to other countries and regions. The importance of this issue is emphasized by the fact that most of the burden of communicable diseases still occurs in low- and middle-income settings. The current bias may therefore leave exactly those policy makers who stand to gain most from better evidence on these matters without it. Previous studies have addressed the challenge of incorporating behavioral aspects into infectious disease models (Funk et al., 2015, 2010). In the studies we selected, only one performed a sensitivity analysis in which the effect of individuals limiting their contact with others on their own initiative was explored (Khazeni et al., 2014). This is a topic on which further research is needed, including aimed at standardization of how to include such behavioral changes in economic evaluations. Another topic which needs further research is the impact of outbreaks on the broader economy: the so-called disruptive effects. None of the included studies attempted to incorporate these effects, while they may have a substantial effect on the estimated cost-effectiveness of interventions. For instance, Prager et al. (Prager et al., n.d.), estimated the economic costs of a pandemic influenza to amount to a possible $25 billion in the US. When incorporating avoidance and resilience behavior the potential loss grew to $43 billion. Further research is needed to link the outcomes of such studies to economic evaluations focusing on specific interventions. Based on our findings, we suggest that studies should strive towards more comprehensiveness in what they include and more standardization in terms of how to include relevant costs and (health) benefits. Future costs and productivity costs are two areas in which standardization is clearly required. We also emphasize the need for a presentation of all elements of costs and health effects in future studies in a manner that allows readers to scrutinize the data and methods used, and facilitates transferability of results. Adopting reporting standards such as Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement would be an improvement in this regard (Husereau et al., 2013).

We note that inclusion of particular costs and benefits may have distributional consequences, also in the context of deciding on interventions aimed at the prevention and mitigation of potential outbreaks. For instance, including productivity losses in the evaluation of an intervention may favor interventions saving or targeted at younger, productive individuals, who participate in the paid labor force. Such distributional consequences should receive due attention, but are not solved by simply ignoring real costs like productivity costs. The increased costs of prolonging life also deserve mentioning in this context. These costs entail both costs of consuming health care in added life year but also the consumption of non-medical goods. It should be noted that these costs currently often are not included in economic evaluations (de Vries et al., 2018).

Overall, this paper concludes that the evidence base regarding the cost-effectiveness of interventions targeted at preventing or mitigating the effects of major outbreaks at this stage is biased towards specific settings and outbreaks and methodologically diverse. Given the importance of the issue, effort should be taken to improve this.

# Supplemental material

## Search strings

*SCOPUS:*

(TITLE("Middle East respiratory syndrome coronavirus" OR sars OR n5n1 OR h1n1 OR cholera OR mers-cov OR h7n9 OR ebola) OR ABS("Middle East respiratory syndrome coronavirus" OR sars OR h5n1 OR h1n1 OR cholera OR mers-cov OR h7n9 OR ebola)) AND (TITLE(economic OR cost* OR costing) OR ABS(economic OR cost* OR costing)) AND (TITLE(benefits OR effectiveness OR cost-effectiveness OR cost-benefit OR cost-utility) OR ABS(benefits OR effectiveness OR cost-effectiveness OR cost-benefit OR cost-utility)) AND NOT DBCOLL(medl) AND ( EXCLUDE ( DOCTYPE,"re " ) OR EXCLUDE ( DOCTYPE,"ch " ) OR EXCLUDE ( DOCTYPE,"bk " ) OR EXCLUDE ( DOCTYPE,"sh " ) ) AND ( LIMIT-TO ( PUBYEAR,2018 ) OR LIMIT-TO ( PUBYEAR,2017 ) OR LIMIT-TO ( PUBYEAR,2016 ) OR LIMIT-TO ( PUBYEAR,2015 ) OR LIMIT-TO ( PUBYEAR,2014 ) OR LIMIT-TO ( PUBYEAR,2013 ) OR LIMIT-TO ( PUBYEAR,2012 ) OR LIMIT-TO ( PUBYEAR,2011 ) OR LIMIT-TO ( PUBYEAR,2010 ) OR LIMIT-TO ( PUBYEAR,2009 ) OR LIMIT-TO ( PUBYEAR,2008 ) OR LIMIT-TO ( PUBYEAR,2007 ) OR LIMIT-TO ( PUBYEAR,2006 ) OR LIMIT-TO ( PUBYEAR,2005 ) OR LIMIT-TO ( PUBYEAR,2004 ) OR LIMIT-TO ( PUBYEAR,2003 ) ) AND ( LIMIT-TO ( LANGUAGE,"English" ) )

*PUBMED:*

(Middle East respiratory syndrome coronavirus[Title/Abstract] OR SARS[Title/Abstract] OR H5N1[Title/Abstract] OR H1N1[Title/Abstract] OR Cholera[Title/Abstract] OR MERS-CoV[Title/Abstract] OR H7N9[Title/Abstract] OR ebola[Title/Abstract]) AND (((economic[Title/Abstract] OR cost*[Title/Abstract] OR costing[Title/Abstract]) AND (benefits[Title/Abstract] OR effectiveness[Title/Abstract])) OR cost-effectiveness OR cost-benefit OR cost-utility) AND ( "2003/01/01"[PDat] : "3000/12/31"[PDat] NOT Animals[Mesh:noexp])

## Excluded articles after full-text review

| Author | Title | Year | Reason for exclusion |
|---|---|---|---|
| Ssematimba | Estimating the between-farm transmission rates for highly pathogenic avian influenza subtype H5N1 epidemics in Bangladesh between 2007 and 2013. | 2017 | Animal subjects |
| Sun | Assessment of China's H5N1 routine vaccination strategy. | 2017 | Animal subjects |
| Tran | An Alternative Vaccination Approach for The Prevention of Highly Pathogenic Avian Influenza Subtype H5N1 in The Red River Delta, Vietnam -A Geospatial-Based Cost-Effectiveness Analysis. | 2016 | Animal subjects |
| Pitrelli | Introduction of a quadrivalent influenza vaccine in Italy: a budget impact analysis. | 2016 | Budget impact analysis |
| Zhao | [A cost-benefit analysis of the influenza H1N1 vaccination in the primary and junior school in Shanghai]. | 2011 | Chinese |
| Lewnard | Strategies to Prevent Cholera Introduction during International Personnel Deployments: A Computational Modeling Analysis Based on the 2010 Haiti Outbreak. | 2016 | No cost comparison |
| Cauchemez | Estimating the impact of school closure on influenza transmission from Sentinel data. | 2008 | Effectiveness study |
| Ciavarella | School closure policies at municipality level for mitigating influenza spread: a model-based evaluation. | 2016 | Effectiveness study |
| Xia | Identifying the relative priorities of subpopulations for containing infectious disease spread. | 2013 | Effectiveness study |
| Sander | Is a Mass Immunization Program for Pandemic (H1N1) 2009 Good Value for Money? Early Evidence from the Canadian Experience. | 2010 | Final study included |
| Anparasan | Resource deployment and donation allocation for epidemic outbreaks | 2017 | Methodology paper |
| Jeuland | Incorporating Cholera Vaccine Herd Protection into Economic Cost-Benefit and Cost-Effectiveness Models | 2009 | Methodology paper |
| Park | A real option analysis for stochastic disease control and vaccine stockpile policy: An application to H1N1 in Korea | 2016 | Methodology paper |
| Harling | Leveraging contact network structure in the design of cluster randomized trials. | 2016 | Methodology paper |
| Mubayi | A cost-based comparison of quarantine strategies for new emerging diseases. | 2010 | Methodology paper |
| Phelps | Beyond cost-effectiveness: Using systems analysis for infectious disease preparedness. | 2016 | Methodology paper |
| Praditsuwan | The efficacy and effectiveness of influenza vaccination among Thai elderly persons living in the community. | 2005 | No access |
| Cao | Evaluating the impacts of vaccination, antiviral treatment and school closure on H1N1 influenza epidemic | 2014 | No access (conference) |
| Yarmand | Cost-effectiveness analysis of vaccination and self-isolation in case of H1N1 | 2010 | No access (conference) |
| Yarmand | A simulation-based analysis of different control policies for H1N1 | 2010 | No access (conference) |

| Author | Title | Year | Reason for exclusion |
|---|---|---|---|
| Clemens | When, how, and where can oral cholera vaccines be used to interrupt cholera outbreaks? | 2014 | No access (book chapter) |
| Sandhu | An intelligent system for predicting and preventing MERS-CoV infection outbreak | 2015 | No economic evaluation |
| Sandhu | Smart monitoring and controlling of Pandemic Influenza A (H1N1) using Social Network Analysis and cloud computing | 2016 | No economic evaluation |
| Basili | Swine influenza and vaccines: an alternative approach for decision making about pandemic prevention. | 2013 | No economic evaluation |
| Shim | Optimal H1N1 vaccination strategies based on self-interest versus group interest. | 2011 | No economic evaluation |
| Tracht | Mathematical modeling of the effectiveness of facemasks in reducing the spread of novel influenza A (H1N1). | 2010 | No economic evaluation |
| Tuite | Optimal pandemic influenza vaccine allocation strategies for the canadian population. | 2010 | No economic evaluation |
| Wells | Accuracy, Precision, Ease-Of-Use, and Cost of Methods to Test Ebola-Relevant Chlorine Solutions. | 2016 | No economic evaluation |
| Weng | Early detection for cases of enterovirus- and influenza-like illness through a newly established school-based syndromic surveillance system in Taipei, January 2010 ~ August 2011. | 2015 | No economic evaluation |
| Srivastav | Analysis of a simple influenza A (H1N1) model with optimal control | 2016 | No economic model |
| Dorratoltaj | Epidemiological and economic impact of pandemic influenza in Chicago: Priorities for vaccine interventions. | 2017 | Not based on relevant outbreak |
| Fast | Cost-Effective Control of Infectious Disease Outbreaks Accounting for Societal Reaction. | 2015 | Not based on relevant outbreak |
| Franke | Comparison of two control groups for estimation of oral cholera vaccine effectiveness using a case-control study design. | 2017 | Not based on relevant outbreak |
| Yaesoubi | Identifying cost-effective dynamic policies to control epidemics. | 2016 | Not based on relevant outbreak |
| Gamache | Development and Assessment of a Public Health Alert Delivered through a Community Health Information Exchange. | 2010 | Not evaluating interventions against outbreak |
| Gache | The 2009 A(H1N1) influenza pandemic in the French Armed Forces: evaluation of three surveillance systems. | 2012 | Not quantitative |
| Deans | Influenza vaccines provide diminished protection but are cost-saving in older adults. | 2010 | Review |
| Mogasale | Oral Cholera Vaccination Delivery Cost in Low- and Middle-Income Countries: An Analysis Based on Systematic Review. | 2016 | Review |

| Author | Title | Year | Reason for exclusion |
|---|---|---|---|
| Chocontá-Piraquive | [Cost-effectiveness of vaccinating pregnant women against pandemic influenza in Colombia]. | 2012 | Spanish |
| González-Canudas | [Cost-effectiveness in the detection of influenza H1N1: clinical data versus rapid tests]. | 2011 | Spanish |
| Rosello | Infectious disease risk and international tourism demand | 2017 | Not quantifying impact of intervention |
| Wilson | A national estimate of the hospitalisation costs for the influenza (H1N1) pandemic in 2009 | 2012 | Not quantifying impact of intervention |

# CHAPTER 3

## Costs and benefits of early response in the Ebola virus disease outbreak in Sierra Leone

## Abstract

The 2014-2016 Ebola virus disease (EVD) outbreak in West Africa was the largest EVD outbreak recorded, which has triggered calls for investments that would facilitate an even earlier response. This study aims to estimate the costs and health effects of earlier interventions in Sierra Leone. A deterministic and a stochastic compartment model describing the EVD outbreak was estimated using a variety of data sources. Costs and Disability-Adjusted Life Years were used to estimate and compare scenarios of earlier interventions. Four weeks earlier interventions would have averted 10,257 (IQR 4,353–18,813) cases and 8,835 (IQR 3,766–16,316) deaths. This implies 456 (IQR 194-841) thousand DALYs and 203 (IQR 87-374) million $US saved. The greatest losses occurred outside the healthcare sector. Earlier response in an Ebola outbreak saves lives and costs. Investments in healthcare system facilitating such responses are needed and can offer good value for money.

## Background

The West African Ebola virus disease (EVD) outbreak was the largest EVD outbreak since the virus was discovered. The outbreak mainly affected Guinea, Liberia, and Sierra Leone which together reported 28,616 confirmed, probable and suspected cases and 11,310 deaths (World Health Organization, 2016). Disruptive effects also affected health-seeking behavior and healthcare delivery (Elston et al., 2015; Parpia et al., 2016; UNICEF and Ministry of Sanitation of Health, 2014; Walker et al., 2015) . As the case counts grew, the outbreak drew international attention. In August 2014 the WHO published the Roadmap for response, outlining three phases of response initiatives to combat the outbreak (Organization, 2014). In October 2014, during the first phase, the UN Mission for Ebola Emergency Response (UNMEER) was launched (Ki-moon, 2014a). UNMEER had several aims: that 70 percent of cases would be isolated and that 70 percent of the burials would be conducted in a safe manner. Approximately two months after the UNMEER initiated interventions were implemented, the national weekly case counts decreased (WHO, 2016). Although the response operations seemed to effectively control the outbreak, critical voices raised an issue with the timeliness of the responses. Both the recognition of the outbreak and the implementation of the interventions came too late according to critics (Currie et al., 2016; Moon et al., 2015; UN High-Level Panel on the Global Response to Health Crises Protecting humanity from future health crises, 2016). The EVD epidemic highlighted the importance of surveillance systems for early detection as the virus remained undetected for the first three months of the EVD outbreak (CDC, 2016; Tambo et al., 2014; UN High-Level Panel on the Global Response to Health Crises Protecting humanity from future health crises, 2016).

Previous studies have estimated the effectiveness of various interventions, both real and hypothetical aimed at mitigating the outbreak (Barbarossa et al., 2015; Camacho et al., 2014; Dong et al., 2015; Fisman et al., 2014; Fisman and Tuite, 2014; Kucharski et al., 2015; Nishiura and Chowell, 2014; Rivers et al., 2014; Siettos et al., 2016; Towers et al., 2014; White et al., 2015; WHO Ebola Response Team, 2014). In an early stage of the outbreak Rivers *et al.* explored several different interventions and found that those would not effectively control the outbreak (Rivers et al., 2014). Kucharski *et al.* estimated the number of averted cases due to the introduction of additional hospital beds in Sierra Leone, and found that the increased capacity averted approximately 56,000 cases (Kucharski et al., 2015). Barbarossa *et al,* estimated the effect of the response efforts on the number of cases and concluded that a five-week earlier implementation would halve the outbreak size (Barbarossa et al., 2015). Other studies have investigated the health effects of the EVD outbreak caused by disruption of the health care system (Bolkan et al., 2014; Evans et al., 2015; Takahashi et al., 2015). Apart from interventions, the economic effect of the outbreak has also been studied (Bartsch et al., 2015; Kirigia et al., 2015; World Bank, 2016a). Bartsch *et al.* performed a cost of illness study comprising EVD treatment costs and productivity losses, suggesting

that the total cost of the epidemic in Sierra Leone was approximately 30 million US$ (Bartsch et al., 2015). Additionally, Kirigia *et al.* estimated future production losses due to EVD mortality to approximately 60 million international$ in Sierra Leone (Kirigia et al., 2015). Finally, The World Bank estimated the outbreaks' impact on the GDP of the outbreak-affected economies affected to be 2.8 billion US$, where Sierra Leone was most affected and incurred a loss of 1.9 billion US$ (World Bank, 2016a).

Although studies have investigated the effects of the outbreak in different intervention scenarios little work has been performed on the combination of potential health benefits and cost savings of earlier interventions. In this paper, we focus on providing estimates of costs and health consequences of the outbreak and the potential benefits of an earlier response. Moreover, this study also provides relevant input for discussions on more general investments to strengthen relatively weak health systems (Fallah et al., 2015). To enable comparability, we measure health losses in Disability Adjusted Life Years (DALY) and take into account the costs associated with an outbreak both within and outside the healthcare sector. DALYs are a summary measure of health that comprise both length and quality of life (Murray et al., 2002), being widely used in cost-effectiveness studies which facilitates comparison with similar studies. Furthermore, DALYs lost because of early death are closely linked to productivity losses as health facilitates productivity. Given that the EVD outbreak affects people in their working age/productive years, an exclusive focus on the costs incurred within the health system would result in an incomplete picture of the impact of earlier response (Baltussen et al., 2004).

## Methods

To estimate the incremental health benefits and potential costs of earlier interventions in the scenario of the EVD outbreak in Sierra Leone we used a compartment model to describe the transmission under the baseline scenario- the actual outbreak -, and several counterfactual scenarios. The counterfactual scenarios mimic earlier interventions varying from one day earlier up to four weeks earlier. We attached treatment costs and production losses to the transmission model compartments. We also attached disability weights to the compartments, from which DALYs were calculated. The sum of costs and DALYs were calculated under the baseline and the two counterfactual scenarios. We assessed the uncertainty of our results with respect to the uncertainty surrounding input parameters and carried out a sensitivity analysis for several key parameters.

### *Transmission model*

To explore the potential benefits of earlier response we used an extended SEIR compartment model, based on the model of Kucharski *et al.* (Kucharski et al., 2015). The model aims at describing the natural course of the disease and incorporating setting specific context such as hospitalization in either holding centers or treatment

centers, which is then run on a district level. Figure 1 depicts the model schematics: upon contracting the virus the individual leaves the Susceptible compartment (S) and enters the latent compartment (E). From the E compartment the individuals' transition to the infectious compartment (I). When entering the I compartment, the individuals are infectious to others. As not all cases are assumed to be reported, the I compartment is differentiated in reported cases and cases not being reported. We assumed that the infection rate is the same for both I compartments and from there on infected individuals may die or recover from the EVD. If the infected individuals are reported then, if district beds are available, they are hospitalized. During hospitalization, they are assumed not to be infectious to others. During the outbreak, facilities with different functions existed such as holding centers and treatment centers. In our model we treated the different facilities as the same, assuming that the fatality rates did not differ. Within each district, homogenous mixing was assumed and no spatial interaction was accounted for. The whole population was assumed to be susceptible. Due to the small number of reported cases we excluded the Bonthe district.

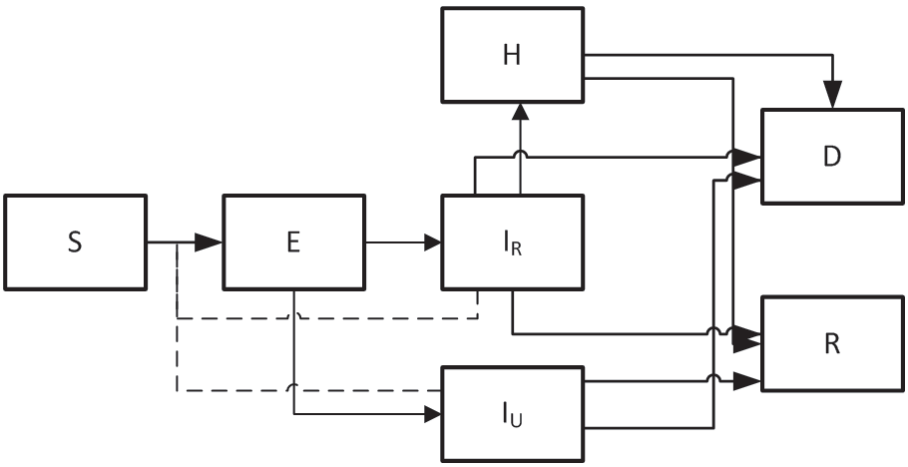


*Figure 1: Compartment model schematic. Solid lines indicate transition paths; dashed lines indicate transmission routes. With the following compartments, Susceptible (S), Exposed (E), Infectious and reported (IR), Infectious and not reported (IU), Hospitalized (H), Dead (D) and lastly Recovered (R)*

The transmission rate and parameters capturing the effect of the interventions implemented during the outbreak were fitted to the reported number of cases by weighted least squares, from the WHO's situation reports (World Health Organization, 2016). The parameters were fitted separately for each district, to reduce identifiability issues we derived some parameter values from other studies (see supplementary material for more information). In Table 1 the parameters used in the model that are not district dependent are presented.

Table 1. Parameters used in the simulation model and their sources

| Parameter | Description | Value | Reference |
|---|---|---|---|
| | Maximum value of transmission rate | Estimated | See supplementary material |
| | Slope of transmission rate parameter | Estimated | |
| | Midpoint of transmission rate parameter | Estimated | |
| | Slope of intervention rate parameter | Estimated | |
| | Midpoint of intervention rate parameter | Estimated | |
| $1/\sigma$ | Latent period | 10.4 days | (WHO Ebola Response Team et al., 2015) |
| $1/\gamma_{CR}$ | Time to recovery in the community | 11.7 days | (WHO Ebola Response Team et al., 2015) |
| $1/\gamma_{CD}$ | Time to death in the community | 6.8 days | (WHO Ebola Response Team et al., 2015) |
| $1/\gamma_{HR}$ | Discharge rate | 11.6 days | (WHO Ebola Response Team et al., 2015) |
| $1/\gamma_{HD}$ | Time to death for hospitalized | 5.2 days | (WHO Ebola Response Team et al., 2015) |
| | Proportion reported | 83% | (WHO Ebola Response Team et al., 2015) |
| $1/\omega$ | Time to notification | 4.8 days | (WHO Ebola Response Team et al., 2015) |
| $1/\eta$ | Hospitalization rate | 4.6-1.3 days | See supplementary material |
| $\delta_C$ | Fatality rate in the community | 91.9% | (WHO Ebola Response Team et al., 2015) |
| $\delta_H$ | Fatality rate for hospitalized | 60.3% | (WHO Ebola Response Team et al., 2015) |

We allowed the infection rate to vary to accommodate different outbreak paces between districts. After the 1st of October 2014, the date of the UNMEER implementations (Ki-moon, 2014b), we introduced the effect of interventions in the model. We allowed the effect of the interventions to vary between districts. As the weekly number of reported cases declined at different speeds we did not force a linear decrease on the effect of the interventions.

### *Translating morbidity and mortality effects into DALYs and costs*

The health loss due to EVD expressed in DALYs is the sum of health losses during an illness and the health lost because of an early death. To estimate health losses we attached disability weights from the Global Burden of Disease (GBD) study to the relevant compartments (Vos et al., 2015). Health losses because of early death were assumed to be equal to Health Adjusted Life Expectancy (HALE) estimates for Sierra Leone from GBD. To estimate the remaining HALE for each case the observed age

distribution of reported cases was applied to the final outbreak size (WHO Ebola Response Team, 2014). The full societal costs as a consequence of EVD include not only direct costs such as treatment costs for EVD but also indirect costs such as production losses, due to sickness and death at a young age. As in Bartsch *et al.* two treatment options were included: supportive and extensive supportive care (Bartsch et al., 2015). Supportive care consists of paracetamol, oral rehydration salts, metoclopramide for nausea. Extensive care adds morphine for pain, diazepam for convulsions, Ringer's lactate against shock and broad-spectrum antibiotics. As no proportion of the severity of cases was available a random number was drawn from a uniform distribution from 0 and 1 for each run representing the proportion of cases receiving supportive care. For treatment costs, the costs estimated by Bartsch *et al.* were used (Bartsch et al., 2015). For reasons of international comparability, we calculated the production losses according to the Human capital method (Krol and Brouwer, 2014). GDP per capita was used as a proxy for annual production losses and was multiplied by the HALE lost for early deaths to estimate lifetime production losses. An implicit assumption here is that life years spent in poor health do not result in productivity gains in our estimation. For recoveries, the productivity loss from Bartsch *et al.* due to absenteeism was used (Bartsch et al., 2015). Costs are all expressed in 2014 US dollars.

Table 2. Costs and health parameters included, mean and 95% Confidence Interval in brackets. By age groups and costs groups. Expressed in 2014 $US.

| | | Age group: | | Reference: |
|---|---|---|---|---|
| Cost group: | <15 years | 15–44 years | ≧45 years | |
| Supportive care: | | | | |
| Patient recovers | 431 (413–450) | 446 (428–466) | 447 (428–464) | (Bartsch et al., 2015) |
| Patient dies | 178 (163–195) | 185 (169–202) | 185 (168–202) | (Bartsch et al., 2015) |
| Extensive supportive care: | | | | |
| Patient recovers | 598 (576–622) | 830 (800–862) | 830 (801–859) | (Bartsch et al., 2015) |
| Patient dies | 238 (217–259) | 321 (292–351) | 322 (291–351) | (Bartsch et al., 2015) |
| Personnel costs: | | | | |
| Patient recovers | 59 (57–61) | 59 (57–61) | 59 (57–61) | (Bartsch et al., 2015) |
| Patient dies | 21 (19–23) | 21 (19–23) | 21 (19–23) | (Bartsch et al., 2015) |
| Productivity losses due to: | | | | |
| Absenteeism during illness episode | 23 (22–24) | 23 (22–24) | 23 (22–24) | (Bartsch et al., 2015) |
| Mortality | 42 747.2<br>(12 355.9-128 273.4) | 29 640<br>(7 599.2-90 040.3) | 13 227.5<br>(2 934.1-42 393.5) | Calculated using the wealth distribution (World Bank, 2016b) |
| Disability weights: | | | | |
| Acute phase of illness | 0.133 (0.088-0.19) | | | (Vos et al., 2015) |
| Post-sequelae | 0.219 (0.148-0.308) | | | (Vos et al., 2015) |
| Mortality, HALE (range) | 51.3 (48.11 – 53.51) | 34 (24.76 – 43.84) | 13.92 (7.32 - 21.38) | (Vos et al., 2015) |
| Duration of illness: | | | | |
| Acute phase, recover | 15.1 (14.6 – 15.6) days | | | (Vos et al., 2015) |
| Acute phase, death | 8.2 (7.9 – 8.4) | | | (Vos et al., 2015) |
| Post-sequelae | 0.75 years (0.417–1.135) | | | (Vos et al., 2015) |

*Interventions and counterfactual scenarios*

To explore the potential benefits and costs of timely interventions we created counterfactual scenarios of earlier interventions. In our initial analysis we compare the baseline scenario - interventions as they were implemented by the UNMEER - to a counterfactual scenario of interventions taking place four weeks earlier. We then continued to investigate the effect on health and costs with interventions taking place between the baseline scenario and four weeks earlier in steps of one day. The counterfactual scenarios were modeled by moving the time of interventions in the transmission model four weeks earlier. This affected the transmission parameter and also the hospitalization rate and the case fatality rates for those hospitalized.

*Assessment of uncertainties of transmission models*

We assessed the uncertainty of our outcomes by taking into account the uncertainty around the input parameters of the compartment model and our health and cost estimates. In our main scenario of a four week earlier counterfactual we implemented a stochastic model using the tau-leaping approximation of the Gillespie's algorithm with a time step of .01 days (Gillespie, 1977; Gillespie, 2001). The approximation treats individuals as discrete units and translates the rates into probabilities allowing for stochasticity in all transitions. We performed several univariate sensitivity analysis to explore the impact of key input parameters on our outcomes. We varied the proportion of underreporting by ten percentage points, the time for cases to be reported, the time to hospitalization and the timing of interventions by one day each.

## Results

*Model fit*

Fig. 2 shows the fit of the reported cases of the models median and interquartile range by district and nationally against the reported number of weekly cases. Our model estimated 8 609 (3882-8609) reported cases which is a bit lower than the number actually of reported cases, with the largest discrepancy being in the Western Area Rural district reported cases. Distinct temporal differences between districts can be observed such as in Kailahun and Kenema, which experienced a peak of reported cases earlier than other districts. These two districts displayed a decrease in cases before the implementation of the UNMEER interventions. For the fitted parameter values per district and results per district, see supplementary materials.

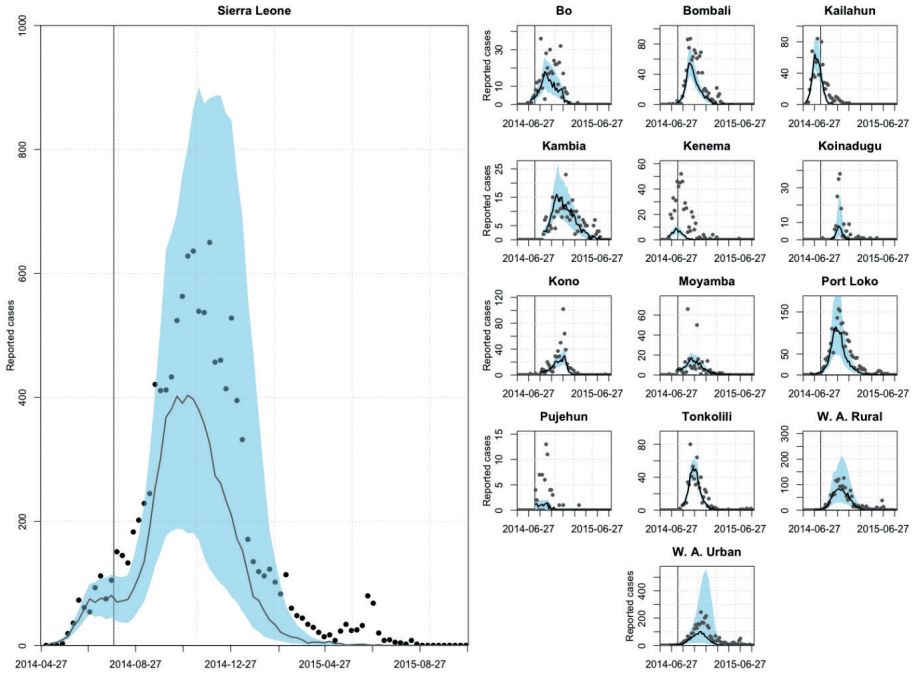


*Figure 2: Stochastic model fit on the national and district level. Solid line shows the median number of reported cases of 1500 model runs. Blue areas are the interquartile range. Reported cases by the WHO patient database are given as black dots. Vertical line shows the date of implementation of interventions*

## *Effect of earlier interventions*

Districts with a large number of cases and exponential growth showed the greatest savings of costs and health. In a large number of the districts, the time of interventions and the decrease of cases correlated well. Four weeks earlier interventions resulted in cost savings and health gains compared to the baseline scenario. The savings in both costs and health were largely due to the averted mortality as seen in Table 3 where results are shown based on outcomes of the stochastic model. Our result suggests that interventions implemented four weeks earlier would have halved both the costs and the health losses. Results by district are available in Supplementary Material 2.

Table 3. Incremental results of scenarios compared to baseline. Median and interquartile range based on outcomes produced with the stochastic mode

| | **4 weeks earlier (IQR)** |
|---|---|
| Cases averted | 10257<br>(4353 - 18813) |
| Deaths averted | 8835<br>(3766 - 16316) |
| DALY s averted (thousand) | 455.8<br>(194.1 - 841.11) |
| DALYs averted by preventing Ebola episodes<br>(time spent with Ebola times number of cases) | 0.23<br>(0.1 - 0.41) |
| DALYs averted by preventing premature deaths<br>(deaths averted times remaining health adjusted life expectancy) | 455.57<br>(194 - 840.7) |
| Costs saved (million US$) | 202.82<br>(87.42 - 373.86) |
| Within health care sector: ebola treatment | 1.77<br>(0.86 - 2.52) |
| Outside healthcare sector: productivity losses | 201.05<br>(86.56 - 371.34) |



Figure 3 shows the incremental benefits of intervening earlier, from one day to 8 weeks, using the deterministic model. At four weeks, the same number of days earlier as in our main scenario, the estimated benefits gained from earlier interventions were estimated to 182 million US$. One week later would have averted 32 million US$ and 47 thousand DALYs less. Conversely, implementation one week earlier would yield an additional 25 million US$ and 38 thousand DALYs gained. Beyond our main scenario intervention date, the incremental benefits are diminishing in returns. Note that the average outcomes of the stochastic model as displayed in Table 3 differ from the outcomes produced with the deterministic model given the non-linearities in the model. Therefore, the numbers in Figure 3 differ somewhat of those reported in Table 3.

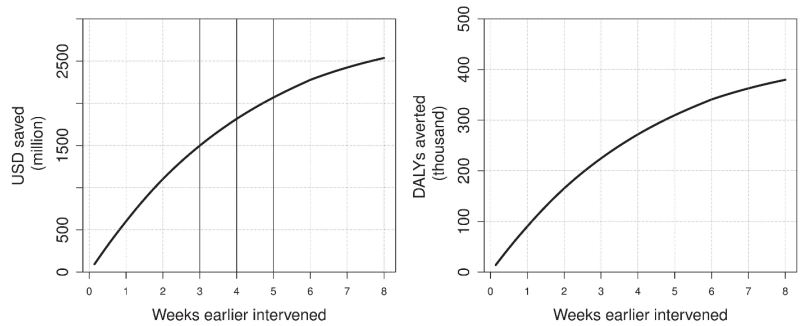


*Figure 3: Benefits of earlier interventions in one-day increments based on outcomes produced with the deterministic model. Left-hand panel shows the costs saved, right-hand panel shows the DALYs gained.*

From the univariate sensitivity analysis, presented in Figure 4, we found that the parameter with the greatest impact is time to hospitalization. Reducing the time of intervention by one day would avoid 500 cases and reducing the time to hospitalization by one day would avoid 3,671 cases, for the time to notification the estimate is 668 cases avoided. When decreasing the underreporting by one percentage point it showed a smaller effect of 28 cases avoided. The relative decrease in values is substantially larger for the time to notification and hospitalization than for the timing of interventions.

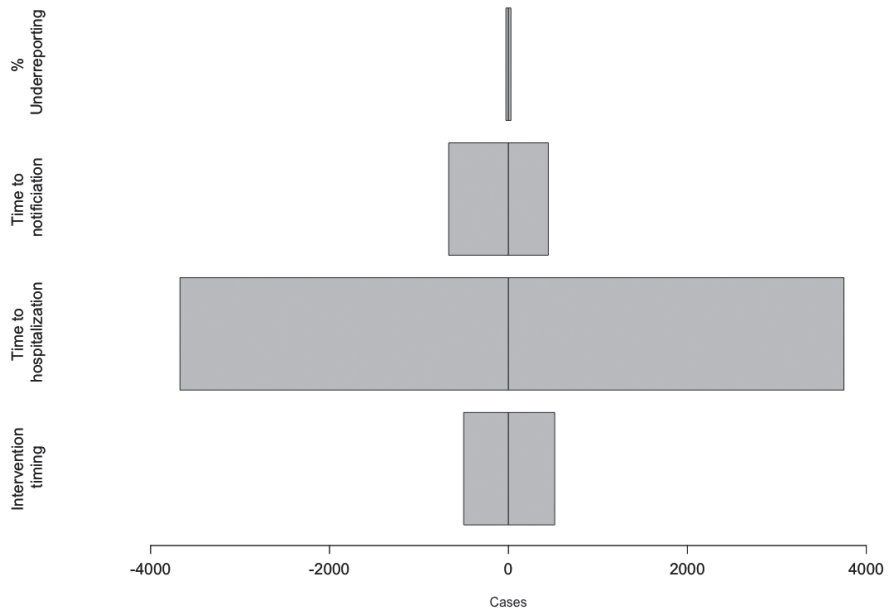


*Figure 4: Sensitivity analysis of key parameters based on outcomes produced with the deterministic model. The parameters of interest are located on the y-axis and difference in cases compared to the baseline scenario on the x-axis. Estimates are on the left-hand side varied with ten percentage points less for the percentage of underreported, one day less for the time to notification, time to hospitalization and time of intervention. Right-hand side shows the difference in cases from an increase of the same amounts for the same parameter values*

## Discussion

This paper estimated the costs and health losses of the EVD outbreak in Sierra Leone from a societal perspective and provided estimates of the benefits from earlier interventions. The results suggest that timely interventions can reduce the loss of health and drastically reduce the economic impact of outbreaks. This emphasizes the importance of timely interventions. The largest contribution to the total cost in all scenarios was productivity losses, which arise from mortality at a young age. In our deterministic analysis, we showed that much benefit may be gained by even earlier interventions, albeit at a diminishing rate.

Before we highlight some implications of our findings, we note some limitations of this study. Importantly, several assumptions had to be made due to lacking data or poor quality data. Models previously used for EVD (e.g. (Legrand et al., 2007)), allowed for explicit modeling of several transmission routes. To avoid fitting several transmission parameters and identifiability problems we did not model funeral transmissions or hospital transmissions explicitly. Evidently, funeral transmissions were an important driver of the outbreak and a facilitator of super-spreading events (Lau et al., 2017). We assumed in our model that infectiousness remains the same throughout the symptomatic period, which may not be fully accurate and may rather be increasing closer to death (Towner et al., 2004). The implication of this assumption is that we may have underestimated the benefits of earlier interventions, as the infected are hospitalized sooner after interventions and transmission rates are lower in hospitalized settings. Our model assumed homogenous mixing within compartments, meaning that all individuals have the same probability of contact. In reality, this assumption may not hold as individuals mix within their respective contact network primarily which may limit spread. For the current purpose, we did not include transmission caused by district interaction of individuals in different districts. This may again have underestimated the impact of the health gained and costs saved due to earlier interventions, as earlier interventions may prevent infected individuals from spreading the virus to other districts. Underreporting is assumed to occur during an EVD outbreak, however, few studies have provided concrete evidence of the proportion of underreporting. We, therefore, assumed a moderate estimate (compared to estimates by the CDC) whereby for each reported case, 2.5 cases were not reported (Meltzer et al., 2014). As uncertainty exists regarding the interventions performed, assumptions had to be made to calculate the effects of the interventions. We assumed that the decline in transmission after the 1st of October 2014 was solely caused by the interventions, and not taking into account independent behavior which was not due to for example information campaigns or community leader engagement. We did not differentiate between different types of interventions as this was not our aim, we were interested in the total effect. However, in our sensitivity analysis we saw that time to hospitalization proved very important in limiting the number of new cases. Another limitation is in the use of a single date to account for the interventions performed by the UNMEER. This assumes that the interventions and the effects were more homogenous than in reality. Our estimate of the production losses is much larger than that of the cost of illness study by Bartsch *et al.* (Bartsch et al., 2015). Our approach estimated the years of productivity lost due to EVD mortality as the HALE lost multiplied by average annual GDP of Sierra Leone and also included the latest data on reported cases. The total estimated economic loss in the baseline scenario mounted to 635 million US$. This is a smaller estimate than previously estimated by the World Bank (WB). The difference is due to the choice of approach, as the WB applied a macroeconomic level to determine the GDP loss in short and medium term. Our focus remained on individual costs to the health care system and the long-term production losses arising from deaths. An underexplored issue here

is which approach is most suitable to estimate these productivity costs. In economic evaluations sometimes the human capital approach is replaced with the friction cost method, under the assumption that replacement of ill or deceased workers (through a reshuffling of labor or employing previously unemployed) will help to reduce total productivity costs (e.g. Brouwer *et al.* (Brouwer et al., 1997)). In countries and circumstances like the outbreak studied, it is unclear whether similar mechanisms exist and would lower productivity cost estimates. If we would assume this to be the case and production levels would be restored after 1 or 5 years, production costs would be estimated to be 7.07 (3.08-13.08) and 34.14 (14.61-63.29) million US$ respectively.

## Conclusions

The consequences of this outbreak proved devastating. However, it has been shown that EVD can be stopped in an early phase. Illustrated by the example of Nigeria, where quick response and actions managed to halt the outbreak containing the number of cases to 19 with seven deaths (Shuaib et al., 2014), however, this occurred at a later phase when the outbreak was known and the responders ready. Swift detection and isolation saved not only lives but was done at a cost of approximately 13 million US$ using the existing Polio surveillance infrastructure. This cost estimate is approximately 6 percent of the cost *savings* with interventions four weeks earlier in Sierra Leone. This study does not provide guidance on which preventive measures are best suited to preventing or limiting outbreaks. However, we do know that the virus was first discovered after several months of circulating in the population which advocates for systems capable of detecting emerging viruses before they spread more widely. The most important result from this study is that is considerable gains to be made from timely interventions, and that the losses primarily occurred outside the healthcare sector. To improve the capabilities for handling the next outbreak preferably before a new outbreak occurs. Timeliness is not only important in intervening, but also in the context of clear policy action.

## Supplementary material

Equation set 1 describes the equations governing the transmission model. In the susceptible compartment β is the force of infection, ϕ is the effectiveness parameter of the interventions whose value before the time of intervention is fixed to 1 and thereafter decreases. In the compartment of the latent stage (E compartment) σ is the time individuals spent in the phase of being infectious but not showing symptoms or being infectious to others. The proportion of ρ is set to move to the infectious compartment and eventually become reported cases, while the remaining proportion transitions to the infectious compartment and will not become reported cases. The $I_C$ compartment represents individuals that are infectious to others but not reported. The infected compartment has a recovery rate of $\gamma CR$ and the proportion $1-\delta C$, while the proportion $\delta C$ dies at rate $\gamma CD$. The $I_{R0}$ compartment contains those infected that will become but are not yet reported. They become reported cases at rate ω and die and recover at the same rate and proportion as those in the $I_C$. After the transition to the $I_{R1,}$ the infected in the model are considered reported; they die and recover at the previously mentioned proportion and rates minus the time spent in the $I_{R0,}$ but they may be hospitalized if beds are available at rate η. When hospitalized, compartment H, a proportion of $1-\delta H$ individuals recover and are discharged at rate $\gamma HR$; the other proportion dies at rate $\gamma HD$. Values used from the literature are available in table 1 and estimated values are available in table 2.

$$
\begin{aligned}
\frac{dS}{dt} &= -\frac{1}{N}(\beta\varphi I_C S + \beta\varphi I_R S),\\
\frac{dE}{dt} &= \frac{1}{N}(\beta\varphi I_C S + \beta\varphi I_R S) - \sigma E,\\
\frac{dI_C}{dt} &= (1-\rho)\sigma E - (1-\delta_C)\gamma_{CR} I_C - \delta_C \gamma_{CD} I_C,\\
\frac{dI_{R0}}{dt} &= \rho\sigma E - \omega I_{R0} - (1-\delta_C)\gamma_{CR} I_{R0} - \delta_C\gamma_{CD} I_{R0},\\
\frac{dI_{R1}}{dt} &= \omega I_{R0} - (1-\delta_C)(\gamma_{CR}-\omega) I_{R1} - \delta_C(\gamma_{CD}-\omega) I_{R1} - \eta I_{R1},\\
\frac{dH}{dt} &= \eta I - (1-\delta_H)\gamma_{HR} H - \delta_H\gamma_{HD} H,\\
\frac{dR}{dt} &= (1-\delta_C)\gamma_{CR} I_C + (1-\delta_C)\gamma_{CR} I_{R0} + (1-\delta_C)(\gamma_{CR}-\omega) I_{R1} + (1-\delta_H)\gamma_{HR} H,\\
\frac{dD}{dt} &= \delta_C \gamma_{CD} I_C + \delta_C\gamma_{CD} I_{R0} + \delta_C(\gamma_{CD}-\omega) I_{R1} + \delta_H\gamma_{HD} H,
\end{aligned}
\qquad (1)
$$

and the total population (N) being:

$$N = S + E + I_C + I_{R0} + I_{R1} + R \qquad (2)$$

And β being:

$$\beta(t) = \frac{a_2}{1 + e^{a_1(t - a_{t_j})}} \tag{3}$$

And φ being:

$$\varphi(t) = \begin{cases} 1, & \text{for } t < \text{intervention start} \\ (1 - \frac{1}{1 + e^{b_1(t - b_{t_j})}}), & \text{for } t \geq \text{intervention start} \end{cases} \tag{4}$$

To allow the infection rate to vary due to reasons other than the interventions of UNMEER, the rate was modeled through a sigmoid function. The intervention efficacy was modeled as a logistic function multiplied by the transmission parameter after the date of the intervention of the 1st of October 2014. The logistic function allows for a gradual implementation in both time and efficacy.

The parameter η, time to hospitalization among reported cases, was modeled as a linear function of time as in Kucharski *et al*. Data was gathered from WHO situation reports [1], and for months where estimates were missing, we assumed the closest value available. The values ranged from 4.6 days in the early epidemic to 1.3 days in the late epidemic. To reduce computational load, the bed capacity restraints of hospitalization was controlled through equation 5, where *Hmax* is the maximum bed capacity at a given time for a given district. When comparing the model with the term in equation 5 to the model with bed constraints modeled through roots, the two models corresponded well.

$$\eta = \eta - \frac{\eta}{((\widehat{H}_{t,j} + 1) - H_{t,j})^2} \tag{5}$$

### *Parameter inference*

For fitting the model, we used data from the patient database provided by the WHO website. The data are the weekly reported cases counts on a district level which we fitted against the weekly difference of the $I_{R_I}$ compartment. We fixed the following parameters with values observed by the WHO Ebola Response Team et al., 2015. The time of the latent phase as 10.4 days, the time from onset to death in the community: 6.8 days, onset to recovery in the community: 11.7 days, onset to notification to authorities for the reported cases: 4.8 days, hospitalization to death: 5.2, hospitalization to recovery and discharge: 11.6. Time to hospitalization was modeled as a linear function using data reported by the WHO situation reports [1], resulting in a range of 4.6-1.3 days from the beginning of the outbreak to the end of the outbreak. Reported opening dates and bed numbers from the Humanitarian Data Exchange were cleaned and checked for inconsistency by comparing it to various sources such as NGOs, Situation Reports by UNMEER and Sierra Leone's Ministry of Health. In the case of fatality rates we used observed values of 60.3 percent for hospitalized cases, 91.9 percent non-

hospitalized cases [32]. The model accounts for underreporting using an estimate of 83% of the cases being reported, an empirical estimate of underreporting [49]. An estimate smaller than for example the estimates in the study by Kucharski *et al* and the estimate of the CDC [13,25]. The transmission parameter was modeled as a time-dependent logistic function in order to handle the temporal heterogeneity of districts transmission. Resulting parameter values by district are available in table 2.

Table 2. District specific parameters

| **District** | | | | | |
|---|---|---|---|---|---|
| Bo | 0,3899 | 137,0676 | -0,0037 | 0,2387 | 241,5276 |
| Bombali | 0,5067 | 242,2816 | -0,0019 | 0,0015 | 279,8948 |
| Kailahun | 0,5000 | 50,0000 | -0,0390 | 0,0127 | 739,2832 |
| Kambia | 0,5091 | 35,2471 | -0,0024 | 1,8922 | 436,6217 |
| Kenema | 0,5468 | 60,5284 | -0,0274 | 0,3494 | 741,8758 |
| Koinadugu | 0,7352 | 20,6048 | 0,0909 | 0,0978 | 173,9795 |
| Kono | 0,6307 | 299,6713 | 0,0061 | 1,9659 | 247,7990 |
| Moyamba | 0,7034 | 445,4053 | 0,0032 | 0,0005 | 741,9642 |
| Port loko | 0,4008 | 1,0003 | 0,0037 | 0,0018 | 218,6708 |
| Pujehun | 0,2204 | 160,1710 | -0,1313 | 0,6885 | 326,8079 |
| Tonkilili | 0,5686 | 56,6040 | -0,0005 | 0,0061 | 154,0043 |
| Western area rural | 0,5056 | 500,0000 | -0,0005 | 0,0181 | 251,7345 |
| Western area urban | 0,4876 | 492,1892 | -0,0004 | 0,0261 | 239,8340 |

### *Remaining HALE*

We used disability weights from the GBD for suffering from EVD of 0.133 (0.088-0.19) and for a period of post EVD weights of 0.219 (0.148-0.308). The length of the period on which the post EVD weight was applied was done in a similar manner as in the Global Burden of Disease study to 0.75 years (0.417–1.135). As was the acute phase of EVD of 15.1 (14.6 – 15.6) days for recoveries and 8.2 (7.9 – 8.4) days for the deceased. From the GBD we also used remaining HALE in age groups of five years as shown in article table 2. We assumed a normal distribution from which we sampled individual HALE estimates. The lifetime production losses were estimated by multiplying the individual HALE and the annual production losses. For the production losses, we used the annual GDP per capita from the World Bank. The distribution between the age groups among the recovered and fatalities was determined by applying the observed distribution of the WHO response group [22]. Among the distribution of recovered by age groups of <15, 15-44, and ≥45 was 12.6%, 73.1%, 14.3% respectively. For deaths by age groups 14.2%, 56.5%, 29.3% respectively.

# CHAPTER 4

## Estimating the costs of non-medical consumption in life-years gained for economic evaluations

## Abstract

Including the costs of non-medical consumption in life years gained in economic evaluations of medical interventions has been controversial. This paper focuses on the estimation of these costs using a long series of cross-sectional household surveys and relates the estimates to the theoretical discussion. We decomposed consumption into age, period and cohort effects and modelled the non-linear age and cohort patterns of consumption using P-splines. As consumption patterns depend on household composition, we also estimated household size using the same regression modelling strategy. Estimates of non-medical consumption and household size were combined with life tables to estimate the impact of including non-medical survivor costs on an incremental cost-effectiveness ratio (ICER). Results revealed that including non-medical survivor costs substantially increases the ICER, but the effect varies strongly with age. The impact of cohort effects is limited but ignoring household economies of scale results in a significant overestimation of non-medical costs.

## Introduction

Medical interventions can increase life expectancy of patients and, as a consequence, may cause consumption of both medical and non-medical goods and services during the additional life time. This consumption in gained life time can be related to treatment of additional diseases (medical costs) or simply related to food, housing or clothing (non-medical costs). By definition, these costs would not have occurred if life had not been prolonged. While this may be a seemingly straightforward observation about the economic consequences of prolonging life, including these additional costs in economic evaluations conducted from a health care (medical costs) or a societal perspective (medical and non-medical costs) has been the topic of considerable debate (de Vries et al., 2018). As a result, the inclusion of both future medical and future non-medical costs, is still uncommon (de Vries et al., 2018). Disagreement is strongest concerning the inclusion of non-medical costs, sometimes also referred to as survivor consumption (Feenstra et al., 2008; Gandjour, 2006a; Garber and Phelps, 2008, 1997b; Lee, 2008; Lundin and Ramsberg, 2008; Meltzer, 2008, 1997a; Nyman, 2011, 2004a; Richardson and Olsen, 2006a). While the debate on whether to include these costs in life years gained is ongoing, only a few studies have concentrated on the empirical estimation of future non-medical costs and their influence on outcomes of economic evaluations (Kruse et al., 2012; Manns et al., 2003a; Meltzer, 1997a; Meltzer et al., 2000b). These studies consistently found that including non-medical costs in economic evaluations increased the incremental cost-effectiveness ratios (ICERs) substantially, but that the impact varied with age of patients.



Estimates of non-medical consumption used in economic evaluation so far have used estimates of per capita costs of consumption by age coming from a single cross section (Kruse et al., 2012; Manns et al., 2003a; Meltzer, 1997a; Meltzer et al., 2000b) and have ignored two issues. First, economies of scale within households were ignored as per capita consumption in these studies was calculated by dividing household consumption by household size. Economies of scale allow members of larger households to achieve the same level of utility with less consumption (Nelson, 1988). Second, as data from a single cross section were used, correcting the age profile of consumption for period and cohort effects was not possible. Empirical studies on consumption conducted outside the context of economic evaluation have shown that life-time household consumption patterns are hump-shaped, peaking at middle ages and decreasing afterwards (Alessie and Ree, 2009; Fernández-Villaverde and Krueger, 2007). The hump can partly be explained by differences in household composition by age after taking take into account economies of scale of consumption within households. This implies that prolonging the life of a patient living in a multi-person household may have a different impact on consumption than doing the same for a patient living in a single-person household. Therefore, household size and economies of scale within households are relevant when estimating the costs of non-medical consumption resulting of life extension; not doing

so leads to an overestimation of the impact of future costs on ICERs for multi-person households. However, even after controlling for household size, consumption exhibits a (hump-shaped) age pattern. This means that we also have to take the age-pattern into account when including non-medical consumption in cost-effectiveness analysis. An estimate based on the age distribution of consumption in one particular year might not suffice, as consumption can depend on (economic) events in that particular year. Similarly, different birth cohorts have different consumption patterns, ceteris paribus (Dahlberg and Nahum, 2003). This is relevant, as many health care interventions are targeted at specific birth cohorts, which thus might have different age profiles of consumption. Consequently, correctly identifying the age pattern means controlling for period and cohort effects. This requires datasets with all relevant variables, observed over several years. If such data sources are available, identifying an age-period-cohort model is not trivial, because age, periods, and cohorts, are linearly dependent. Several solutions to this problem have been applied, which always involve relaxing the linear dependency between the three variables, by restricting one or more of the effects, requiring strong assumptions (Deaton, 1997). Fernández-Villaverde and Krueger (Fernández-Villaverde and Krueger, 2007), for instance estimated consumption age profiles using a kernel function, while Alessie and Ree (Alessie and Ree, 2009), used linear splines for the age and cohort effects and, both studies modelled period effects using dummies for different calendar years or quarters.

This paper will present estimates of future non-medical costs and relates the estimates to the theoretical discussion. We add to the existing literature on future non-medical consumption by (i) using state-of-the-art methods to estimate non-medical spending patterns while accounting for age, period and cohort effects, (ii) including economies of scale within households in these estimates, and (iii) highlighting the consequences of including these costs in economic evaluations. As a starting point for our analyses, and as a comparator in estimating the impact of including future non-medical costs on the ICER, we take an economic evaluation conducted from a societal perspective in which future medical costs and productivity gains are already included while excluding future non-medical costs. This seems the most relevant and common comparator given current practice in cost effectiveness analysis.

## Theoretical model

To better understand the role of future non-medical costs in economic evaluation and the controversies surrounding its inclusion, we will first describe a formal model of the decision rules of cost effectiveness adopting a societal perspective. As a starting point we will take an intervention ($x$) that influences quality of life ($Q$), production ($P$), medical consumption ($M$) and non-medical consumption ($C$) in two periods (denoted with subscripts 1 and 2). Note that both the direct healthcare investments in $x$ as well as the impact of $x$ on other medical spending are included in $M$. We are interested in the

amount *i* we should spend on x. The impact of the intervention *on* health, production and consumption in period 2 is partly determined by its impact on the probability to survive from period 1 to period 2 denoted by *S*:

$$H = Q_1(i) + \beta S(i)\, Q_2(i) \quad (1)$$

$$N = M_1(i) + C_1(i) - P_1(i) + \beta S(i)\{M_2(i) + C_2(i) - P_2(i)\} \quad (2)$$

Equation (1) shows lifetime discounted health (where  acts as the time preference discount factor) denoted *H* as a function of the level of spending *i* on intervention *x* and Equation (2) shows lifetime discounted net resource use denoted *N* (medical and non-medical consumption minus production) as a function of the level of spending *i* on intervention *x*. From a societal perspective, an ICER can be interpreted as the change in net resource use, which is defined as medical and non-medical consumption minus production, divided by QALYs gained. Assuming decreasing marginal health gains from spending on *x*, the decision rules of cost effectiveness imply that we should invest in the intervention up until the point that the ICER equals the consumption value of health (denoted *V*): (denoted *V*): $\frac{dN/di}{dH/di} = V$. Using Equations (1) and (2) we can write this as:

$$\frac{\frac{\partial M_1}{\partial i} + \frac{\partial C_1}{\partial i} - \frac{\partial P_1}{\partial i} + \beta S(i)\left\{\frac{\partial M_2}{\partial i} + \frac{\partial C_2}{\partial i} - \frac{\partial P_2}{\partial i}\right\} + \beta \frac{\partial S}{\partial i}\{M_2(i) + C_2(i) - P_2(i)\}}{\frac{\partial Q_1}{\partial i} + \frac{\partial Q_2}{\partial i}\beta S(i) + \frac{\partial S}{\partial i}\beta Q_2(i)} = V. \quad (3)$$

Equation (3) shows the role of non-medical consumption costs in economic evaluations. These costs are influenced by changes in survival times levels of non-medical consumption ($\beta \frac{\partial S}{\partial i} C_2(i)$) and, conditional on survival, changes in the level of consumption. The discussion on the inclusion of non-medical costs so far has only focused on the first part ($\beta \frac{\partial S}{\partial i} C_2(i)$) and it is usually assumed that non-medical consumption, conditional on being alive, is not affected by healthcare interventions ; ($\frac{\partial C_1}{\partial i} = 0, \frac{\partial C_2}{\partial i} = 0$).

Using a similar welfare economic framework as in equation (3), Meltzer concluded that decisions based on cost-effectiveness information are only consistent with welfare maximization when all future costs, including non-medical consumption, are included (Meltzer, 1997a). However, this also requires that the denominator of Equation (3) captures the full benefits of the intervention including the utility derived from leisure and non-medical consumption. Whether this is the case is unclear (Meltzer, 1997a). For this reason, Nyman has argued that future non-medical costs could be excluded from economic evaluations since the related utility gains are not captured either, as

quality of life instruments used in economic evaluation are designed to only capture health-related utility (Nyman, 2011, 2004a). In response to Nyman, it has been suggested that even if quality of life instruments have not been developed to explicitly capture the utility related to non-medical consumption it might still be the case that some benefits of non-medical consumption are implicitly included (Gandjour, 2006a; Lundin and Ramsberg, 2008). Equation (3) can provide us more insight in these arguments. First of all, at least some level of consumption is required to stay alive after a life prolonging intervention. In other words: marginal changes in survival through the intervention ($\frac{\partial S}{\partial i} > 0$) would require that at least some parts of $\frac{\partial S}{\partial i} C_2(i)$ is included in the numerator of the ICER. Similarly, interventions that increase quality of life should include consumption costs, if the marginal increases in quality of life ($\frac{\partial Q_1}{\partial i} + \frac{\partial Q_2}{\partial i} \beta S(i)$) also (implicitly) require additional non-medical consumption. Furthermore, the benefits of non-medical consumption are not only captured through changes in quality and life and survival but also through baseline levels of quality of life and survival. Non-medical consumption (e.g. healthy food, safe cars, sports) is a known determinant of life expectancy (Cutler et al., 2006). Any change in quality of life ($\frac{\partial Q_2}{\partial i}$) due an intervention therefore captures some benefits of non-medical consumption as these changes are multiplied by life expectancy using the term . For an intervention that affects survival, we have to weigh the additional life years gained with some level of quality of life (as reflected in the term $\frac{\partial S}{\partial i} \beta Q_2(i)$ in Equation (3)). If that level of quality of life indeed requires a certain level of non-medical consumption, this should be included as costs. Finally, even if the QALY does not fully capture utility derived from non-medical consumption, the cost-effectiveness threshold, based on the consumption value of health *V*, might. This value is often derived from willingness to pay (WTP) exercises, and it's likely that individual based their valuation on the full welfare gains with possibly higher *V's* for higher consumption levels, in line with the commonly observed positive association between income and WTP for QALY gains (see e.g. Bobinac et al., 2010).

It should be noted that in practice, economic evaluations conducted from a societal perspective tend to include changes in productivity (P) associated with the intervention. For these costs (or benefits) it is also unknown to what extent the associated utility changes are fully captured in QALY gains (Nyman, 2011). When the additional production generated by the intervention is taken into account, it seems consistent to also include the part of this production that is consumed by the individual itself on the cost side. In this paper, we take the position that leaving out real costs and benefits (even in a 'balanced' way) from an economic evaluation risks welfare lowering decisions. Even if the benefits of non-medical consumption are not perfectly reflected in the QALY measure, the appropriate response should not be to exclude the real societal costs of non-medical consumption to balance the incomplete QALY, as this leaves policy makers uninformed about real societal impacts (in terms of costs and benefits) of their decisions. Rather the response should be to capture these benefits in

another way, as the overall challenge is to provide decision makers with a full account of societal impacts, including all costs and all benefits.

In Equation (3), the intervention can also affect the level of consumption through the terms $\frac{\partial C_1}{\partial i}$ and $\frac{\partial C_2}{\partial i}$. . An example we mentioned above is an intervention that improves quality of life, for which additional consumption is required. Other channels can be out-of-pocket payments for medical consumption, and changes in the marginal utility of consumption because of changes in health. In the remainder of this paper we will focus on a solely lifesaving intervention (e.g. a decrease in fatal accidents). The assumption we make is that this intervention is targeted at the general population, and those affected the intervention will have a quality of life pattern that is equal to that of the general population. This allows us to follow the approach taken in the existing literature on non-medical consumption and assume that that this consumption is not directly impacted by the intervention ($\frac{\partial C_1}{\partial i} = \frac{\partial C_2}{\partial i} = 0$). We can concentrate on the estimation of changes in lifetime non-medical consumption that are purely the result of increases in life expectancy ($\frac{\partial S}{\partial i} C_2(i)$), and we can use the age profile of consumption of the general population for $C_2(i)$. We return to the issue of how health care interventions might change levels of non-medical consumption in the discussion. We will focus on the estimation of the non-medical consumption costs versus quality of life ratio, $\frac{\beta \frac{\partial S}{\partial i} C_2(i)}{\frac{\partial Q_1}{\partial i} + \frac{\partial Q_2}{\partial i} \beta S(i) + \frac{\partial S}{\partial i} \beta Q_2(i)}$ in our theoretical model. This ratio directly shows the impact including non-medical consumption cost would have on an existing ICER. Moving from our theoretical model to the more general case where interventions have an impact beyond two periods and where spending, survival and quality of life vary by age, we will refer to $\frac{\Delta nmc}{\Delta Qalys}$ in the remainder of this paper. $\Delta Qalys$ stands for the total discounted QALYs gained over the lifetime and $\Delta nmc$ for the total discounted incremental costs of non-medical consumption due to increases in survival.

## Methods

### *Data*

Data from the Dutch budget survey (Budgetonderzoek) from 1978 to 2004 were used to estimate non-medical consumption per capita by age. The budget survey was a yearly cross-sectional survey collected among the non-institutionalized population of the Netherlands which ran from 1978 until 2004 (while the survey was not conducted in 2001 and 2002) and was coordinated by Statistics Netherlands.[2] The budget survey data are publicly available from http://www.dans.knaw.nl. The survey included expenditures on a detailed and comprehensive set of consumption categories (e.g. consumption related to eating, transport, housing, vacation but also consumption related to hobbies)

2 In the years 2003 and 2004 the survey methodology differed slightly in the way that the age of respondents above 80 years old was categorized as one category. We assumed an average age of 82.5 for these years based on the average age of those over 80 in the previous five surveys.

as well as information on income, family composition and background information on all members of the household. Households took part in the survey for an entire year and expenditures were monitored using diaries which were collected by interviewers on a regular basis during the year. Consumption on both durable as well as non-durable goods was tracked with the use of these diaries. The consumption data includes value added taxes on consumer goods. Such taxes are transferred back through the state to society, and could therefore be seen as redistributions of wealth rather than costs (although redistribution is not costless). Therefore, the true costs of non-medical consumption may be somewhat overestimated in our study. The sample consists of households who answered all the necessary questions, with a household breadwinner age of 18 or higher, which resulted in a sample size of 56,566 households with an average household size of 2.78 persons and annual household costs of non-medical consumption of 11,288 euro (2017 prices). For our purposes, we excluded all consumption related to medical care. In the Netherlands, health care insurance is compulsory and out-of-pocket spending on medical care is low (Schäfer et al., 2010). Using consumer price indices from Statistics Netherlands we adjusted the data to 2017 prices.

Figure 1 displays average non-medical household consumption by age, household size by age, log of non-medical consumption by survey year, and log of non-medical consumption by birth year. The average non-medical household consumption by age (top left) illustrates that consumption increases with age until the age of roughly 40-50, after which it decreases. This pattern is in line with previously published research on the relationship between age and non-medical consumption (Alessie and Ree, 2009; Fernández-Villaverde and Krueger, 2007). Household size by age (top right) shows a plateau in the ages 35-35 and then decreases afterwards. The bottom part of the graph illustrates increasing trends of non-medical consumption both by year of survey and by birth year. For household size we see strong cohort patterns, with household sizes peaking for those born in the 1940's.

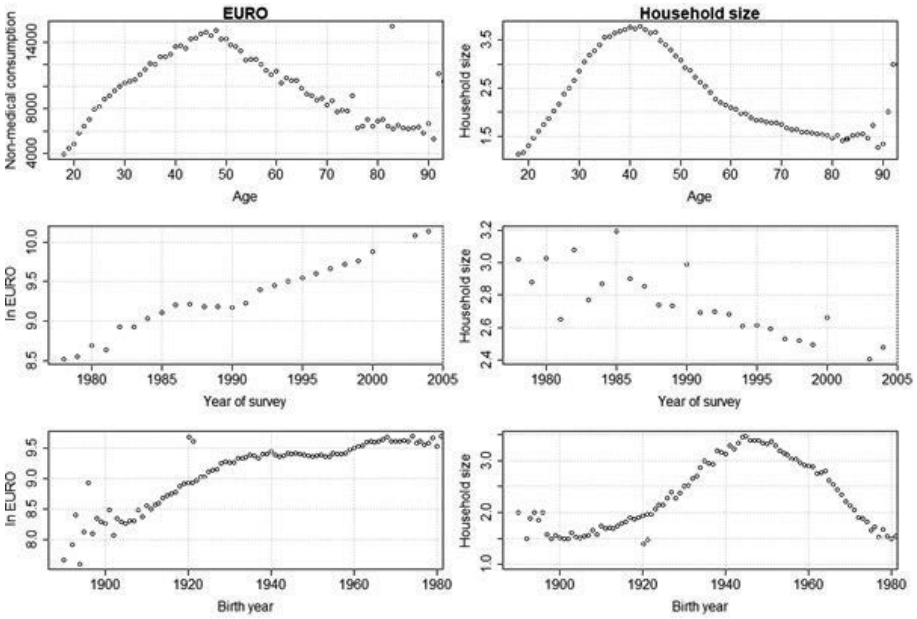


*Figure 1: Average annual household consumption in 2020 prices (upper left graph) and average household size (upper right graph) by age (average age of the adults in the household; age categorized in years as calculated from the Budget survey from the Netherlands for the years 1974 to 2004. Average annual household consumption by year of survey (lower left graph), and average household consumption by birth year (lower right graph).*



## *Model specification*

Our approach consisted of two steps that deal with the two main empirical challenges: the accurate estimation of an age profile of consumption, correcting for calendar year and cohort effects, and the correction for household economies of scale. In the first step, we estimated per capita consumption stratified by age as this allows us to identify the additional consumption cost as a result of living longer for one household equivalent. Our data set spans a large number of years, which allowed us to separate cohort effects from age and period effects using an age-period-cohort (APC) model. We used cubic P-splines for age and birth year. P-splines are a combination of B-splines and penalized regression and offer a flexible alternative to both dummy variables and polynomial functions while not suffering their disadvantages (Eilers and Marx, 1996). Our model is:

$$ln(hh\ equiv) = f(age) + f(birth\ year) + \gamma \cdot year + \varepsilon\,, \qquad (4)$$

where denotes annual non-medical consumption per household equivalent. To translate household consumption into per capita consumption we used the OECD-modified equivalence scale (Hagenaars et al., 1994b). The scale assigns a weighing of 1

to the first adult household member, 0.5 to each additional adult and 0.3 to each person under 14 years of age. is the smooth function of age with modeled using *P*-splines; *f(birth year)* the smooth function of birth year modeled using *P*-splines; $\gamma$ a vector of coefficients that capture the differences between survey years; $\varepsilon$ and  is a normally distributed error term.

We used cubic P-splines for two reasons. First, we expected consumption to be a smooth function of age and of birth year. The disadvantage of dummy variables in such a case is that the age gradient would be irregular. On the other hand, a polynomial function might be too restrictive, and values for high ages can strongly influence the fit for lower ages (and vice versa). Because we did not necessarily expect macroeconomic shocks on consumption to be smooth functions of time, we included year dummies for the period effects. Second, a common problem with APC models estimated on repeated cross sectional data is that age, birth year, and period are not separately identified (as age is a linear function of period and cohort). Splines are nonlinear transformations of age and birth year, so that the variables are no longer perfectly collinear and the model can be identified. Age-period-cohort models, based on splines, have been estimated mostly in the context of mortality rates (Alkema and New, 2014; Clements et al., 2005; Jiang and Carriere, 2014).

Cubic P-splines are estimated by first defining a large number of equally-spaced cubic B-spline functions over the age interval. B-splines are polynomial functions that have a non-zero value only within a specified range. Any linear combination of the basis cubic spline functions will result in a smooth function with a second-order derivative that is continuous at the joining points. The drawback of B-splines and other forms of local regression is that it is difficult to determine the number of knots and spacing of the basis cubic spline functions. As a solution to this problem, P-splines use a relatively large number of evenly spaced B-splines and put a penalty on the difference between the coefficients of adjacent B-spline functions. In our analyses, we used 10 evenly spaced cubic B-splines for each smooth. A smoothing parameter determines the influence of the penalty in the estimation: the stronger the penalty, the smoother the curve. The optimal smoothing parameters in our analysis were found by minimizing the Aikaike Information Criterion (AIC). The model was fitted using iteratively reweighted least squares.

The second step in order to estimate the non-medical consumption per capita caused by preventing the death of an adult for an average household in the general population, is modeling adult household composition. Since we used the OECD-modified equivalence scale we predicted the proportion of households with more than one adult, as additional consumption due to prolonging life differs whether life is prolonged in a multi-person household or in a single-person household. To estimate this proportion, we used the probability of a household having more than 1 adult as a dependent variable and estimated a binomial logistic regression model. The model specification followed

a similar choice of covariates as equation 4; resulting in the following specification:

$$p(adults\ in\ hhs > 1) = \frac{\exp\left(f(age)+f(birth\ year)+\gamma \cdot year+\varepsilon\right)}{1+\exp\left(f(age)+f(birth\ year)+\gamma \cdot year+\varepsilon\right)} \quad (5)$$

The OECD -modified equivalence scale assigns a value of 1 for the first adult and 0.5 for each following adult. This accounts for the economies of scale within household as a single person household spending as much as a multi-person household will deliver less utility. To account for the different effect a death has in a single-person household versus one in a multi-person household, we therefore need to scale back households into these two separate types when predicting for an average household. Here, we take advantage of the equivalence scale once again to address the impact of prolonging life on consumption in the two different types of households. In a single household the future annual consumption is the full per capita estimated consumption. In a multi-adult household, the consumption is, in accordance with the equivalence scale, half the per capita consumption estimated. After estimating (4) and (5), annual non-medical consumption by age caused by preventing a death an average household by combining equations 1 and 2, can be calculated as:

$$nmc(age) = p(adults\ in\ hhs > 1|age) \cdot hh\ equiv(age) \cdot 0.5 + (1 - p[adults\ in\ hhs > 1|age]) \cdot hh\ equiv(age) \quad (6)$$

As the budget survey is not entirely representative for the Dutch population of households we used sample weights provided by Statistics Netherlands. As the sample weights of Statistics Netherlands were partly determined by age we centered these weights to 1 for each age class strata.

### *ICER calculations*

We estimated $\frac{\Delta nmc}{\Delta Qalys}$ in the scenario where a death at a certain age is prevented due to a hypothetical intervention. In that scenario QALYs gained can be calculated by estimating remaining quality adjusted life expectancy, and can be estimated using remaining estimated lifetime non-medical costs using the following equation:

$$\frac{\Delta nmc}{\Delta Qalys} = \frac{\sum_a L(age=a) \times nmc(age=a)}{\sum_a L(age=a) \times Q(age=a)}.$$

Where $L(age = a)$ is the number of years lived at age $a$ and $Q(age = a)$ is the average quality of life at age $a$. Estimates of non-medical consumption by age were taken from predictions from the regression models as denoted in equation (6). Predictions for non-medical consumption were retransformed taking into account the fact that an OLS on the log scale underestimates the mean on the normal scale (Manning and Mullahy, 2001). Estimates of $L(age)$ and $Q(age)$ were taken from a recent study that estimated the quality of life and mortality in the Netherlands (Gheorghe et al., 2014). In

accordance with Dutch guidelines, QALYs were discounted with 1.5% annually and costs with 4% annually (voor Zorgverzekeringen, 2006). Costs were expressed in 2017 prices.

In our main prediction, we fixed the period effect to that estimated for the most recent year in the data (2004), and the birth year equal to the actual birth year of the individuals with age *a* in 2004 when predicting costs by age. Thus, if we predicted remaining lifetime non-medical consumption for 30-year olds in 2004, we set the birth year equal to 1974 in our predictions of the age profile. This may be viewed as relevant for an intervention that is targeted to a specific birth cohort in the current calendar year, for example screening programs at a certain age.

In sensitivity analyses, we relaxed various assumptions. First of all, using the estimated regression models from equations (4) and (5) we ignored cohort effects by not fixing the birth-year but letting the birth-year increase as age increases when predicting the age profile. This way, we use the regression estimates to create a 2004 cross-section consisting of different birth cohorts. Second, we estimated equations (4) and (5) also without cohort effects and without period effects (results of regression models are displayed in the Appendix, Figures 1 and 2) and recalculated the ICERs. Third, to explore the influence of household equivalence scales we also calculated ICERs by using results from a regression model in which per capita consumption was simply calculated by dividing household consumption by household size (thus not using equivalence scales and without predictions of household size). We also performed various sensitivity analyses with respect to discount rates used in other countries. Finally, in order to mimic previous studies, we made predictions from a regression model fitted using data from just one cross-section (2004 data only) where per capita consumption was calculated by dividing household consumption by household size.

## Results

Figure 2, displays the included smooth functions describing the age and cohort effects and the estimated coefficients for the period dummies. The left column displays the parameter's contribution to the non-medical consumption estimates and the right column displays the smooths and parametric variables used in the logistic model estimating the probability of a household having more than one adult. The age pattern for consumption shows a peak round about 55 and decreases thereafter, while for household size we see a decrease after the age of 40. Our estimates show cohort and period effects for both consumption and household size. Household size and consumption increase for cohorts births up until roughly 1945 and thereafter decrease. Period effects show an upward trend for consumption but generally a downward trend for household size.

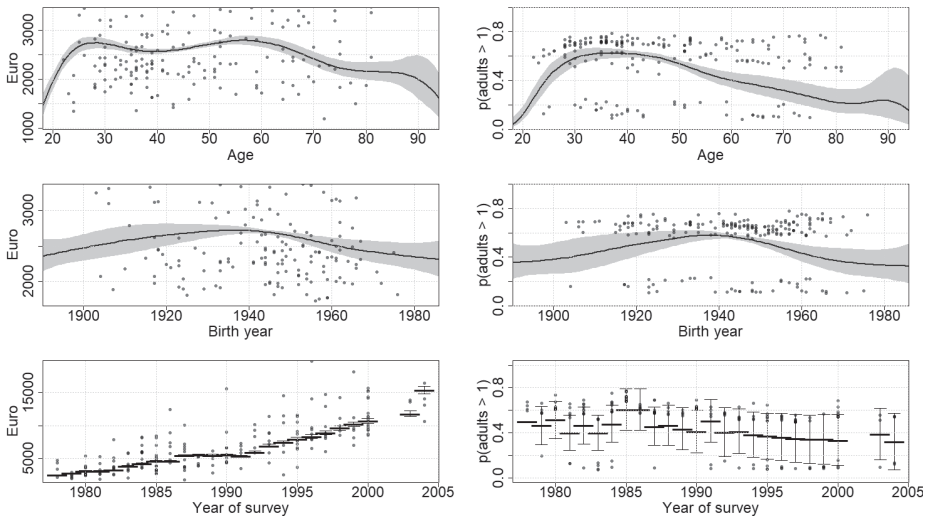


*Figure 2: Partial effects of fitted smooths and parameter estimates from the consumption model (left column) and the partial effect of the probability of having more than one adult in the household (right column) with 95% confidence intervals and a random sample of size 100 of partial residuals. Top row displays the of age on consumption, middle row displays the effect of birth year and the bottom row displays the effect of year of survey.*

In Figure 3 we present the first steps of our main findings (equations 1 and 2). We predict the age profile of annual non-medical consumption per household equivalent and the probability of a household having more than one adult in a hypothetical cohort with a birth year of 1974 and period effect fixed at 2004 (straight lines). To assess the effect of adjusting for cohort effects we also display age profiles fixing the period effect to 2004 but letting the birth year vary from 1974 (2004 minus 30) to 1919 (2004-85) parallel with age (the dotted lines).

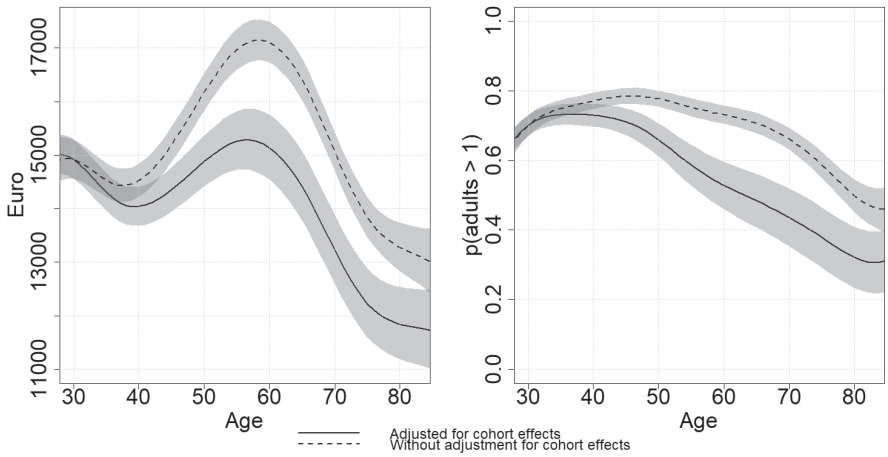


*Figure 3: Predictions of equivalence scaled consumption (left graph) with adjustment for cohort effects and without adjustment for cohort effects, and predicted probability of a household having more than one adult (right graph) with 95% prediction intervals. Lines indicates predictions with our main model specification accounting for cohort effects, dotted lines indicate predictions without accounting for cohort effects.*

For consumption, the impact of adjusting for cohort effects is most noticeable around age 60 where consumption is lower when adjusting for cohort effects. For household size, the impact of cohort effects is most prominent at middle age where the probability that a household is comprised of more than one person is much lower when we take into account cohort effect.

In figure 4 we show the impact of including costs of non-medical consumption on the ICER. We show predictions for our main specification for an average household adjusting for cohort effects (the birth-year is fixed when we predict an age profile). The impact on the ICER is compared to predictions in which we do not control for cohort effects or ignore economies of scale within households (here we use predictions from a regression in which we define one household equivalent of consumption as household consumption divided by household size). In the main prediction, the impact of including non-medical consumption on the ICER increases by age even though household equivalent consumption decreases with age. This is due to the fact that at older age people are more often single and their quality of life is lower. When not accounting for economies of scale within the household the impact on the ICER is much larger. While adjusting for cohort effects results in lower consumption household equivalent age profiles it also results in more single-person households which increases the non-medical costs of life extension. On balance these effects more or less cancel each other out and thus adjusting for cohort effects only has a small impact on the ICER.

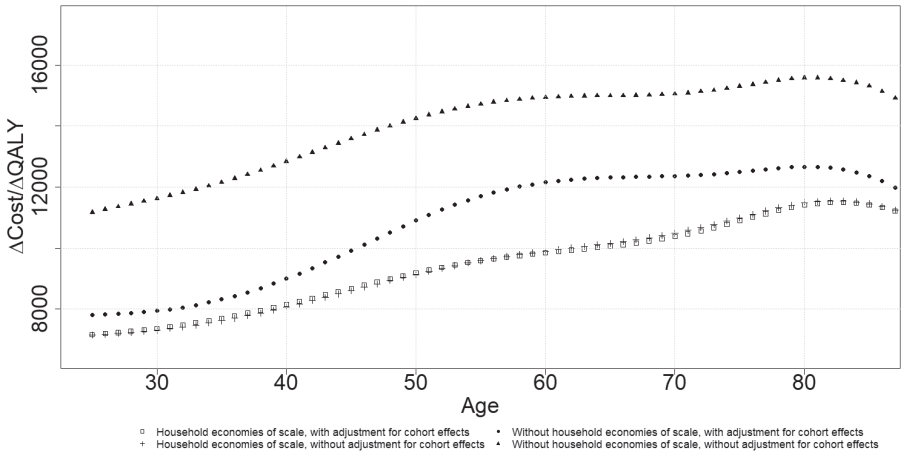


*Figure 4: The impact of non-medical consumption costs on the ICER of saving a life by age under different prediction specifications.*

In Table 1 we show results of the impact of including non-medical consumption on the ICER, by age and under different assumptions. The different sensitivity analyses do not alter the main conclusions and are in line with the results presented in Figures 3 and 4. Even though household equivalent consumption decreases with age, the impact on the ICER increases by age which is due to the fact that both average household size and quality of life decrease at higher ages. Not adjusting for cohort effects only has a limited impact on the ICER. Not including period effects in our model specification also has a limited impact on the ICER for the same reason. However, not accounting for economies of scale within households, resulted in a (strong) overestimation of consumption. This is also the main reason that our main predictions are much lower than those based on predictions using 2004 data only without adjusting for household economies of scale; as is currently done in economic evaluations. Finally, the effects of different discounting assumptions are shown, and compared to our main model, the effects are larger in the younger ages and converges with the main prediction model when the expected remaining life years decreases.

| **Model specification**<br>*Prediction settings* | **Age** | | | | |
|---|---|---|---|---|---|
| | 30 | 45 | 65 | 75 | 85 |
| Main model specification | | | | | |
| Average household<br>Birth year fixed when predicting age profiles<br>Discount rates: 4% cost and 1.5% QALYs | 7,000 | 8,300 | 9,600 | 10,400 | 10,900 |
| Average household<br>Ignoring cohort effects when predicting age profiles<br>Discount rates: 4% cost and 1.5% QALYs | 7,000 | 8,200 | 9,700 | 10,500 | 10,900 |
| Single household<br>Birth year fixed when predicting age profiles<br>Discount rates: 4% cost and 1.5% QALYs | 10,400 | 12,300 | 14,000 | 14,200 | 14,100 |
| Average household<br>Birth year fixed when predicting age profiles<br>Discount rates: 3% cost and 3% QALYs | 11,400 | 12,100 | 12,000 | 12,100 | 11,800 |
| Average household<br>Birth year fixed when predicting age profiles<br>Discount rates: 0% cost and 0% QALYs | 11,700 | 12,100 | 11,900 | 12,000 | 11,700 |
| W/o equivalence scale* | | | | | |
| Birth year fixed when predicting age profiles<br>Discount rates: 4% cost and 1.5% QALYs | 7,600 | 9,400 | 11,700 | 11,900 | 11,800 |
| Alternative model w/o cohort variables** | | | | | |
| Average household<br>Discount rates: 4% cost and 1.5% QALYs | 6,900 | 8,200 | 9,800 | 10,500 | 10,800 |
| Alternative model w/o period variables*** | | | | | |
| Average household<br>Birth year fixed when predicting age profiles<br>Discount rates: 4% cost and 1.5% QALYs | 39,400 | 28,500 | 18,600 | 15,300 | 11,100 |
| Predictions only using data from 2004**** | | | | | |
| Average household<br>Discount rates: 4% cost and 1.5% QALYs | 6,800 | 8,000 | 9,800 | 10,600 | 11,300 |

*Same regression model specification as in equation (4) but the dependent variable is calculated as household consumption divided by household size. As household economies of scale are ignored there is no need to use predictions of household size.
**Same regression model specification as in equations (4) and (5) but without parameters to model the cohort effects
***Same regression model specification as in equations (4) and (5) but without parameters to model the period effects
**** The dependent variable is calculated as household consumption divided by household size. As household economies of scale are ignored there is no need to use predictions of household size. As data from only 1 cross-section is used, period and cohort effects are not modelled.
Estimated smooth function and estimated parametric parameters for all alternate model specifications are available in the appendix

## Conclusion and discussion

There is an ongoing theoretical debate on whether to include future non-medical costs in economic evaluations in health care. In this paper, we provided empirical evidence regarding the impact of including such costs on the ICER. In doing so, we explicitly addressed two issues that thus far were ignored in the scarce empirical literature on future non-medical costs. First, we have used a very long series of repeated cross sections data, which allowed us to identify the age profile by correcting for period- and cohort effects. Second, we have accounted for the fact that saving a life can have a different impact on consumption depending on household size, because of economies of scale.

Our findings provide three important insights. First, we have confirmed the findings from previous studies that including the costs of future non-medical consumption can have a substantial impact on the ICER of life-prolonging interventions and the impact increases with age (Kruse et al., 2012; Manns et al., 2003a; Meltzer, 1997a; Meltzer et al., 2000b). This means that, regardless of whether the benefits of non-medical consumption are perfectly reflected in the QALY measure, non-medical consumption costs are non-trivial and are important societal costs of medical interventions which should be part of a full welfare economic analysis, and about which policy makers should be informed. Second, accounting for economies of scale within households is important and lowers the impact of including future non-medical costs on the ICER because if life is prolonged in a multi-person household this results in lower additional consumption than in a single-person household. However, to be able to account for household economies of scale one also needs predictions of average household size by age. Third, the influence of correcting for possible cohort and period effects on consumption cost estimates was limited in our study. The reason for this is that cohort and period effects in consumption and household size had opposing effects on the ICER.

Some limitations of this study need noting. A first limitation is that, like most consumption studies (e.g. (Alessie and Ree, 2009; Domeij and Johannesson, 2006; Fernández-Villaverde and Krueger, 2007)), we had to rely on repeated cross section data of consumption. This means that, although we have used a very flexible approach based on splines, we still have had to make some implicit assumption to separately identify age, period and cohort effect. An important restriction might be that, in our empirical model, these effects are additive and separable. It could be that for instance macroeconomic events have a different impact on different age groups. An example is the financial crisis that seems to have had a different impact on the wealth holding of younger and older cohorts, which in turn affects consumption across the whole lifecycle. It should be noted, however, that our estimates of the age profile of consumption are in line with previous empirical research (Alessie and Ree, 2009; Domeij and Johannesson, 2006; Fernández-Villaverde and Krueger, 2007). However, compared to the study by Allesie and Ree (Alessie and Ree, 2009), who used data from the same surveys we estimated that younger birth cohorts consume less. Second, in this study, we have

focused only on consumption, not on production or income. We assumed that existing ICERs already include the effects on productivity, and showed how also including non-medical consumption would affect the ratio. Third, when assessing the impact of including non-medical costs we used population averages for consumption as well population averages for mortality and quality of life. As such, our estimates should be interpreted with caution whenever a target population of an actual intervention deviates from the average population. The impact of such deviations will probably be most influenced by differences (compared to population average) in mortality and quality of life because of the intervention. Hence, we believe our estimates of non-medical consumption are still informative for actual economic evaluations (and likely better than current zero estimates). Fourth, in our empirical application we assumed that health care interventions have no effect on lifetime consumption other than through increased survival. However, there are at least three additional channels through which the intervention might have an impact on consumption. First, the intervention might affect out-of-pocket spending on medical care. In our application, we have focused solely on the additional impact of including non-medical consumption to an evaluation, assuming the effects on medical consumption and productivity are already included. If the effect of the intervention on medical consumption is indeed included in the ICER, the effect of the out-of-pocket medical spending on non-medical consumption should be taken into account as well to prevent double counting (although in the Netherlands this is a minor issue, due to low out-of-pocket payments). Second, the intervention might have a positive effect on human capital (productivity) and thus increase the lifetime resources that can be used for consumption (although some of this might be mitigated by social insurance or other income transfers). Again, if the productivity gains are included, the income effects on consumption should be as well. The third channel through which the intervention might have an impact on consumption is through the relation between the utility of consumption and health. Health state dependence of the utility of consumption is often suggested as an explanation for the declining consumption pattern at older ages, such as the one we, like many other empirical studies, have found (Finkelstein et al., 2009). If the marginal utility of consumption is lower in poor health, that means that individuals tend to shift their lifetime consumption towards the younger years, where they can expect to be in better health. Likewise, if an intervention affects health in different life years, individuals might reallocate consumption across their remaining life or might increase overall consumption at the costs of lower bequests. Although theoretically appealing, actually identifying health state dependence is difficult and the direction of the effect has been found to be ambiguous and may likely depend on the type of health state change (Finkelstein et al., 2009; Gyrd-Hansen, 2016). Given this ambiguity, we have focused on the age pattern of consumption without adjusting for health status as we were interested in consumption patterns that conditional on age are not altered by the intervention under investigation. Future research could focus on the impact of healthcare interventions on non-medical consumption patterns conditional on being alive. Cost effectiveness studies might actually be able to provide valuable

insights into the question of health-state dependence, as often intervention are randomly assigned to individuals with similar individual with the same health condition as control group. Extending the data collection in those studies to include consumption data could thus be valuable. Another, less data intensive, way to quantify the impact of health on non-medical consumption for the purpose of treatment evaluation could be to follow the approach already used for medical consumption and exploit the relation with time to death. As health losses and health care consumption are usually clustered at the end of life (Gheorghe et al., 2016a; Payne et al., 2007), it might well be the case that non-medical consumption strongly decreases at the end of life to be shifted into medical consumption.

Although it is common practice not to include costs of non-medical consumption in cost effectiveness analysis, a theoretical foundation for this practice is lacking, and the practice is not in line with common proposals (Meltzer, 1997a; Sanders et al., 2016). A possible explanation for this might be that guidelines for cost effectiveness analysis typically do not pay (much) attention to costs of non-medical consumption (possibly due to the lack of theoretical consensus on its inclusion), while they do often pay more attention to measuring and valuing production gains (Krol et al., 2013). Economic evaluations that do include future non-medical consumption often use data from a single cross-sectional survey and do not adjust for household economies of scale (Kruse et al., 2012; Manns et al., 2003a; Meltzer, 2012). Such estimates are clearly different from our main estimates and likely constitute overestimations of real non-medical consumption due to life prolonging interventions. Important in the theoretical debate regarding the in- or exclusion of future non-medical costs is the extent to which the benefits of non-medical consumption are captured in the QALY gains of life-prolonging interventions. This can be captured in terms of functioning (i.e. being in a particular health state) or in the valuation of such states (see e.g. (Tilling et al., 2010)). If the benefits from non-medical consumption are not captured in QALYs, it could be considered inconsistent to include the related cost. While this inconsistency argument is valid and worth to be studied empirically, we note two things. First, current practice in economic evaluations taking a societal perspective is to include productivity gains, for which it is also unknown to what extent the costs and benefits (e.g. in terms of sacrificed leisure time) are fully captured in QALY gains (Nyman, 2011). Hence, excluding future non-medical costs on the same grounds could be seen as inconsistent in itself. Second, using our theoretical model we indicated that at least part of the utility of non-medical consumption is included in economic evaluations. More specifically, with regard to the theoretical debate it is important to empirically investigate whether benefits of non-medical consumption are considered when people value QALY gains using WTP exercises. More generally, if the current economic evaluation framework for health interventions does not fully capture the benefits of non-medical consumption, other ways of capturing them could be sought. This seems a more sensible response than leaving out real costs to account for a too narrow measurement of benefits. If these costs are to be included, then the estimates needs to be reliable.

The debate about the inclusion of non-medical consumption costs is still ongoing, but there are good reasons to argue that the inclusion of these costs is important. This also means that we need sound estimates of these costs, which are largely lacking. We have contributed by presenting estimates for The Netherlands, based on a longitudinal dataset and an analysis that takes age-period-cohort effects and the influence of household economies of scale into account. Our findings not only show that it is important to take the non-medical consumption costs of medical interventions into account, but also that without properly taking economies of scale into account these societal costs are misrepresented.

4

# CHAPTER 5

## Practical Guidance for Including Future Costs in Economic Evaluations in the Netherlands: introducing and applying PAID 3.0

## Abstract

A consensus has been reached in the Netherlands that future medical costs should be included in economic evaluations. Furthermore, internationally, there is the recognition that in countries that adopt a societal perspective estimates of future non-medical consumption are relevant for decision makers as much as production gains are. The aims of this paper are twofold: To update the tool 'Practical Application to Include future Disease costs (PAID 1.1)', based on 2013 data, for the estimation of future unrelated medical costs and introduce future non-medical consumption costs; further standardizing and facilitating the inclusion of future costs, and to demonstrate how to use the tool in practice; showing the impact of including future unrelated medical costs and future non-medical consumption in a case-study where a life is hypothetically saved at different ages and two additional cases where published studies are updated by including future costs. Using the latest published Cost of Illness (COI) data from the year 2017, we model future unrelated medical costs as a function of age, gender, and time to death - which varies per disease. The Household Survey from Centraal Bureau Statistiek is used to estimate future non-medical consumption by age. The updated Incremental Cost-Effectiveness Ratios (ICERs) from the case-studies show that including future costs, can have a substantial effect on the ICER, possibly affecting choices made by decision makers. This paper improves upon previous work and provides the first tool for the inclusion of future non-medical consumption in the Netherlands.

## Introduction

While cost-utility analysis (CUA) is increasingly used to assess whether new interventions in healthcare yield sufficient value for money (Garber and Sculpher, 2011), there are still several methodological issues that require attention. One such issue is the extent to which future costs should be included in CUA (de Vries et al., 2018; Rappange et al., 2008), where future costs are costs that arise from extending individuals' lives and include all costs in the life-years gained (LYG) from an intervention. They are typically divided into medical (relevant for both societal and healthcare perspectives) and non-medical costs (only relevant for the societal perspective). Non-medical costs here refer to consumption (e.g. costs for housing and food) minus production (benefits from additional work in LYG). For medical costs, a distinction is made between *related* (e.g. costs for check-ups by a cardiologist after a heart-attack) and *unrelated* costs (e.g. costs for treating pneumonia after said heart-attack). Future related medical costs are typically included in CUA. However, including future unrelated medical costs has been frequently debated. Early in the debate, the extent to which future costs should be included was discussed using theoretical models aiming to optimize societal welfare. This led to multiple views on the topic (Garber and Phelps, 1997a; Meltzer, 1997b), the most compelling being that all future costs and benefits should be considered (Meltzer, 1997b). Later, the discussion was extended with the more practical view that since future unrelated medical consumption benefits are generally included, the costs thereof should be included to be consistent (Nyman, 2004b). This argument was also used to state that future non-medical costs should *not* be included, arguing that the benefits thereof are not systematically included in the QALY (Nyman, 2011). However, there are different views on the extent to which the benefits from non-medical consumption and production are actually included (Gandjour, 2006b; Meltzer, 2012; Richardson and Olsen, 2006b), and there is so far no compelling (empirical) evidence regarding this (de Vries et al., 2018). The inclusion of future unrelated medical costs in CUA is now required in the Netherlands (Zorginstituut Nederland, 2016a) and recommended in the United States (Sanders et al., 2016). While production in LYG is often considered part of productivity costs in CUA using a societal perspective, the inclusion of future non-medical consumption costs is only recommended in the United States (Sanders et al., 2016).

To facilitate the inclusion of future unrelated medical costs in the Netherlands, the Practical Application to Include future Disease costs (PAID 1.0) was introduced in 2011(van Baal et al., 2011b) and updated in 2016 (PAID 1.1). This tool provides age and gender specific average medical spending estimates, which can be specified to exclude the costs of specific providers and diseases. Estimates are based on a conceptual model that combines various streams of literature. Costs by age are corrected for 'time-to-death' by estimating costs separately for survivors and decedents. 'Time to death' refers to the finding that health care costs are often higher in the last period of life

(Zweifel et al., 1999a). Since older people are more likely to die, not correcting for this leads to an overestimation of the impact of age on medical expenditures (Zweifel et al., 1999a) and ignores the fact that saving a life at a given age leads to the postponement of this high-cost last period of life (Gandjour and Lauterbach, 2005). Future related medical costs of specific diseases already included in the analysis can be excluded to prevent double counting.

This paper provides an extensive update of PAID, to PAID 3.0. First, it uses most recent available COI data (2017). Second, and the largest difference from PAID 1.1, future costs of non-medical consumption are included. We provide guidance on how to use PAID 3 supported by three case-studies. PAID 3.0 can be used free of charge via https://imta.shinyapps.io/PAID3/ and consists of a webapp made in Shiny in R..

## Methods

As stated by Meltzer (Meltzer, 1997b), if the aim of economic evaluations is to maximize social welfare given available resources, all costs following from an intervention should be considered. This implies that both medical costs, related and unrelated, and non-medical costs should be included. The Incremental Cost-Effectiveness Ratio (ICER) including all costs can be written as follows:

$$ICER = \frac{\Delta\left[LY \times (RMC + PC)\right]}{\Delta\, QALY} + \frac{\Delta LY \times UMC}{\Delta\, QALY} + \frac{\Delta LY \times NMC}{\Delta\, QALY} \qquad \text{(eq. 1)}$$

Where:

- LY = life years
- RMC = related medical costs
- PC = productivity costs
- UMC = unrelated medical costs
- NMC = costs of non-medical consumption

Splitting the ICER equation into three ratios distinguishes the elements that are currently included in economic evaluation, related medical costs and productivity costs, from the additional costs that are not usually considered, future unrelated medical costs and future costs of non-medical consumption. Equation (1) also illustrates that differences in unrelated medical costs and future costs of non-medical consumption are purely the result of differences in survival. In our estimation of the ICER, in which future costs are included, we use per capita medical and non-medical consumption cost patterns by age as a starting point.

Lifetime costs of unrelated medical and non-medical consumption $LLY \times [UMC + NMC]$ for an individual aged $a$ dying at age $n$, can be written as shown in equation 2:

$$LY \times [UMC + NMC] = \sum_{a}^{n-1} \sum_{i} sc_i(a,) + \sum_{i} dc_i(n) + \sum_{a}^{n} nmc(a) \qquad \text{(eq. 2)}$$

Where:

- a = age in years
- n = age at death
- dc = decedent costs (healthcare costs in last year of life)
- sc = survivor costs (healthcare costs in other years)
- nmc = average costs of non medical consumption
- i = index of unrelated diseases



### *Unrelated medical costs*

Rather than taking a bottom-up approach and predicting the risk of all unrelated diseases and connecting these to costs, we take a top-down approach and use total per capita healthcare costs by age and gender as a starting point for estimating unrelated medical costs. Using methods identical to those of van Baal and colleagues (van Baal et al., 2011b), we first break down total healthcare costs by disease, enabling the exclusion of costs for diseases already included in the analysis. Although we explain these methods in the ensuing text, for a more detailed description we refer to the original paper by van Baal and colleagues (van Baal et al., 2011b). Disease-specific per capita healthcare costs were estimated using data from the Dutch COI from 2017 (Rijksinstituut voor Volksgezondheid en Milieu (RIVM), n.d.). Rather than using the System of Health Accounts (SHA) (World Health Organisation and European Commission; Organisation for Economic Co-operation and Development, 2011) perspective (used in PAID 1.1) we use the classification from the National Institute for Public Health and the Environment (RIVM). Although the SHA is internationally recognized, the RIVM definition includes imore healthcare costs, such as international care. While average per capita spending hardly changed between 2013 and 2017, age and disease patterns have changed. For example, between 2013 and 2017, costs of psychological disorders increased , 14% when using 2017 prices far more than costs in other disease categories such as diseases of the central nervous system (2% when using 2017 prices).

COI data are specified by gender and 21 age-classes, which we interpolated using cubic splines to obtain age-year-specific per capita expenditures, and are calculated from population spending totals. The data are further attributed to 100 disease categories

and 11 healthcare provider categories (overview in Appendix A). These disease categories include 'Not disease related' and 'Not allocated', meaning that well-care is also included in our definition of unrelated medical costs. As healthcare costs are strongly determined by both age and time to death (Wong et al., 2011b), individual lifetime healthcare costs can be estimated as shown in the first two parts of equation 2. To obtain estimates for survivors and decedents, average per capita expenditures are decomposed into one part attributable to those dying and one part to those surviving at that particular age, assuming average costs are a weighted average of costs for survivors and decedents (age and gender indices are left out here for notational purposes):

$$ac_i = (1 - m) \times sc_i + m \times dc_i \qquad \text{(eq. 3)}$$

Where:

- $ac_i$ = average per capita healthcare expenditure for disease i
- m = mortality rate

Disease-specific costs for survivors and decedents can be estimated using equation 4, using mortality rates and the gender- and age-dependent ratio between costs for decedents and survivors ($r_i$):

$$dc_i = r_i \times sc_i \qquad \text{(eq. 4)}$$

$$ac_i = sc_i + (r_i - 1) \times m \times sc_i$$

$$sc_i = \frac{ac_i}{1 + (r_i - 1) \times m}$$

Mortality rates from 2017 were obtained from Statistics Netherlands (Central Bureau for Statistics (CBS), n.d.). We used the same disease-specific ratios for costs between decedents and survivors for the hospital sector e as used in previous versions of PAID For ambulatory healthcare, drugs and appliances, and nursing and residential care, ratios from 1999 based on total expenditures were used (Polder et al., 2006). To obtain disease-specific ratios for these providers, we exponentiated disease-specific hospital ratios by a scaling constant describing the relation between costs for decedents and survivors between hospital care and other providers (see Appendix C). For providers for which no ratios were available we assumed that costs for decedents were equal to costs for survivors, as it is predominantly in hospitals that differences in survivor and decedent costs are observed (de Meijer et al., 2011; Wong et al., 2011b).

### *Non-medical consumption*

To estimate costs of non-medical consumption by age we used data from the cross-sectional Dutch Household Consumption survey from 2004 adjusted to 2017 price-levels using consumer price indices from Statistics Netherlands. In previous literature, economies of scale within households have been found to be important when estimating non-medical consumption (Alessie and Ree, 2009; Kellerborg et al., n.d.), implying lower per person consumption costs when household size is larger. For instance, spending on housing can be divided amongst more people when household size is larger, however the utility obtained from housing is likely to be the same whether someone lives on their own or not. This has important implications for estimating future costs of non-medical consumption, as preventing a death in a single-person household will result in more future non-medical consumption than preventing a death in a multi-person household (Nelson, 1988). To estimate costs of non-medical consumption for an average household by age, we fit two generalized additive models using penalized B-splines on age. The first model estimates annual consumption per household equivalent. Consumption per household equivalent is calculated from household consumption using the OECD modified equivalence scale (Hagenaars et al., 1994a). The OECD modified equivalence-scale assigns a weighting factor of .5 to each additional adult household member and 0.3 to each child in a multi-person household. The second model estimates the probability of a household having more than one adult; we are interested in making predictions for an average household. Using this equivalence scale implies that preventing a death in a single person household results in twice as much non-medical consumption as compared to a multi-person household with two adults. Details on these models and testing of assumptions can be found elsewhere (Kellerborg et al., n.d.). The models are used to estimate average annual non-medical consumption by age of preventing a death in an average household as in Equation 5:

$$nmc(a) \quad = [hh\ equiv(a) \times h(a) \times w] + [hh\ equiv(a) \times \big(1 - h(a)\big)] \qquad \text{(eq. 5)}$$

Where:

- $h$ = probabilitity of household having >1 adult
- $hh\ equiv$ = annual non-medical consumption per household equivalent
- $w$ = weight of deceased household member, .5 for and adult and .3 for a child

### *Case-studies*

We demonstrate the impact of including future costs on the ICER via three case-studies. Benefits are discounted at 1.5% per year and costs at 4% per year, in adherence with Dutch guidelines (Zorginstituut Nederland, 2016a). For the first case-study a life is hypothetically saved at ages 0-100, while in the second and third case studies we replicate survival curves from previous studies. In the first case-study life-tables for

estimating life-expectancy at all ages are used and combined with quality of life (QoL) data from Gheorghe and colleagues (Gheorghe et al., 2014).

For the second case-study, we replicated survival curves from a previously published cost-effectiveness study on oxaliplatin plus fluoropyrimidines versus fluoropyrimidines-only as adjuvant treatment of stage III colon cancer (Van Gils et al., 2013), wherein oxaliplatin showed an incremental QALY gain of 1.02 and 0.68 LYG, incremental costs of €9,961, and a corresponding ICER of €9,766. The sample consisted of patients previously diagnosed with stage 3 colon cancer whom where randomized to either treatment or control groups. The median age of patients was 60 years. This study is then updated by including estimates of future medical costs, after excluding costs related to colon cancer, and including future non-medical consumption.

For the third case-study, we used the results from a clinical trial assessing survival of pembrolizumab monotherapy compared to platinum-based chemotherapy in a group of previously untreated patients with locally advanced or metastatic non-small-cell lungcancer (Mok et al., 2019). The paper from which the survival curves are extracted, does not perform a CEA, and therefore there is no 'baseline' ICER or QALY gains. In this clinical trial the median age at baseline was 64 years of age and and 71 percent of patients were male. This case-study demonstrates how to use PAID when survival is short. We recommend using estimates of living one year longer when studies have a relatively short time-horizon (< 5 years as rule of thumb), especially when survival between the new treatment and comparator are highly different in the first study-year. In that case, using decedent costs would create large differences in costs at baseline between the new treatment and the comparator for unrelated diseases. This is implausible as it implies a different past trajectory of costs for the same person before getting the treatment and conflicts with the definition of unrelated medical costs. Costs for living one year longer, $c(a,g)$, can be calculated as follows:

$$c(a,g) = sc(a,g) + dc(a+1,g) - dc(a,g) \qquad \text{(eq. 6)}$$

Where:

- c = costs of living one year longer
- g = gender
- a = age in years

Furthermore, while the approach discussed above assumes independence between the healthcare intervention and cost of non-medical and unrelated medical consumption, we provide a framework allowing for a correlation between the intervention and unrelated medical costs - applied in the third case study. We show the impact of adjusting PAID estimates of unrelated medical costs for this correlation, which is relevant when the studied population is expected to have a different health care use for

unrelated diseases than the average population. Estimates can be adjusted using the framework as displayed in equation 7, where per capita costs are shown as the product of disease prevalence and per patient costs:

$$sc(a)_i = p(i|i) \times sc(a|i)_i \quad \text{(eq. 7)}$$

$$dc(a)_i = m(a|i) \times dc(a|i)_i$$

Where:

- $p(i|a)$ = probability of disease $i$ conditional on age $a$;
- $m(a|i)$= mortality rate at age $a$ conditional on having disease $i$.
- $sc(a|i)$ = survivor costs at age $a$ conditional on having disease $i$.
- $dc(a|i)$ = decedent costs at age $a$ conditional on having disease $i$.

Given the relationships displayed in equation 7 we adjusted unrelated costs to reflect higher prevalence and mortality for stroke among lung cancer patients (Chen et al., 2011). We adjusted the unrelated costs for stroke by extracting the costs for stroke separately, multiplying stroke costs with the relative risk of stroke - 1.47 - as estimated by Chen and colleagues (Chen et al., 2011) and adding these back to the sum of unrelated medical costs, as shown in the equations below.

$$sc(a) = \sum_{i \neq j} sc_i(a) + sc_j(a) \times \lambda \quad \text{(eq. 8)}$$

$$dc(a) = \sum_{i \neq j} dc_i(a) + dc_j(a) \times \lambda$$

Where

- $j$ = unrelated disease with higher costs (e.g. stroke).
- $\lambda$ = multiplier

To demonstrate how to use PAID with survival data on an individual level we fitted two parametric survival models assuming a Weibull distribution to overall survival results presented in the Kaplan-Meier plot (Mok et al., 2019) from which we randomly drew individual survival times.

## Results

*Unrelated medical costs and non-medical costs*

Panels A and B in Figure 1 show how average healthcare expenditures rise sharply after age 75 while per capita non-medical consumption by show a less strong age pattern but decrease at old age and peak at middle age (identical numbers for males and females since estimates are not gender-specific). These graphs show that up until around age 75, people have higher non-medical than healthcare consumption, whereafter healthcare exceeds non-medical consumption.

Age-specific per capita medical costs for survivors and decedents are presented in graphs C and D, showing comparable patterns in spending by gender; although women's expenditures are higher, especially at older ages. These graphs show that differences between survivor and decedent costs are highest in the first year of life and between 50 and 75 years, and become smaller at the highest ages. This can largely be attributed to causes of death and related periods of illness before dying at different ages. In the first year of life, death often follows a period with high use of medical care. The same holds for middle age. At the highest ages, survivors as well as decedents typically incur higher healthcare expenditures, narrowing the difference in costs.

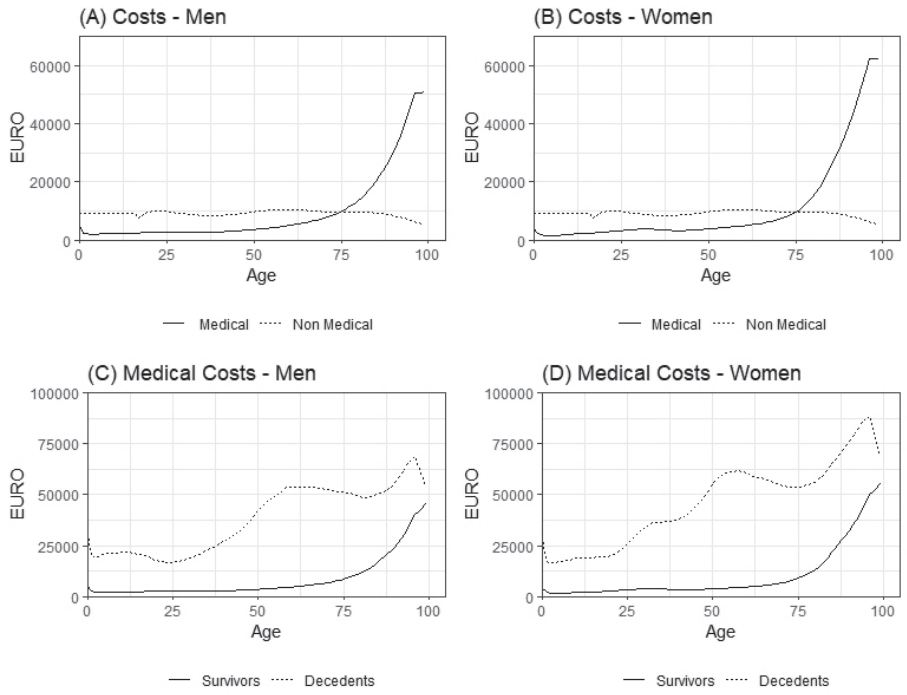


*Figure 1: A & B - Average per capita medical costs and non-medical consumption by age. C&D - Medical costs, split into survivor and decedent costs by age.*

*Case-studies*

For the first case-study we estimated the impact of including future costs on the ICER when death is prevented at a certain age (see Figure 2). It shows that the older people get the more expensive it is to be saved.

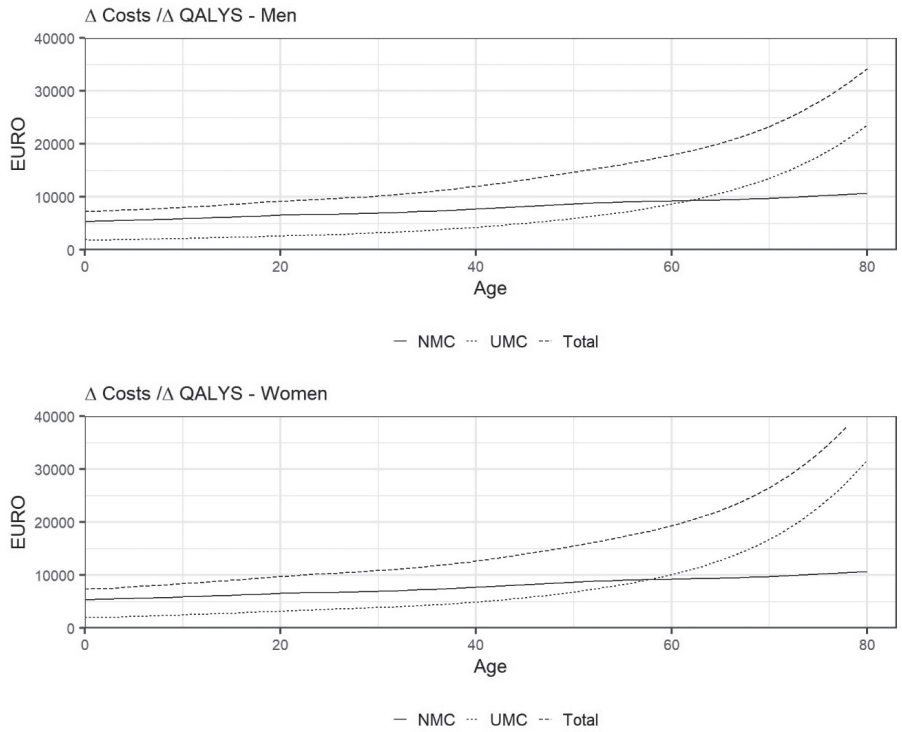


*Figure 2: Case-study 1. The hypothetical impact of including future unrelated medical costs (UMC) and future non-medical consumption (NMC) on the ICER when death is prevented (for free) at a certain age.*

The results of the second and third case-study are summarized in Table 1. Figures 4 and 5 shows differences in costs and survival over time for the two case studies. Including future unrelated medical costs in case study 2 leads to an increase of €3,761 in the ICER; including non-medical consumption adds another €5,440 to the ICER.

Table 1 The impact of including future costs on the ICER for case-studies 2 and 3.

| | Case-study 2 - € per QALY* | Case-study 3 - € per life-year | |
|---|---|---|---|
| | | Unadjusted | Adjusted for stroke |
| Original ICER | 9,580 | N/A | N/A |
| Impact including unrelated medical costs on ICER | 3,761 (13,341) | 5,546 | 5,619 |
| Impact including non-medical costs on ICER | 5,440 (15,020) | 9,126 | 9,126 |
| Total impact on ICER | 9,201 (18,781) | 14,672 | 14,745 |

*Total ICER shown in brackets

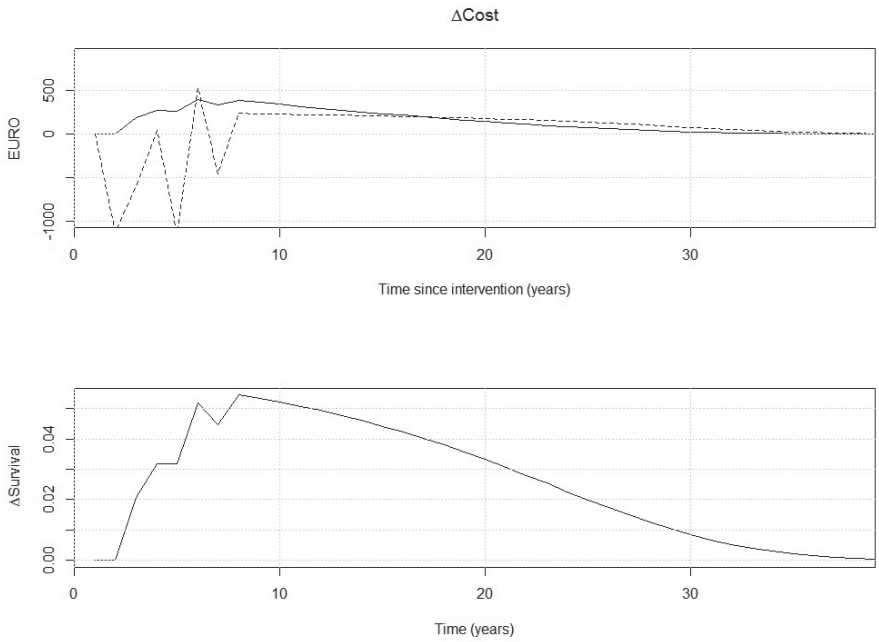


*Figure 3: Case study 2. The added costs for including unrelated consumption and non-medical consumption (top), and the difference in survival between intervention and comparator group (bottom).*

For the third case-study we estimated a mean survival of 25.1 months for the intervention group (Pembrolizumab) and 15.3 months for the comparator group (chemotherapy); Figure 5 (bottom) shows difference in survival. As stated above, in this study no baseline ICERs and QALYs were available. Therefore, only the impact of inclusion on the ICER

can be estimated and impact is shown as cost per LYG. We estimated a discounted LYG of 0.77 for the intervention group compared to the comparator. Inclusion of future unrelated medical costs increased the ICER by €5,546, or €5,619 after adjustments for stroke incidence. Including future non-medical consumption further increased the ICER with €9,126. Note here that the impact on the ICER will be different when QALYs instead of life-years are used. If the LYG will be in less than perfect health, this will increase the impact on the ICER.

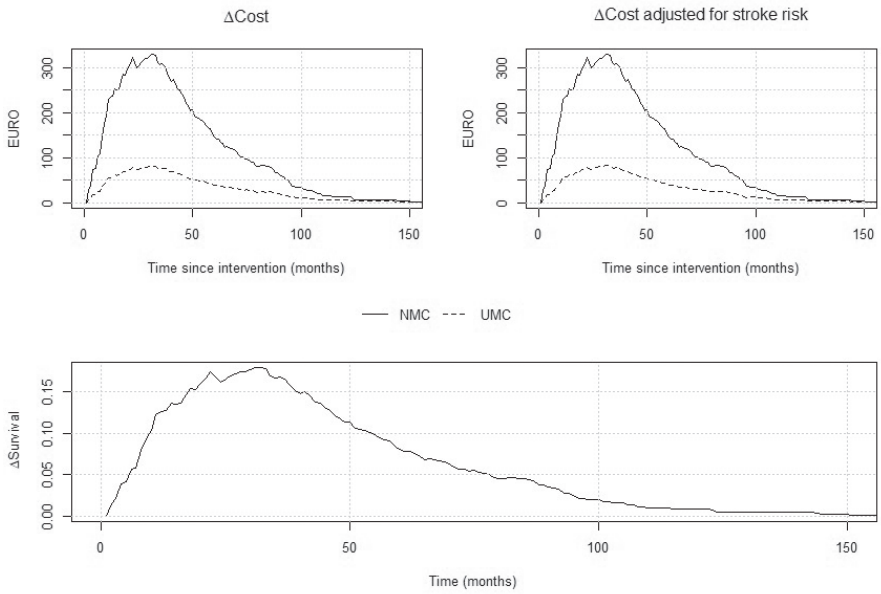


*Figure 4: Case study 3. The additional costs by time for the lung cancer intervention (top left), and the additional costs by time when adjusted for increase stroke risk (top right). Difference in survival between intervention and comparator group (bottom).*

## Discussion & Conclusion

In 2011 a practical tool to include future unrelated medical costs in a standardized manner was introduced (van Baal et al., 2011b). In this paper we updated the tool with the most recent data on medical costs and included estimates for future non-medical consumption. Recent COI data was combined with mortality data and decedent-survivor cost ratios, to provide disease-specific estimates of medical expenditures per capita in survivors and decedents. Related costs of an intervention are then excluded from total medical expenditure. Non-medical consumption was estimated taking into account household economies of scale. This paper further demonstrated how to use the tool in practice using case studies.

The first case-study refers to the situation of saving a life at a given age, with no intervention costs. It shows that the impact of including future costs becomes larger at higher ages, mainly due to rising healthcare expenditures with age, while in comparison to future medical costs, the impact of including non-medical consumption remains relatively stable over time. The consumption curve (Figure 1) follows a U-shape as seen in previous literature (Alessie and Ree, 2009; Fernández-Villaverde and Krueger, 2007), however when dividing these costs by QALY changes the curve flattens considerably. Another factor affecting the relative impact of including future costs at younger ages versus older ages, is that the more expensive (older) years, are discounted more highly when lives are saved at younger ages. Furthermore, the impact of including future non-medical consumption is larger than including future unrelated medical costs until approximately the age of 60. This may seem surprising when looking at Figure 1, which shows that per capita non-medical consumption is larger than medical consumption until approximately the age of 75. However, when estimating the impact of including future unrelated medical costs on saving a life at different ages, we consider time-to-dea. As a result, high medical spending in the last year is postponed and additional medical spending is less than suggested by Figure 1.

In the second case-study a published evaluation comparing interventions for colon cancer is replicated. Including future unrelated medical costs increases the ICER by almost 40 percent and when all future costs are included the ICER more than doubles. In the Netherlands a cost-effectiveness threshold ranging from €20,000 up to €80,000 per QALY gained is applied, where the height depends on the principle of proportional shortfall (Brouwer et al., 2019; Reckers-Droog et al., 2018) Using the iMTA Disease Burden Calculator (Versteegh et al., 2019), we calculated a proportional shortfall for this case-study of 0.37, which implies that the relevant threshold in this case-study is €20,000 (Reckers-Droog et al., 2018). Including future costs in this study could thus make this intervention not cost-effective as it pushes the ICER near the threshold It is important to note that an intervention being not cost-effective is not an undesirable outcome, but simply the result of correctly estimating the change in costs for an intervention.

In the third case-study, we demonstrate how to adjust for short time-horizons and that PAID estimates can easily be applied to several forms of models. Furthermore, we show how to adjust estimates when costs for unrelated diseasesin the studied population is suspected to differ from the general population. This is adjusted for here by using the increased risk of stroke among patients with lung cancer. In this case the difference between future unrelated medical costs adjusted or unadjusted is relatively small. However, if the costs of a disease for which the risk is increased were large and the additional risk substantial, the impact of such adjustment would be larger, as shown by Manns et al. in their paper on end-stage renal disease care (Manns et al., 2003a).

An important limitation is that there are no more recently estimated decedent-survivor cost ratios than those used here. Although more recent estimates of mean overall spending in the last year of life compared to other years show comparable numbers (Bakx et al., 2016), more detailed estimates may show different patterns. An update of these ratios would be useful for future research. A further limitation with regards to decedent-survivor cost ratios is that we did not have estimates for all providers, and disease-specific estimates for three providers were derived by combining hospital estimates with provider-specific sector estimates. In a similar vein to this, the classification of costs amongst providers was different for 2017 COI data, and therefore fewer costs could be adjusted using these ratios. It is also worth noting that data from the household survey are relatively old; although data are adjusted to 2017 prices, changes in spending-patterns by age may not be captured. Furthermore, we estimated non-medical consumption by age, and assumed no correlation between non-medical consumption and disease. While there is relatively little literature covering this topic, there are some findings that suggest such a correlation. For example, it may be that medical consumption crowds out non-medical consumption for the severely ill (Zaidi and Burchardt, 2005). However, the findings that non-medical consumption decreases from a certain age (Alessie and Ree, 2009; Fernández-Villaverde and Krueger, 2007; Gourinchas and Parker, 2002) may imply that as health decreases (as it does at older ages) so does non-medical consumption. Further research in this area is needed.



Finally, we do not address uncertainty in this paper. Uncertainty could stem from the two key elements of our estimates: survival and costs. While the original costs in this case are averages provided by CBS Netherlands and therefore with little surrounding uncertainty, there are still sources of uncertainty, such as decedent-survivor cost ratios; the larger the TTD effect (larger ratios), the smaller the impact of future costs on the ICER (Meltzer, 1997b).

In general, including future costs may have a systematic effect on reimbursement decisions as the 'upward' effect on the ICER changes differently by population and intervention. As the cost of extending life increases with age, this implies that the age at which an intervention is given will be of increased importance for the cost-effectiveness of an intervention. Another parameter that affects the magnitude of the impact of including future costs, and thus decisions is the ratio of life-years gained to QALYs gained for a particular intervention. It has been shown that the larger this ratio, the larger the impact of including future costs (Meltzer, 1997b).

In this paper no specific attention is paid to future related medical costs and future productivity as these are typically already included in economic evaluations and extensive guidance on how to estimate and include these costs is already available in the Netherlands (Hakkaart-van Roijen et al., 2015). However, when looking at the total impact of including future costs, production gained at working ages would presumably

lead to those years being the least costly. This would, however, also depend on how productivity is measured. In the Netherlands, these costs are typically quantified using the friction costs method and thus limited to the friction period. Using the human capital approach or including informal and household production, would affect the impact of inclusion at different ages. The latter methods would imply higher negative costs (more productivity gains from living longer) and thereby lower ICERs. Another issue worth mentioning is that, although there is agreement that including future unrelated medical costs would improve the internal consistency of the ICER, implying that costs are included when related benefits are included, how much QALYs capture the benefits from non-medical consumption (and also production) is currently unclear (Nyman, 2004b). Furthermore, it is also unclear to what extent thresholds to which ICERs are compared include these benefits (de Vries et al., 2018). The impact of including future non-medical consumption and the comparison with existing thresholds should thus be interpreted with caution.

To conclude, this paper provided an update and extension of PAID and demonstrated through case-studies the application and impact of including future costs in economic evaluations. Updated ICERS show that including future costs, even just unrelated medical costs, can have a substantial effect on the ICER which could affect decision makers' choices. For future research it would be interesting to see the estimates used in a variety of economic evaluations.

# Supplemental Material

## Appendix A: Healthcare providers

Table A.1 Summary of healthcare provider categories in PAID 3.0 (based on the categories distinguished in the Dutch Costs of Illness study)

| **Cost of Illness VTV** *(Volksgezondheid Toekomstverkenning)* **healthcare provider categories** | **% of total costs in 2017** | **Data used to attribute average costs per disease to last year of life and other years** |
|---|---|---|
| Hospitals (HC) | 30.3 | Hospital records linkage |
| Nursing and residential care facilities (LTC) | 20.5 | Hospital records scaled to insurance claims |
| Providers of ambulatory healthcare (GP) | 10.8 | Hospital records scaled to insurance claims |
| Retail sale and other providers of medical goods (Med) | 9.0 | Hospital records scaled to insurance claims |
| Provision and administration of public health programmes* | 1.9 | Not applicable** |
| General health administration and insurance* | 4.4 | Not applicable** |
| Other healthcare* | 3.3 | Not applicable** |
| Welfare* | 0.5 | Not applicable** |
| Ambulance and transport* | 0.6 | Not applicable** |
| Disabled care* | 11.3 | Not applicable** |
| Mental healthcare* | 7.4 | Not applicable** |

* These healthcare providers are grouped together and referred to as 'other healthcare providers'
** Costs for 'other healthcare providers' depend only on age and gender for PAID 3.0

# Appendix B: Disease categories

Table B1: Summary of disease categories in PAID 3.0 (based on the categories distinguished in the Dutch Costs of Illn

| Disease category number | Cost of Illness System of Health Account Disease categories | International Statistical Classification of Diseases and Related Health Problems (ICD) - 10 codes | International Statistical Classification of Diseases and Related Health Problems (ICD) - 9 codes |
|---|---|---|---|
| | Infectious and parasitic disease | | |
| 1 | Intestinal infectious diseases | A00-A09 | 001-009 |
| 2 | Tuberculosis | A10-A19, B90 | 010-018, 137 |
| 3 | Meningitis | A39, A87, G00-G03 | 036, 047, 320-322 |
| 4 | Septicemia | A40-A41 | 038 |
| 5 | HIV/AIDS | B20 | 042-044 |
| 6 | Sexually transmitted diseases | A60, A50-A58 A63, B00, B07, B08 | 054, 078, 090-099 |
| 7 | Hepatitis | B15-B19, K77 | 070, 573.1 |
| 8 | Other infectious diseases | A20-A46, A35, A42, A48, A68-A69, A70-A71, A75, A77-A85, A87-A88, A90, A92, A93, A95, A98, B01-B06, B08, B09, B26-B27, B30, B33, B50-B57, B60, B91, B95-B99, Z11, Z20, Z23, Z41, Z51, Z79 | 019-035, 037, 039-041, 045-046, 048-053, 055-069, 071-077, 079-089, 100-136, 138-139, v01-v07, v73-v75 |
| | Neoplasms | | |
| 9 | Esophagus cancer | C15 | 150 |
| 10 | Stomach cancer | C16 | 151 |
| 11 | Colorectal cancer | C18-C21 | 153-154 |
| 12 | Pancreas cancer | C25 | 157 |
| 13 | Lung cancer | C33-C34 | 162 |
| 14 | Breast cancer | C50 | 174 |
| 15 | Cervical cancer | C53-C55 | 180 |
| 16 | Ovary cancer | C56-C57 | 183 |
| 17 | Prostate cancer | C61 | 185 |
| 18 | Bladder and kidney cancer | C64-C68 | 188-189 |
| 19 | Non-Hodgkin's disease | C82- C83 | 200, 202 |
| 20 | Other lymphoid cancer and leukemia | C81, C90-C95 | 201, 203-208 |
| 21 | Other cancers | C00-C14, C17, C22-24, C26-C32, C38-C43, C50, C69-C80, C7A, Z12 | 140-149, 152, 155-156, 158-161, 163-172, 175-178, 190-199, 209, v76 |
| 22 | Other benign neoplasms | C44, D03, D10-D23, D30-D36 | 173, 210-216, 223-239 |

ıess study)

| | Matched disease-specific ratios estimated using International Shortlist for Hospital Morbidity Tabulation (ISHMT) classification (ICD-9 codes between brackets) | % of total costs in 2017 (disease subcategories show share of costs within header category) |
|---|---|---|
| | | 1.72 |
| | r001 (001-008)<br>r002 (009) | 12.50 |
| | r003 (010-018, 137) | 1.14 |
| | r006 (remainder of 001-139, except 0340, 0993, 0994, 135, 1361) | 2.27 |
| | r004 (038) | 5.68 |
| | r005 (042-044 or 2795, 2796) | 15.91 |
| | r006 (remainder of 001-139, except 0340, 0993, 0994, 135, 1361) | 4.55 |
| | r006 (remainder of 001-139, except 0340, 0993, 0994, 135, 1361)<br>r072 (570, 571.4-573) | 13.64 |
| | r006 (remainder of 001-139, except 0340, 0993, 0994, 135, 1361)<br>r130 (remainder of V01-V82) | 43.18 |
| | | 6.69 |
| | r015 (remainder of 140-208) | 1.46 |
| | r015 (remainder of 140-208) | 0.58 |
| | r007 (153, 154) | 10.20 |
| | r015 (remainder of 140-208) | 1.75 |
| | r008 (162) | 7.87 |
| | r010 (174,175)** | 14.87 |
| | r011 (179,180,182)** | 2.33 |
| | r012 (183)** | 1.46 |
| | r013 (185)* | 6.71 |
| | r014 (188)<br>r015 (remainder of 140-208) | 4.66 |
| | r015 (remainder of 140-208) | 3.79 |
| | r015 (remainder of 140-208) | 12.14 |
| | r015 (remainder of 140-208)<br>r010 (174,175)**<br>r130 (remainder of V01-V82) | 21.57 |
| | r009 (172,173)<br>r016 (230-234)<br>r017 (2113,2114)<br>r019 (remainder of 210-239) | 10.79 |

| Disease category number | Cost of Illness System of Health Account Disease categories | International Statistical Classification of Diseases and Related Health Problems (ICD) - 10 codes | International Statistical Classification of Diseases and Related Health Problems (ICD) - 9 codes |
|---|---|---|---|
| | Endocrine, nutritional and metabolic diseases | | |
| 23 | Diabetes mellitus including diabetic complications | E10-E11, E0842, E0942, E1042, E1142, E1342, E113, N048, N08, N038, N058 | 250, 357.2, 362.0, 581.8, 582.8, 583.8 |
| 24 | Other endocrine, nutritional and metabolic diseases | E009, E01, E04-E09, E15, E21-E22, E24, E27-E29, E30-E32, E34, E40, E41, E43-E46, E50-E51, E53-E56, E65-E67, E70, E74, D80, Z13 | 240-249, 251-279, V77 |
| | Diseases of the blood and the blood-forming organs | | |
| 25 | Diseases of the blood and blood-forming organs | D50, D51, D56-D59, D61, D63-D75, Z13 | 280-289, V78 |
| | Mental and behavioral disorders | | |
| 26 | Dementia | F01-F05, F329 | 290, 311 |
| 27 | Schizophrenia | F20 | 295 |
| 28 | Depression | F30, F341 | 296, 300.4 |
| 29 | Anxiety | F40-F42, F449, F488, F43, F438 | 300.0, 300.10-300.15, 300.2-300.3, 300.5, 308, 309.8 |
| 30 | Personality disorders | F431, F6811, F688, F60 | 300.16-300.19, 301 |
| 31 | Dependency on alcohol and drugs | F10-F16, F18-F19, | 291-292, 303-305 |
| 32 | Other mental disorders | F02-F06, F07, F4320, F4321, F45, F481-F489, F54, F64-F66, F81, F84, F90, F93, F95, Z134 | 293-294, 299, 300.6-300.9, 302, 306-307, 309.0-309.7, 309.9, 310, 312-316, v79 |
| 33 | Mental retardation, including Down's syndrome | F70-F73, F79, Q909 | 317-319, 758.0 |
| | Diseases of the nervous system | | |
| 34 | Parkinson's disease | G20-G21 | 332 |
| 35 | Multiple sclerosis | G35 | 340 |
| 36 | Epilepsy | G40 | 345 |
| 37 | Cataract | H26 | 366 |
| 38 | Disorders of accommodation and refraction | H52 | 367 |

| | Matched disease-specific ratios estimated using International Shortlist for Hospital Morbidity Tabulation (ISHMT) classification (ICD-9 codes between brackets) | % of total costs in 2017 (disease subcategories show share of costs within header category) |
|---|---|---|
| | | 2.85 |
| | r022 (250)<br>r034 (remainder of 320-359)<br>r036 (remainder of 360-379)<br>r090 (580-5834, 5838, 5839, 5900-5902, 5908, 5909, 591, 5933-5935, 5937, 5996)<br>r099 (remainder of 580-629 except 5997) | 63.70 |
| | r023 (remainder of 240-278)<br>r130 (remainder of V01-V82) | 36.30 |
| | | 0.51 |
| | r020 (280-285)<br>r021 (135, 2790-2793, 2798, 286-288, 2890, 2894-2899)<br>r130 (remainder of V01-V82) | 100.00 |
| | | 28.60 |
| | r024 (2900-2902, 2904-2909, 2941)<br>r028 (296, 2980, 3004, 3011, 311) | 35.99 |
| | r027 (295, 2970-2973, 2978-2979, 2983-2989) | 1.64 |
| | r028 (296, 2980, 3004, 3011, 311) | 4.50 |
| | r029 (remainder of 290-319) | 3.07 |
| | r028 (296, 2980, 3004, 3011, 311)<br>r029 (remainder of 290-319) | 2.73 |
| | r025 (291, 303, 3050)<br>r026 (292, 2940, 304, 3051-3059) | 3.27 |
| | r024 (2900-2902, 2904-2909, 2941)<br>r026 (292, 2940, 304, 3051-3059)<br>r029 (remainder of 290-319)<br>r130 (remainder of V01-V82) | 16.02 |
| | r029 (remainder of 290-319)<br>r110 (740-759) | 32.86 |
| | | 6.71 |
| | r034 (remainder of 320-359) | 3.49 |
| | r031 (340) | 3.49 |
| | r032 (345) | 5.23 |
| | r035 (366) | 5.23 |
| | r036 (remainder of 360-379) | 15.41 |

| Disease category number | Cost of Illness System of Health Account Disease categories | International Statistical Classification of Diseases and Related Health Problems (ICD) - 10 codes | International Statistical Classification of Diseases and Related Health Problems (ICD) - 9 codes |
|---|---|---|---|
| 39 | Blindness and low vision | H54 | 369 |
| 40 | Conjunctivitis | H00-H02 | 373-374 |
| 41 | Other diseases of the eye and adnexa | H04-H05, H10, H15-H17, H20, H30, H40, H44, H47, H50, H53, | 360-361, 362.1-362.9, 363-365, 368, 370-372, 375-379 |
| 42 | Ear disorders | H60-H95 | 380-389 |
| 43 | Other diseases of the nervous system and sense organs | G04-G19, G22-G34, G36-G39, G40-G99, Z135 | 323-331, 333-339, 341-344, 346-356, 357.0-357.1, 357.3-357.9, 358-359, v80 |
| | Diseases of the circulatory system | | |
| 44 | Hypertension | I10-I15 | 401-405 |
| 45 | Coronary heart disease | I21-125 | 410-414 |
| 46 | Heart failure | I50-I51 | 428-429 |
| 47 | Other heart disease, including pulmonary circulation | I30-I49 | 390-398, 415-427 |
| 48 | Stroke | I60-I69 | 430-438 |
| 49 | Diseases of arteries | I70-I79 | 440-448 |
| 50 | Other circulatory diseases | I80-199 | 451-459 |
| | Diseases of the respiratory system | | |
| 51 | Acute upper respiratory infections | J00-J06 | 460-466 |
| 52 | Pneumonia and influenza | J09-J18 | 480-487 |
| 53 | Asthma and chronic obstructive pulmonary disease (COPD) | J40-J47 | 490-496 |
| 54 | Other respiratory diseases | J30-J39, J60-J99 | 467-479, 488-489, 497-519 |
| | Diseases of the digestive system | | |
| 55 | Other diseases of teeth, jaw and salivary glands | K00, K030-K039, K04, M26, K080, K082-K089, K09-K14 | 520, 521.1-521.9, 522, 524, 525.0, 525.2-525.9, 526-529 |
| 56 | Gastroduodenal ulcers | K25-K28 | 531-534 |

| | Matched disease-specific ratios estimated using International Shortlist for Hospital Morbidity Tabulation (ISHMT) classification (ICD-9 codes between brackets) | % of total costs in 2017 (disease subcategories show share of costs within header category) |
|---|---|---|
| | r036 (remainder of 360-379) | 7.56 |
| | r036 (remainder of 360-379) | 1.74 |
| | r036 (remainder of 360-379) | 6.98 |
| | r037 (380-389) | 22.97 |
| | r030 (3310)<br>r034 (remainder of 320-359)<br>r130 (remainder of V01-V82) | 27.91 |
| | | 11.66 |
| | r038 (401-405) | 6.35 |
| | r039 (413; ICD-9-CM: 4111, 413)<br>r040 (410)<br>r041 (411-412, 414; ICD-9-CM: 4110, 4118, 412, 414) | 22.24 |
| | r044 (428)<br>r048 (2891-2893, remainder of 390-459 except 435, 446 and 4590) | 8.03 |
| | r048 (2891-2893, remainder of 390-459 except 435, 446 and 4590)<br>r042 (415-417)<br>r043 (426, 427) | 19.40 |
| | r033 (435)<br>r045 (430-434, 436-438) | 14.38 |
| | r046 (440)<br>r048 (2891-2893, remainder of 390-459 except 435, 446 and 4590) | 9.36 |
| | r048 (2891-2893, remainder of 390-459 except 435, 446 and 4590) | 20.23 |
| | | 3.39 |
| | r049 (0340, 460-465, 487; ICD-9-CM: 340, 460-465, 487, 488)<br>r051 (466 (acute lower respiratory infections other than acute bronchitis, acute bronchiolitis and pneumonia were not separated in ICD-9, no J22 equivalent)) | 11.49 |
| | r050 (480-486)<br>r049 (0340, 460-465, 487; ICD-9-CM: 340, 460-465, 487, 488) | 16.67 |
| | r054 (490-492, 494, 496)<br>r055 (493)<br>r056 (remainder of 460-519) | 14.37 |
| | r049 (0340, 460-465, 487; ICD-9-CM: 340, 460-465, 487, 488)<br>r053 (470-473, 475-478)<br>r056 (remainder of 460-519) | 57.47 |
| | | 6.84 |
| | r057 (520-525)<br>r058 (526-529) | 62.11 |
| | r060 (531-534) | 0.57 |

| Disease category number | Cost of Illness System of Health Account Disease categories | International Statistical Classification of Diseases and Related Health Problems (ICD) - 10 codes | International Statistical Classification of Diseases and Related Health Problems (ICD) - 9 codes |
|---|---|---|---|
| 57 | Appendicitis | K35-K38 | 540-543 |
| 58 | Abdominal hernia | K40-K46 | 550-553 |
| 59 | Inflammatory intestinal disease | K50-K52 | 555-556 |
| 60 | Other intestinal diseases | K55-K64 | 557-569 |
| 61 | Chronic liver disease and cirrhosis | K70 | 571 |
| 62 | Other liver diseases | K72, K75, K763-K769, K77 | 570, 572, 573.0, 573.2-573.9 |
| 63 | Gallbladder diseases | K80-K83 | 574-576 |
| 64 | Other diseases of the digestive system | K20, K29-K31, K86-K90 | 530, 535-537, 577-579 |
| 65 | Diseases of the genitourinary system | | |
| 66 | Nephritis and nephropathy | N00-N01, N032-N039, N043-N044, N049, N059, N17-N19 | 580, 581.0-581.7, 581.9, 582.0-582.7, 582.9, 583.0-583.7, 583.9, 584-589 |
| 67 | Acute renal and urinary infections | N11, N30, N34, N390 | 590, 595, 597, 599.0 |
| 68 | Other renal and urinary diseases | N13-521, N32, N35, N360-N369 | 591-594, 596, 598, 599.1-599.9 |
| 69 | Hyperplasia of prostate | N40 | 600 |
| 70 | Other disorders of male genital organs | N41-N51 | 601-608 |
| 71 | Disorders of female genital organs | N60-N92, N94 | 610-627, 629 |
| 72 | Female infertility | N97, Z31 | 628, v26 |
| | Pregnancy, childbirth and the puerperium | | |
| 73 | Pregnancy | O00-O48, Z34 | 630-648, V22-V23 |

| | Matched disease-specific ratios estimated using International Shortlist for Hospital Morbidity Tabulation (ISHMT) classification (ICD-9 codes between brackets) | % of total costs in 2017 (disease subcategories show share of costs within header category) |
|---|---|---|
| | r062 (540-543) | 1.42 |
| | r063 (550)<br>r064 (551-553) | 2.85 |
| | r065(555, 556) | 6.84 |
| | r066 (558)<br>r067 (560)<br>r068 (562)<br>r069 (565, 566, 5690-5694)<br>r070 (557, 564, 5695, 5698, 5699) | 1.71 |
| | r071 (5710-5713)<br>r072 (570, 5714-573) | 1.42 |
| | r072 (570, 5714-573)<br>r076 (remainder of 520-579) | 0.00 |
| | r073 (574)<br>r074 (575, 576) | 3.70 |
| | r059 (530)<br>r061 (535-537)<br>r075 (577)<br>r076 (remainder of 520-579) | 19.37 |
| | | 3.16 |
| | r090 (580-5834, 5838, 5839, 5900-5902, 5908, 5909, 591, 5933-5935, 5937, 5996)<br>r091 (5836, 5837, 584-586)<br>r093 (0994, 587-589, 5903, 5930-5932, 5936, 5938, 5939, 595- 597, 5980, 5981, 5988, 5989, 5990-5995, 5998, 5999, 6256) | 27.78 |
| | r090 (580-5834, 5838, 5839, 5900-5902, 5908, 5909, 591, 5933-5935, 5937, 5996)<br>r093 (0994, 587-589, 5903, 5930-5932, 5936, 5938, 5939, 595- 597, 5980, 5981, 5988, 5989,5990-5995, 5998, 5999, 6256) | 8.64 |
| | r090 (580-5834, 5838, 5839, 5900-5902, 5908, 5909, 591, 5933-5935, 5937, 5996)<br>r092 (592, 594, 7880)<br>r093 (0994, 587-589, 5903, 5930-5932, 5936, 5938, 5939, 595- 597, 5980, 5981, 5988, 5989, 5990-5995, 5998, 5999, 6256) | 28.40 |
| | r094 (600)* | 4.94 |
| | No estimates | 4.94 |
| | No estimates | 18.52 |
| | No estimates | 6.79 |
| | | 2.07 |
| | No estimates | 34.91 |

| Disease category number | Cost of Illness System of Health Account Disease categories | International Statistical Classification of Diseases and Related Health Problems (ICD) - 10 codes | International Statistical Classification of Diseases and Related Health Problems (ICD) - 9 codes |
|---|---|---|---|
| 74 | Childbirth | O60-O84, Z76, Z37, Z38 | 650-669, V20, V27, V30-V39 |
| 75 | Puerperium | O85-O92, Z39 | 670-676, V24 |
| 76 | Contraception | Z30 | V25 |
| | Diseases of the skin and subcutaneous tissue | | |
| 77 | Eczema | L22-L25 | 691-692 |
| 78 | Decubitus | L89 | 707 |
| 79 | Other diseases of the skin and subcutaneous tissue | L02-L21, L27, L29, L40, L43, L44, L50-L51, L53, L60, L65-L66, L70, L74, L81-L98 | 680-690, 693-706, 708-709 |
| | Diseases of the musculoskeletal system and connective tissue | | |
| 80 | Rheumatoid arthritis | M05-M08 | 714 |
| 81 | Osteoarthrosis | M15 | 715 |
| 82 | Dorsopathy | M40-M54 | 720-724 |
| 83 | Osteoporosis | M810, M844 | 733.0-733.1 |
| 84 | Internal derangement of the knee | M23 | 717 |
| 85 | Unspecified musculoskeletal diseases or conditions | M35, M75, M60, M61, M65, M79 | 725-729 |
| 86 | Other diseases of the musculoskeletal system | M00, M12-M14, M20-M21, M24-M25, M32-M35, M40-M42, M85- M86, M88-M89, M91-M92, M95, M99 | 710-713, 716, 718-719, 730-732, 733.2-733.9, 734-739 |
| | Congenital malformations | | |
| 87 | Congenital anomalies of nervous system | Q00-Q05 | 740-742 |
| 88 | Congenital anomalies of circulatory system | Q20-Q25 | 745-747 |
| 89 | Other congenital anomalies, excluding Down's syndrome | Q11, Q16, Q30, Q35, Q38, Q41-Q43, Q50, Q60, Q67-Q97, Z36 | 743-744, 748-757, 758.1-758.9, 759, v28 |

| | Matched disease-specific ratios estimated using International Shortlist for Hospital Morbidity Tabulation (ISHMT) classification (ICD-9 codes between brackets) | % of total costs in 2017 (disease subcategories show share of costs within header category) |
|---|---|---|
| | No estimates | 37.74 |
| | No estimates | 20.75 |
| | No estimates | 7.55 |
| | | 1.64 |
| | r078 (690-693, 6943, 696-6983, 6988, 6989) | 13.10 |
| | r079 (remainder of 680-709) | 13.10 |
| | r077 (680-686)<br>r078 (690-693, 6943, 696-6983, 6988, 6989)<br>r079 (remainder of 680-709) | 75.00 |
| | | 7.47 |
| | r083 (0993, 711-716, 718, 719, 7271, 7284) | 9.92 |
| | r080 (Not a concept in ICD-9 at four-digit level. Can only be defined by using the optional fifth digit 5 to 715, i.e. 715.15, 715.25, 715.35 and 715.95)<br>r081 (Not a concept in ICD-9 at four-digit level. Can only be defined by using the optional fifth digit 6 to 715, i.e. 715.16, 715.26, 715.36 and 715.96)<br>r083 (0993, 711-716, 718, 719, 7271, 7284) | |
| | r085 (720, 721, 7230, 7235, 7240, 737)<br>r086 (7220-7227, 7229)<br>r087 (7231, 7234, 7236, 7241-7243, 7245) | 14.36 |
| | r089 (remainder of 710-739) | 1.83 |
| | r082 (717) | 5.74 |
| | r083 (0993, 711-716, 718, 719, 7271, 7284)<br>r084 (1361, 2794, 446, 710, 725, 7285)<br>r086 (7220-7227, 7229)<br>r088 (726, 7270, 7272-7279)<br>r089 (7280-7283, 7286-7289, 729) | 37.08 |
| | r083 (0993, 711-716, 718, 719, 7271, 7284)<br>r084 (1361, 2794, 446, 710, 725, 7285)<br>r089 (remainder of 710-739) | 31.33 |
| | | 0.58 |
| | No estimate | 3.33 |
| | No estimate | 26.67 |
| | No estimate | 70.00 |

| Disease category number | Cost of Illness System of Health Account Disease categories | International Statistical Classification of Diseases and Related Health Problems (ICD) - 10 codes | International Statistical Classification of Diseases and Related Health Problems (ICD) - 9 codes |
|---|---|---|---|
| | Certain conditions originating in the perinatal period | | |
| 90 | Disorders relating to premature birth | P07 | 765 |
| 91 | Other conditions originating in the perinatal period | P00-P04, P08-P15, P22-P28, P50-P90 | 760-763, 766-767, 769-770, 772-779 |
| | Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified | | |
| 92 | Symptoms, signs and ill-defined conditions | R40-R99 | 780-799 |
| | Injury, poison and certain other consequences of external causes | | |
| 93 | Skull-brain injury | S02, S04- S06 | 800-801, 803-804, 850-854, 950-951 |
| 94 | Fractures of upper extremities | S42-S52 | 810-819 |
| 95 | Hip fracture | S72 | 820-821 |
| 96 | Other lower extremity fracture | S82, S92 | 822-829 |
| 97 | Superficial injury | S00, S05, S09-S10, S20, S30, S40, S60, S70, S80, S90, T07 | 910-924 |
| 98 | Other injury | S01, S03, S07-S08, S11-S19, S21-S29, S31-S39, S41, S53-S59, S61-69, S71, S73-S79, S81, S83-S89, S91, S91-S99 | 802, 805-809, 830-849, 855-909, 925-949, 952-999 |
| | Not allocated/ Not disease related | | |
| 99 | Not allocated | Z01, Z03, Z09, Z13, Z43, Z45, Z48- Z51, Z65, Z76-Z79, Z80-Z84, Z85-Z88, Z91 | V10-V19, V21, V40-V57, V58.0-V58.4, V58.6-V58.9, V63-V64, V66-V68, V71-V72, V81-V82 |
| 100 | Not disease-related | Z00, Z02, Z52, Z56, Z59, Z60, Z69, Z71, Z74, Z75, Z76 | V59-V62, V65, V70 |

*disease-specific ratio only estimated for men
**disease-specific ratio only estimated for women
No estimate: no disease-specific ratio found for both men and women

| | Matched disease-specific ratios estimated using International Shortlist for Hospital Morbidity Tabulation (ISHMT) classification (ICD-9 codes between brackets) | % of total costs in 2017 (disease subcategories show share of costs within header category) |
|---|---|---|
| | | 0.23 |
| | No estimate | 75.00 |
| | No estimate | 16.67 |
| | | 1.91 |
| | No estimate | 100 |
| | | 3.28 |
| | No estimates | 12.50 |
| | No estimate | 7.14 |
| | No estimate | 16.07 |
| | No estimate | 14.29 |
| | No estimates | 2.38 |
| | No estimates | 48.21 |
| | | 10.68 |
| | No estimates | 91.97 |
| | No estimates | 8.03 |

## Appendix C: Derivation scaling factor ratios

To obtain disease-specific ratios for these providers, we exponentiated the disease-specific hospital ratios by a scaling constant describing the relation between costs for decedents and survivors between hospital care and the other providers (equation C.1). The log scale, instead of multiplying by a constant, is chosen for scaling to prevent that negative ratios would become positive (or vice versa).

$$r_{i,j>1} = r_{i,j=1}^{x_j>1} \quad \text{(eq. C.1)}$$

Where:

- $j$ = index denoting the healthcare provider;
- $j = 1$ implies hospital care;
- $ri,j_{>1}$ = ratio for disease $i$ for healthcare provider $j$ other than hospital care;
- $xj_{>1}$ = scaling constant for healthcare provider $j$ other than hospital care.

Equation C.1 implies that age- and sex-specific distributions of ratios are proportional on the log scale for each healthcare provider. Using equation C.1 for a baseline disease (i=1), this can be rewritten as equation C.2:

$$r_{i=1,j>1} = r_{i=1,j=1}^{x_{j>1}} \rightarrow \log(r_{i=1,j>1}) = x_{j>1} \log\left(r_{i=1,j=1}\right) \rightarrow x_{j>1} = \frac{\log(r_{i=1,j>1})}{\log\left(r_{i=1,j=1}\right)} \quad \text{(eq.}$$

We assume that the scaling factor is equal for all diseases, which leads to equation C.3:

$$x_{j>1} = \frac{\log(r_{i=1,j>1})}{\log\left(r_{i=1,j=1}\right)} = \frac{\log(r_{i>1,j>1})}{\log\left(r_{i>1,j=1}\right)} \; for\ all\ values\ of\ i \quad \text{(eq.}$$

The scaling factor was found by minimizing the distance between total survivor costs using the estimated ratios for total expenditures and total survivor costs as the sum of disease-specific survivor costs (equation C.4):

$$\left(sc_{tot,j>1} - \sum_i \frac{ac_{i,j>1}}{1 + \left(r_{i,j=1}^{x} - 1\right) \times m}\right)^2 \quad \text{(eq.}$$

# 5

# CHAPTER 6

## Distributional consequences of including survivor costs in economic evaluations

## Abstract

Medical interventions that increase life expectancy of patients result in additional consumption of non-medical goods and services in 'added life years'. This paper focuses on the distributional consequences across socio-economic groups of including these costs in cost effectiveness analysis. In that context, it also highlights the role of remaining quality of life and household economies of scale. Data from a Dutch household spending survey was used to estimate non-medical consumption and household size by age and educational attainment. Estimates of non-medical consumption and household size were combined with life tables to estimate what the impact of including non-medical survivor costs would be on the incremental cost effectiveness ratio (ICER) of preventing a death at a certain age. Results show that including non-medical survivor costs increases estimated ICERs most strongly when interventions are targeted at the higher educated. Adjusting for household size (lower educated people less often live additional life years in multi-person households) and quality of life (lower educated people on average spend added life years in poorer health) mitigates this difference. Ignoring costs of non-medical consumption in economic evaluations implicitly favors interventions targeted at the higher educated and thus potentially amplifies socio-economic inequalities in health.

## Introduction

When medical interventions postpone death, costs arise in added life-years due to consumption of medical and non-medical goods (Meltzer, 1997a). Whether or not to include these costs in economic evaluations conducted from a societal perspective remains an issue of controversy (de Vries et al., 2018). Many national guidelines for economic evaluation currently do not recommend the inclusion of survivor costs (Eldessouki and Dix Smith, 2012). However, the recently updated, influential US guidelines do specifically recommend their inclusion (Sanders et al., 2016). The few studies that investigated the impact of inclusion of future non-medical costs on the ICERs of lifesaving interventions show it can be substantial (Kruse et al., 2012; Manns et al., 2003b; Meltzer, 1997a; Meltzer et al., 2000b).

Many countries adopting a societal perspective include production gains in economic evaluations but exclude costs of non-medical consumption (Eldessouki and Dix Smith, 2012). This difference can be considered inconsistent, since many of the theoretical arguments (not) to include non-medical consumption also pertain to production (Meltzer, 1997a; Nyman, 2004a). Moreover, this practice of including production gains but excluding non-medical consumption has potential distributional consequences: it benefits the higher socio-economic groups, who are the most productive (Meltzer, 1997a) but also have the highest non-medical consumption across the lifecycle (Attanasio and Pistaferri, 2016; Fernández-Villaverde and Krueger, 2007).



This paper estimates the distributional consequences of including non-medical consumption costs in economic evaluations across groups with different socio-economic status (SES). Doing so, we add an important element to the literature on cost-effectiveness and inequality. There is a growing interest in distributional consequences in cost-effectiveness evaluations, and many health policies are explicitly targeted at reducing inequalities in health (Asaria et al., 2015; Cookson et al., 2017). As health problems vary strongly with socio-economic status (Cutler and Lleras-Muney, 2010; Meara et al., 2008; Smith, 1999), the relevant future non-medical costs incurred are likely to differ per intervention or even target group. Using a rich dataset from The Netherlands, we estimate age profiles of consumption by education.

In addition, we adjust for differences in household size across educational groups at different ages. The (marginal) costs of non-medical consumption are lower for individuals in multi-person households than for singles, as the first group benefits from economies of scale (Kellerborg et al., n.d.). Due to lower life expectancy of lower educated, they are at greater risk of living alone at older age relative to their higher educated counterparts (Hotz et al., 1997). We also account for the fact that the quality of life of persons from low SES groups in general is lower than that of people from high SES groups (Gheorghe et al., 2016b). This is important, as the impact of including future costs is stronger when life years are gained in poor health.

# Methods

## *Data*

We used data from the Dutch budget survey (Budgetonderzoek) from the years 2003 and 2004 which is a yearly cross-sectional survey collected among the non-institutionalized population of the Netherlands. The households taking part in the survey report on a comprehensive set of consumption categories (e.g. consumption related to eating, transportation, housing, vacation) using diaries which were collected by interviewers on a regular basis. We removed all medical consumption of the household and adjusted the data to 2017 prices. Age was defined as the age of the household head. Educational attainment was determined by the highest educational attainment of the household head and categorized in three categories: low, middle and high (for more details on the data and methods see the online supplementary file). Figure 1 gives an overview of the data.

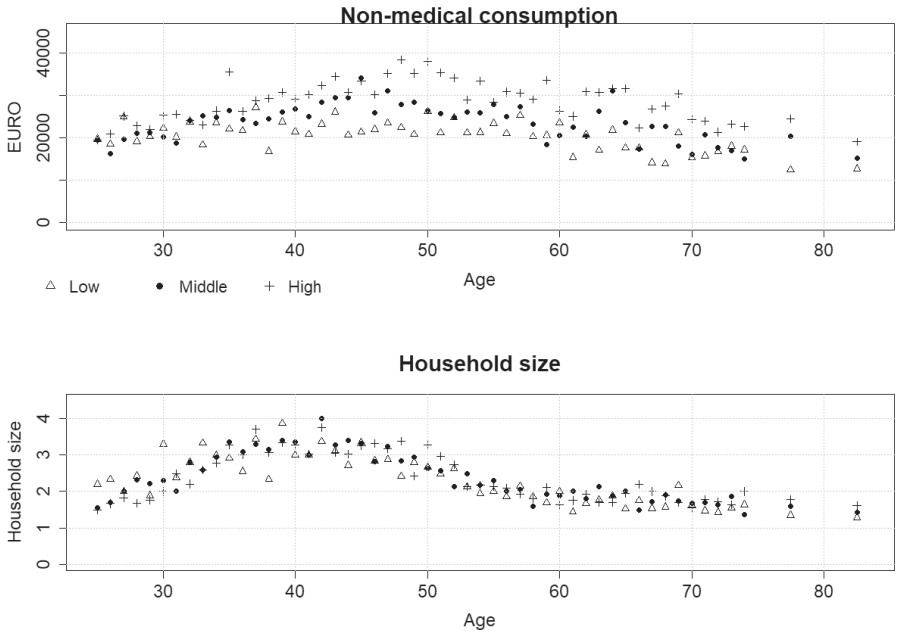


*Figure 1: Non-medical consumption per household (top panel) and household size (bottom panel) by education and age. Non-medical consumption is shown in 2017 EURO prices.*

*Model specification*

Our approach to estimating the impact of education on the ICER consists of several steps. First, we translate household consumption into per household equivalent consumption using the OECD-modified equivalence scale (Hagenaars et al., 1994b). This scale assigns a weighting factor per additional individual in a household of 0.5 for each adult and 0.3 per child. We then estimated log scaled household equivalent consumption as a function of age, stratified by education with the following model:

$$\ln(hh\ equiv.) = S(age \cdot edu) + \varepsilon \qquad (1)$$

Where *Hh equiv*. denotes annual non-medical consumption per household equivalent. We used cubic P-Splines to model the non-linear age pattern with an interaction term for education and ε is a normally distributed error term (Eilers and Marx, 1996).

Given that we want to estimate the average costs of non-medical consumption in case of a prevented death, we need to know the average household size at different ages for different educational classes. Preventing a death in a single person household will result in more additional consumption than preventing one in a multi-person household. Therefore, we also estimated the probability of a household having more than one adult as a smooth function of age and education using a binomial logistic P-splines model:

$$p(Y = adults > 1) = \frac{\exp\left(S(age \cdot edu) + \varepsilon\right)}{1 + \exp\left(S(age \cdot edu) + \varepsilon\right)} \qquad (2)$$

As in the first model, we apply P-Splines on age with education as an interaction term. The average costs of non-medical consumption caused by living one year longer by age and education (*nmc(age,edu)*) are then calculated as in Equation 3:

$$nmc(age, edu) = \qquad (3)$$

$$p(adults\ in\ hhs > 1|age, edu) \times hh\ equiv(age, edu) \times 0.5$$

$$+ (1 - p[adults\ in\ hhs > 1|age, edu]) \times hh\ equiv(age, edu)$$

The first part denotes the consumption for individuals in households with more than one adult times the probability of a death being prevented in a multi-person household. The second part represents the consumption for individuals in single households times the probability of a death being prevented in a single-person household.

### *ICER calculations*

Equation (4) shows the elements included in the ICER when both production gains and costs of non-medical consumption costs are taken into account:

$$ICER = \frac{\Delta medical\ costs + \Delta production}{\Delta QALY} + \frac{\Delta nmc}{\Delta QALY}. \quad (4)$$

To calculate the impact on the ICER we focus solely on the second part of this equation: the additional costs from non-medical consumption over the QALY gained $\frac{\Delta nmc}{\Delta QALY}$ from saving a life at different ages. These estimations may then be added to the ICER of a life prolonging intervention. $\frac{\Delta nmc}{\Delta QALY}$ was calculated in the following manner:

$$\frac{\Delta nmc}{\Delta QALY} = \frac{\Sigma_a\{L(age = a, edu) \times nmc(age = a, edu)\}}{\Sigma_a\{L(age = a, edu) \times QoL(age = a, edu)\}} \quad (5)$$

Where $L(age{=}a,edu)$ is the number of years lived at age for a particular educational group and $Q(age{=}a,edu)$is the average quality of life at age $a$ for a particular educational group. Estimates of $L(age,edu)$, $QoL(age,edu)$ were taken from a study that estimated the quality of life and mortality in the Netherlands stratified by education (Gheorghe et al., 2016b). We estimated the additional costs separately for the ages 25 to 82.5 over a lifetime horizon. We present estimates for deaths prevented in an average household but also for deaths prevented in a single-person household. When calculating the costs for a death prevented in a single person household, we use one full household equivalent by age and education times added survival. Costs were discounted at 4 percent and effects at 1.5 percent in accordance with the Dutch guidelines (Zorginstituut Nederland, 2016b). The ICERs as calculated using equation (5) can be interpreted as the cost effectiveness of hypothetical interventions in which a death at a certain age is prevented at zero intervention costs. Previous research (e.g. (Kellerborg et al., 2020; Meltzer, 1997b)) has shown that such ICERs give a good indication of what the impact is of including future costs on the ICER of non-hypothetical interventions.

Using Equations (3), (4) and (5), the influence of the three mechanisms that affect the ICER for different SES groups can be illustrated. First, equation (4) shows that including non-medical consumption increases the numerator of the ICER, resulting in an increase of the ICER. As non-medical consumption is lower for low SES groups than for high SES groups, including these survivor costs is *relatively* favorable for the interventions targeted at the low SES groups (although it increases the ICER for all interventions). Second, the higher educated enjoy both lower mortality rates as well as a higher quality of life resulting in a higher quality-adjusted life expectancy at all ages (Gheorghe et al., 2016b). Equation (5) highlights that lower quality of life values for the lower educated imply that non-medical consumption is divided by a smaller

number and hence a relative increase of the ICER. Third, accounting for differences in household size across SES groups involves accounting for the fact that low SES groups are less often part of multi-person households. Thus, they benefit less often from economies of scale than high SES groups (equation 3). This leads to relatively higher ICERs for interventions aimed at low SES groups.

## Results

Figure 2 shows the predictions of the regression models to illustrate the impact of education and age on consumption and household size.

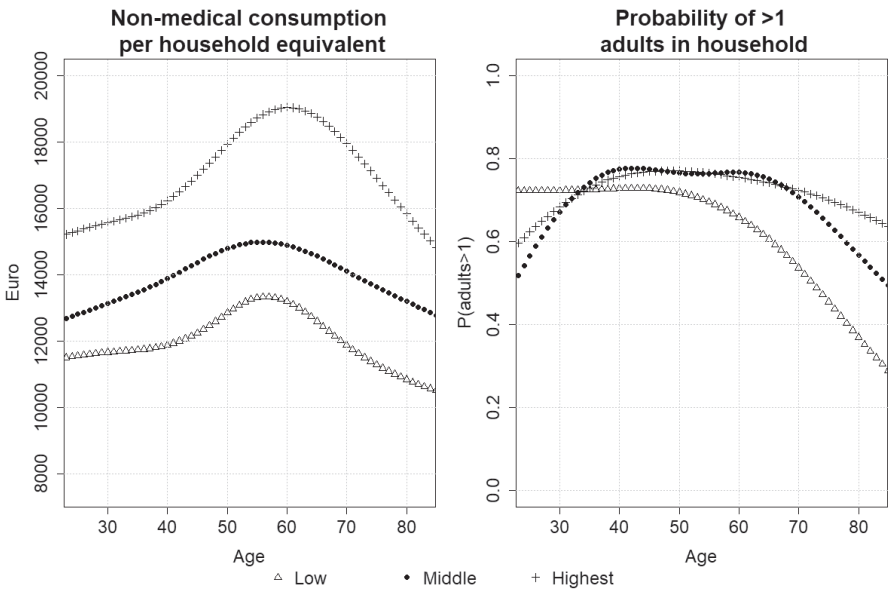


*Figure 2: Prediction of non-medical consumption by household equivalent (left) by education and age. Prediction of probability of households having more than one adult by age and education (right).*

Figure 3 displays the impact of including non-medical survivor costs on the ICER by educational attainment. To better understand the effect of the different mechanisms, the ICER is calculated for preventing a death in a single-person household as well as preventing a death in a household of average size (by age and education as estimated in equation 3), and using Life Years (LY) or QALYs in the denominator. The impact of survivor costs on the ICER differs substantially between the educational groups when we do not account for differences in household size. Using QALYs instead of life-years as outcome increases the impact on the ICER, but it does not substantially

affect the (absolute) differences across education groups. Controlling for household size decreases the impact on the ICERs, as well as the differences between the education groups. This can be seen by comparing the left panels in Figure 3 for single-person households with the right panels in which we made predictions for an average household size using equation 3. Especially at high ages, the high educated on average live in larger households (as shown in Figure 2) which results in a stronger decrease of the impact on the ICER than for the low educated.

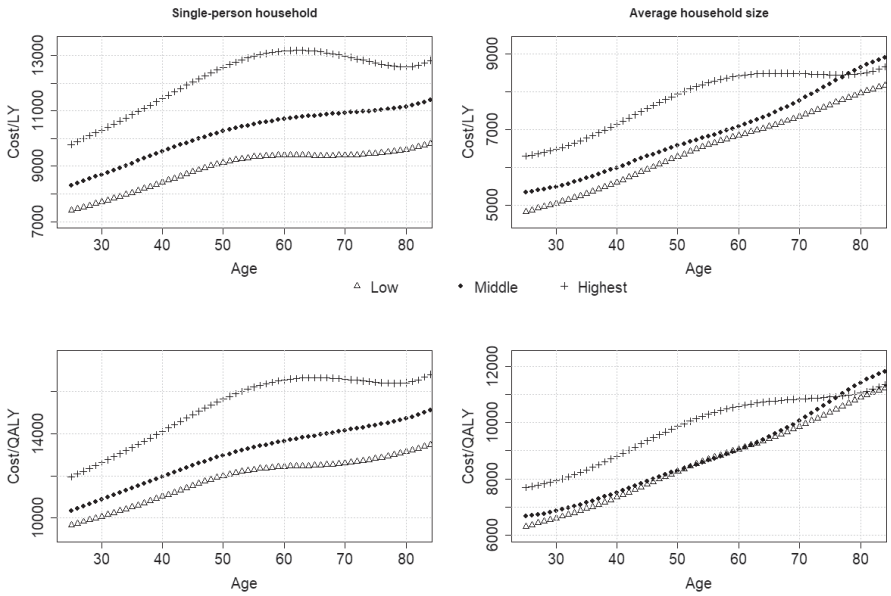


*Figure 3: Impact on the ICER when saving a life at various ages by education. Left panels show predictions for preventing a death in a single-person household and the right panels show predictions for preventing a death in an average household, top panels show estimations calculated with LYs and bottom panels with QALYs. Costs were discounted at a 4% annual rate and health effects at a 1.5% annual rate.*

To further illustrate the differences across model specifications we summarized the impact on the ICER for selected ages and assumptions in Table 1.

**Table 1: Impact of including future non-medical costs on the ICER.** Incremental costs and health effects are the result of a hypothetical intervention in which a death at a certain age is prevented at zero intervention costs. Incremental costs and health effects are the average of men and women at a particular age. Costs are expressed in EURO adjusted for 2017 prices. Costs were discounted at a 4% annual rate and health effects at a 1.5% annual rate.

| Household | Age | Educational attainment | ΔCosts | ΔLY | ΔQALY | ΔCost/ ΔLY | ΔCost/ ΔQALY |
|---|---|---|---|---|---|---|---|
| Average household | 30 | Low | 169,000 | 33.45 | 25.59 | 5,100 | 6,600 |
| | | Middle | 193,300 | 35.28 | 28.25 | 5,500 | 6,800 |
| | | High | 237,200 | 36.51 | 29.81 | 6,500 | 8,000 |
| | 65 | Low | 104,400 | 14.76 | 11.08 | 7,100 | 9,400 |
| | | Middle | 117,500 | 16.23 | 12.64 | 7,200 | 9,300 |
| | | High | 147,500 | 17.34 | 13.69 | 8,500 | 10,800 |
| | 85 | Low | 39,700 | 4.84 | 3.52 | 8,200 | 11,300 |
| | | Middle | 45,600 | 5.44 | 4.09 | 8,400 | 11,100 |
| | | High | 50,900 | 5.87 | 4.47 | 8,700 | 11,400 |
| Single household | 30 | Low | 257,800 | 33.45 | 25.59 | 7,700 | 10,100 |
| | | Middle | 306,800 | 35.28 | 28.25 | 8,700 | 10,900 |
| | | High | 376,500 | 36.51 | 29.81 | 10,300 | 12,600 |
| | 65 | Low | 138,600 | 14.76 | 11.08 | 9,400 | 12,500 |
| | | Middle | 175,900 | 16.23 | 12.64 | 10,800 | 13,900 |
| | | High | 228,200 | 17.34 | 13.69 | 13,200 | 16,700 |
| | 85 | Low | 47,800 | 4.84 | 3.52 | 9,900 | 13,600 |
| | | Middle | 62,300 | 5.44 | 4.09 | 11,500 | 15,200 |
| | | High | 75,800 | 5.87 | 4.47 | 12,900 | 16,900 |



## Conclusion and discussion

Although the impact of including costs of non-medical consumption on the *overall level* of the ICER is substantial, the differences in impact *across* educational groups are smaller. This is importantly related to two issues: (i) lower educated persons enjoy their added life-years in a lower quality of life than higher educated, and (ii) lower educated persons more often form a single-person household at an old age, which implies relatively high additional consumption costs compared to people in a multi-person household. Especially this latter effect turned out to mitigate the socio-economic differences induced by including the costs of non-medical consumption. Finally, it needs to be noted that these influences also need to be viewed in relation to the inclusion of other costs (such as productivity costs) which may, on average, have opposite distributional effects.

Our findings are in line with previous studies that investigated the costs of non-medical consumption (Kruse et al., 2012; Manns et al., 2003a; Meltzer, 1997b; Meltzer et al., 2000c). The observation that consumption declines at older ages may be related to changing preferences and opportunities, but also to liquidity constraints: consumption seems to strongly follow the age pattern of disposable income (Alessie and Ree, 2009). This might also explain the differences in the age profiles of consumption between education groups. Moreover, Gyrd-Hansen suggested that the hump-shaped pattern of consumption may also be explained by lower marginal utility from consumption for people in lower health (Gyrd-Hansen, 2016).

An important and novel finding from this study is that the large differences in consumption between educational classes are mitigated due to concurrent differences in quality of life and household size. Differences in the probability to live in a multi-person household were observed throughout the life-course in different groups. Specifically, lower educated people live in a multi-person household earlier than the other two education groups, but the peak in household size also occurs at an earlier age for the low educated. As we do not have data regarding the type of relationships within these households, several explanations for the observed differences are possible and these may also vary by age. Socioeconomic status for instance has been found to have an indirect effect on divorce rates through earlier marriages and worse economic status (Clarke and Berrington, 1998). Furthermore, differences in life expectancy between lower and higher educated might also explain why at old ages lower educated people are single more often (Gheorghe et al., 2016b).

Although decisions about the availability of technologies are usually made at a fairly aggregate population level without distinguishing groups based on SES, it has been well documented that some health problems are relatively common in lower SES groups (Cutler and Lleras-Muney, 2010; Smith, 1999). This makes distributional consequences of inclusion of particular costs increasingly relevant.

Summarizing, this paper provided empirical estimates of non-medical survivor costs and an indication of the distributional consequences of including them in economic evaluations of life prolonging interventions. The current practice of including production gains but excluding future non-medical costs not only has no economic rationale, but potentially also introduces socio-economic inequalities in health following resource allocation decisions based on economic evaluations. Including future non-medical costs may somewhat reduce the resulting socio-economic inequalities. Estimates and methods described in this paper, facilitate their inclusion in economic evaluations and provide insight in the consequences of doing so. Given that influential guidelines like the US guidelines advocate their inclusion, this seems particularly useful and more research on theory, methods, estimates, and consequences of including these costs seems warranted.

# Supplemental Material

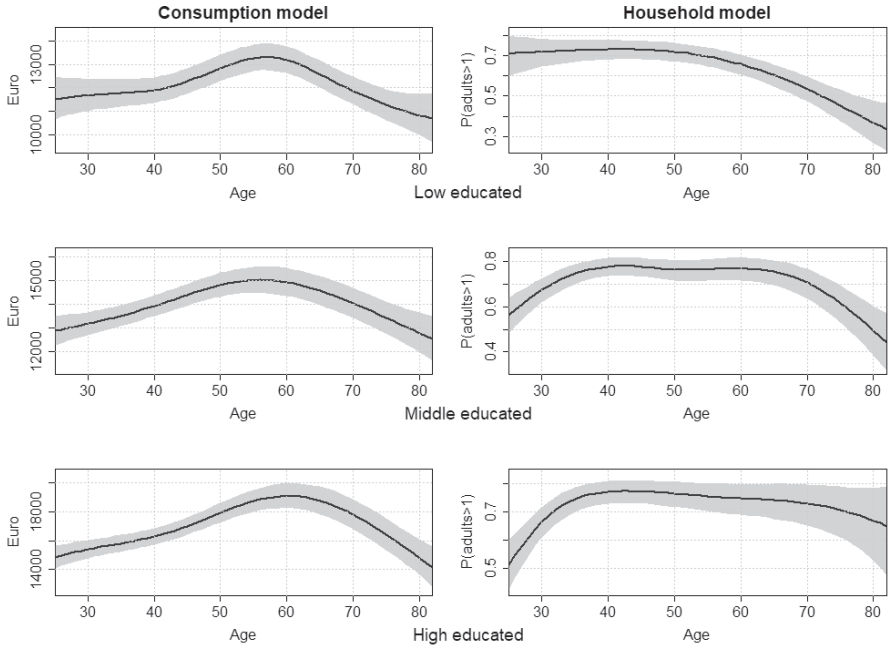


*Figure S1: Consumption model predictions (left) by education and age, and household model predictions by education and age (right) including 95% prediction intervals.*

# CHAPTER 7

## Don't Forget About the Future: The Impact of Including Future Costs on the Cost-Effectiveness of Adult Pneumococcal Conjugate Vaccination with PCV13 in the Netherlands

## Abstract

When vaccines increase longevity, vaccinated people may experience costs and benefits during added life-years. These future benefits and costs may include increased productivity as well as medical and non-medical costs. Such impacts should be considered in cost-effectiveness analyses (CEA) of vaccines but are often omitted. Here, we illustrate the impact of including future costs on the cost-effectiveness of vaccination against pneumococcus disease. We emphasize the relevance of differentiating cost estimates between risk groups. We updated an existing Dutch CEA of vaccination against pneumococcus disease with the 13-valent pneumococcal conjugate vaccine (PCV13) to include all future medical and non-medical costs. We linked costs by age and risk with survival information and estimates of cases prevented per vaccination strategy based on the original study to calculate the impact of inclusion. Future medical costs were adjusted for relevant risk groups. For the base-case strategy, the original incremental cost-effectiveness ratio (ICER) of PVC13 was €9,157 per quality adjusted life-year (QALY). Including all future medical costs increased the ICER to €28,540 per QALY. Also including future non-medical costs resulted in an ICER of €45,691 per QALY. The impact of future medical costs varied considerably per risk group and generally increased with age. This study showed a substantial effect of the inclusion of future costs on the ICER of vaccinating with PCV13. Especially when lives of people with underlying health conditions are extended, the impact of future medical costs is large. This inclusion may make vaccination a less attractive option, especially in relation to low thresholds as often applied for prevention. Although this raises important questions, ignoring these real future costs may lead to an inefficient use of healthcare resources. Our results may imply that prices for some vaccines need to be lowered to be cost-effective.

## Background

Vaccination has greatly reduced the burden of infectious diseases around the world (Andre et al., 2008). The effectiveness and cost-effectiveness of vaccination strategies in preventing both fatal and non-fatal cases typically vary with age and by risk. Given that there are limited resources available for healthcare, it is vital to identify the most efficient strategies and to evaluate whether these interventions provide value for money. For this, cost-effectiveness analyses (CEA) are generally performed, in which the costs and benefits of an intervention are assessed in relation to a relevant alternative (like standard care or another intervention or strategy) (Drummond et al., 2015). The health benefits are typically quantified in quality adjusted life-years (QALYs) and the results summarized in an incremental cost-effectiveness ratio (ICER), the ratio of additional costs to additional benefits (Drummond et al., 2015). The cost-effectiveness of an intervention can then be evaluated by comparing the ICER to a predefined cost-effectiveness threshold (Brouwer et al., 2019). Sound CEA should consider all relevant costs and benefits of interventions, while aligning with the perspective prescribed by the decision maker. For instance, when a healthcare perspective is applied, all costs and benefits within the healthcare system should be considered, whereas for a broader societal perspective all costs and benefits for society are relevant (Drummond et al., 2015).

Some aspects of vaccinations, like externalities (i.e., effects on third parties) including improved herd immunity, are not often observed with other types of interventions yet particularly relevant in the context of CEA (Mauskopf et al., 2018). Since vaccination is often aimed at preventing potentially fatal diseases, future costs, costs that arise in the life-years gained from an intervention, are also specifically relevant for vaccination. When vaccination successfully prevents a fatal case, the survivor will most likely consume healthcare and other goods and services in added life-years, which constitute costs that should be included in a CEA framework (Meltzer, 1997a). The survivor might also work during these added years, a benefit that lowers the net costs of consumption. Part of the healthcare costs in life-years gained flows directly from the intervention (so-called *related* medical costs). An example are the costs for booster vaccination in life-years gained from vaccination. The other part only indirectly flows from the intervention through the extension of life (so-called *unrelated* medical costs (UMC)). As an example, a survivor could need treatment for diabetes or dementia developed during life-years gained. An example of future non-medical consumption (NMC) are the costs for housing in added years to live.

Whether and to what extent future costs should be considered in CEA has been frequently debated (Rappange et al., 2008; de Vries et al., 2018). It was shown, using theoretical models, that including all future medical costs would be required for optimal decisions from a healthcare perspective (van Baal et al., 2016). From a broad societal perspective, the analysis should include future medical as well as non-medical consumption and

productivity costs (Meltzer, 1997b). Nevertheless, practical and theoretical concerns have been used as justifications for not including all future costs in practice (e.g., these costs would be difficult to estimate and it is unclear which costs should be included given that not all non-medical benefits are captured in the QALY) (de Vries et al., 2018). Future related medical costs are generally included in CEA. This, in contrast to future UMC, the inclusion of which is only required in the Netherlands (from 2016) (Zorginstituut Nederland, 2016) and was recently recommended in the US (Sanders et al., 2016). The inclusion of all future non-medical costs, defined as NMC minus productivity costs, is currently only recommended in the US (Sanders et al., 2016).

The impact of including future costs on the ICER, both in absolute numbers and in terms of the relative cost-effectiveness of interventions, depends on several factors. Healthcare expenditures and the impact thereof generally rise with age, partly due to higher costs in the last phase of life ('costs of dying') (Wong et al., 2011b), and NMC and productivity are typically higher in middle ages (Alessie and Ree, 2009), (Hammer et al., 2015). Healthcare costs are also generally higher for people with underlying health conditions for which medical treatment is needed (van Baal et al., 2013a), who are typically also at higher risk of infection and more likely to die from infectious diseases. Simultaneously, differentiation between risk groups generates differences in the impact of future costs through differences in factors such as quality and length of life, which are typically lower for people at higher risk. In general, the impact of inclusion is larger when quality of life in added life-years is lower (lowering the denominator of the ICER) and when interventions are mainly life-extending compared to quality improving.

Although the empirical literature on the impact of including additional future costs in CEA is growing (e.g., (Ratushnyak et al., 2019), (Perry-Duxbury et al., 2020), (Kellerborg et al., 2020)), there is little evidence of the impact of inclusion for different types of interventions and for different sub-groups in a population. To illustrate the relevance and impact of including future costs when evaluating the cost-effectiveness of vaccination, we update a previous Dutch CEA of vaccination of different risk-groups against pneumococcus disease with the 13-valent pneumococcal conjugate vaccine (PCV13) compared to no vaccination (Mangen et al., 2015) by including all future costs. Streptococcus pneumoniae, or pneumococcus, is a preeminent cause of morbidity and mortality with highest rates of infection in individuals with immunocompromised conditions, infants and the elderly (van Hoek et al., 2012). With different vaccination strategies considering several age cohorts and health-based risk groups and a large share of QALYs gained from prevented fatal cases, this study is a suitable illustration of how to adjust UMC based on risk groups and the impact of inclusion for vaccination in general. We also consider the relevant cost-effectiveness thresholds for the different strategies, which are important to evaluate the eventual impact of inclusion on decision making.

## Methods

To evaluate the impact of including more future costs in CEA on the cost-effectiveness of the different strategies for PCV13, we compare results from the CEA with and without these costs. More specific, we compare the ICERs including only related medical costs and productivity costs from the original study with the 'total ICERs' including all future costs. The original CEA estimated costs and benefits of PVC13 compared to no vaccination. The calculation of costs and benefits, including future costs, is shown in equation 1 (notations for age and risk-group are left out):

$$Total\ ICER = \frac{\Delta\,[LY\ \times (RMC + PC)]}{\Delta\ QALY} + \frac{\Delta LY\ \times UMC}{\Delta\ QALY} + \frac{\Delta LY\ \times\ NMC}{\Delta\ QALY} \qquad \text{(eq. 1)}$$

Original ICER Impact. UMC Impact NMC

The first part of the equation shows the ICER including only related medical costs (RMC) and productivity costs (PC), which entails the incremental RMC and PC for PCV13 versus no vaccination in all life-years (LY), divided by QALYs gained from PCV13 versus no vaccination. We obtained these from the original study and adjusted these to 2017 prices using consumer price indices from Statistics Netherlands (Central Bureau for Statistics, n.d.) to align with cost estimates. The second and third parts of the equation represent the impact of including UMC and NMC on the ICER respectively, which entail life-years gained (LYG) multiplied with UMC and NMC in those years divided by QALYs gained.

To estimate the impact of inclusion for the different vaccination strategies, we first estimated the impact of including UMC and NMC for preventing a fatal case at different ages for the different risk-groups. For this, we multiplied remaining life-years based on the survival curves for the different risk-groups with costs and QALYs in these added life-years. All costs were discounted at 4% per year and all benefits at 1.5% per year, in adherence with Dutch guidelines (Dutch National Healthcare Institute, 2016). We combined these estimates and the QALYs gained from preventing non-fatal cases with cases prevented over time by age- and risk-group. Detailed information on cases prevented could not be obtained directly from the original study. For that purpose, we constructed a simplified replication of the original model in which we followed the risk groups (low- medium- and high-risk) within five age cohorts (18–49, 50–64, 65–74, 75–84 and ≥85 years) during the first 15 years after vaccination (vaccine efficacy was limited to those years). For detailed information on the input parameters we refer to the original study (Mangen et al., 2015).

We deviated from the original model in a few ways. First, we only followed the population for the first 15 years after vaccination as opposed to following the cohorts until death or the age of 100 directly as for the original study. Instead, to obtain estimates of costs and QALYs for prevented fatal cases, we combined the numbers of prevented fatal cases with estimates of costs and QALYs gained for preventing fatal cases. We further assumed no transition to higher risk-groups, which was considered in the original model, since we could not obtain information on the approach and assumptions underlying this transition besides that this could only occur in one direction. Consequently, our estimates of cases and QALY losses prevented differed somewhat from the original study. However, for the estimation of the impact of including UMC and NMC on the ICER differences in absolute numbers are less relevant since our main interest is in the ratio of additional costs per QALY gained.

### *Estimating costs*

The costs that were used as input for the estimation of the impact described above were based on the estimates from the Practical Application to Include future Disease costs (PAID) 3.0 (Kellerborg et al., 2020). PAID provides age and gender specific estimates of average medical spending, which can be specified to exclude the costs of specific providers and diseases, and estimates of NMC by age. The estimates of UMC are based on per capita healthcare expenditures by disease and separated into costs for decedents and survivors using mortality information and ratios of spending in the last year to other years to account for the finding that healthcare expenditures are often higher in the last phase of life. NMC are estimated based on information from household expenditure surveys. Economies of scale within households were considered in these estimates as these have been found important when estimating NMC (Nelson, 1988). To do so, consumption for the average household was estimated using equivalence scales for the additional consumption of an additional individual in a household to obtain average per person consumption.

The estimates for NMC were used directly from PAID without further adjustments. Estimates of UMC were obtained from PAID after exclusion of costs related to the treatment (upper respiratory tract infections) to prevent double counting (as related medical costs are already included in the original study). PAID estimates of UMC, based on per capita estimates of yearly spending on healthcare, can safely be used when the study population is comparable to the general population regarding their healthcare expenditures. In the current study, however, several risk-groups were identified based on their current health: (1) those at high-risk, including individuals with an immunocompromising condition; (2) those at medium-risk, including immunocompetent patients with chronic medical conditions; and (3) those at low-risk, including the remainder of the population. The different risk-groups include people that have already other diseases or worse health conditions than the general

population. It is therefore expected that their (unrelated) medical costs are higher than those of the general population, as the costs for the diseases in these risk groups will by definition be incurred by the people in these risk groups. We adjusted PAID estimates for this by transforming the per capita costs per disease to per patient costs for those diseases that only occur in higher risk-groups. We do this by dividing per capita costs for survivors and decedents for the diseases in the risk group by the incidence of that risk group, while taking into account how mortality for the risk group is different from that of the general population. In section 6.1 in the appendix we explain in more detail how we derive per patient estimates.

We used averages of costs for males and females for the adjustment since no specific information was available on how men and women were distributed among the diseases. In some cases, the disease categories distinguished in PAID (which are the same disease categories as those in the Costs of Illness study) did not exactly match those of the categories distinguished in the construction of risk-groups. For those we matched the ICD-10 codes of the disease categories to the closest matching PAID category. The results from the matching procedure can be found in Table A.1 in section 6.2 in the appendix.

### *Cost-effectiveness thresholds*



In the Netherlands, vaccinations in the National Immunisation Programme are typically evaluated by the Dutch Health Council. Indicated prevention, aimed at people already ill or at higher risk of becoming ill, is generally evaluated by the Dutch National Health Care Institute for provision through the standard healthcare benefit package (Zwaap et al., 2015). Separate advices or collaboration between these institutes is sometimes preferred when both national and indicated prevention are considered, as earlier for PCV13 (PCV13 could then not qualify as indicated prevention due to insufficient evidence on its effectiveness in high-risk groups) (Dutch Health Council and Dutch National Healthcare Institute, 2018). These organizations have different approaches regarding cost-effectiveness thresholds, which we both consider since ICERs for both general strategies and strategies only including higher risk groups are updated.

The Dutch Health Council typically applies a fixed threshold of €20,000 per QALY. Cost-effectiveness thresholds used in reimbursement decisions by the Dutch National Health Care Institute vary by severity of disease as based on the principle of proportional shortfall (Zwaap et al., 2015). Proportional shortfall generally reflects the (average) health lost in a population treated. The proportional shortfall is a ratio between the difference in remaining QALYs between an affected individual without the new treatment and population averages for individuals of the same age and gender (i.e. QALYs lost due to being affected), divided by the remaining QALYs of population averages for remaining QALYs of individuals of the same age and gender. For a

proportional shortfall within 0.1 and 0.4 (where one thus lost 10-40% of otherwise lived health), a threshold of €20,000 applies; within 0.41 and 0.7, a threshold of €50,000 applies, and within 0.71 and 1.0, a threshold of €80,000 per QALY applies. A proportional shortfall below 0.1 would be too low for the treatment to be eligible for reimbursement (Zwaap et al., 2015; Reckers-Droog et al., 2018).

The calculation of severity of illness is relatively complicated in prevention since effects are typically further in the future, more uncertain, and affect only a part of the treated population, leading to questions on what point of time should be measured (at vaccination or when the benefit occurs) and whether proportional shortfall should be measured in the population that gets the disease or in the entire vaccinated population (Stolk et al., 2004), (Dutch National Healthcare Institute, 2018). The current guide is to estimate proportional shortfall at the time of the intervention and for the share of those vaccinated who would get the disease (Dutch National Healthcare Institute, 2018). For estimating average proportional shortfall, we thus estimated the undiscounted quality-adjusted life-expectancy (QALE) at different ages for the full population and for those expected to fall ill without vaccination at time of vaccination, for all using the survival and utility information as used in the original study. We calculated average proportional shortfall rather than proportional shortfall for the average ages, since different vaccination strategies considered different risk-groups with different related QALE within these groups.

## Results

### *Cost estimates*

Table 1 shows the estimates of UMC and NMC for the different risk-groups for each first age in a cohort. Estimates are provided for UMC in the last year, other years, and on average (average of decedent and survivor costs, considering mortality). The cost adjustments for risk show large differences between costs for the different risk groups. At age 18, the average UMC for the high-risk group are almost 4 times the costs for the medium-risk group and 15 times the costs for the low-risk group. UMC for the medium-risk group are then almost 4 times the costs for the low-risk group (high-risk €32,010; medium-risk €8.592; low-risk €2,181). The differences in costs between risk groups gradually decline with age. The costs for the high-risk group eventually become smaller than those for the medium-risk group. At age 85, the ratio of costs of medium to high is 1.1. The ratio of high to low is then 1.4 and of medium to low is then 1.6 (high-risk €25,276; medium-risk €28,250; low-risk €17,581). Overall, these results show increasing healthcare expenditures by age, except for the high-risk group, where average and survivor costs in lower and highest ages are highest. Decedents costs in the high-risk group show a hump-shaped pattern, for which an important factor is the large share of costs for treating lymph and blood cancers for this risk-group, for which

per capita costs for decedents increase until approximately age 60 and then decrease. The estimates of the different costs by age and risk-group show a hump-shaped pattern in NMC, indicating highest NMC in middle ages.

**Table 1**: Unrelated medical costs (UMC) for decedents, survivors, and on average; and non-medical consumption (NMC) (all in €), by risk group and for first age in cohorts.

| | | **Age** | | | | |
|---|---|---|---|---|---|---|
| Cost category | Risk group | 18 | 50 | 65 | 75 | 85 |
| UMC decedents | Low | 8,736 | 23,399 | 29,422 | 32,906 | 42,170 |
| | Medium | 28,938 | 31,917 | 41,020 | 44,048 | 59,547 |
| | High | 85,770 | 128,203 | 174,370 | 106,932 | 72,876 |
| UMC survivors | Low | 2,180 | 2,941 | 4,054 | 6,475 | 15,050 |
| | Medium | 8,576 | 6,071 | 7,438 | 10,810 | 23,779 |
| | High | 31,711 | 18,232 | 13,264 | 12,877 | 20,536 |
| UMC average | Low | 2.181 | 2,997 | 4,343 | 7,233 | 17,581 |
| | Medium | 8.592 | 6,262 | 8,126 | 12,423 | 28,250 |
| | High | 32,010 | 20,543 | 17,424 | 16,629 | 25,276 |
| NMC | All | 19,337 | 22,279 | 22,019 | 20,274 | 18,801 |



### *Impact future costs on ICERs for preventing fatal cases*

Figure 1 shows the impact of the inclusion of future UMC and NMC on the ICER for preventing fatal cases at different ages and for different risk groups. The impact of including UMC is relatively stable up until the age of 60 for all risk groups, where after it grows rapidly. Up until the age of 60, the impact of inclusion of UMC for the high-risk group is relatively large in comparison to both the low- and medium-risk group. Thereafter, the impact for the medium-risk group grows more rapidly than the impact for the high-risk group, and the impact for the medium-risk-group is larger than for the high-risk group from around age 80. The impact of including NMC is relatively stable and changes little in the relative impact of including future costs on the ICERs for the different risk groups. Including NMC mainly results in an upward shift of the curves. In Figure A.1 in section 6.3 in the appendix an additional graph is shown only including UMC.

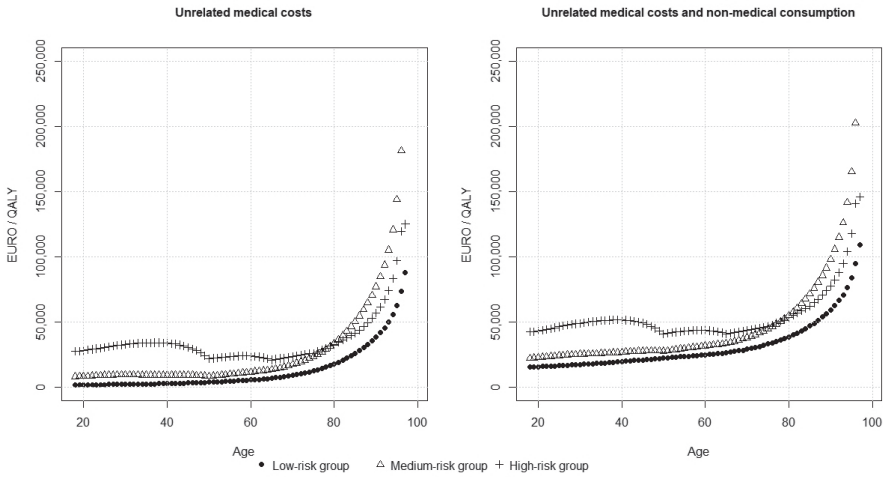


*Figure 1: Impact future unrelated medical costs and non-medical consumption on ICER for saving a life by age and risk group*

### *Impact future costs on cost-effectiveness vaccination strategies*

The first columns in Table 2 display the impact of the inclusion of future UMC and NMC on the ICER for the different vaccination strategies. For the base-case strategy (the full 65-74 cohort), the impact of UMC and NMC was €19,383 and €17,151, respectively. The middle columns in Table 2 show the original ICER and the ICERs after including the different types of future costs. For the base-case strategy, the ICER before inclusion (adjusted to 2017 prices) was €9,157. After including UMC, the ICER was €28,540 and after including both UMC and NMC, the ICER was €45,691. These columns also show the relative ranking of vaccination strategies before and after including future costs in terms of cost-effectiveness. Most notable difference in the ranking before and after inclusion is for the strategy including those at medium risk in the 65-74 cohort. This strategy is the 5$^{th}$ most cost-effective before and the most cost-effective after the inclusion of future UMC. Also including future NMC to the ICERs had little additional impact on the ranking.

The last column in Table 2 shows the cost-effectiveness thresholds based on the average proportional shortfall in the vaccination strategies. According to this, the €20,000 threshold would apply for all but the strategy including those at low risk in the 65-74 cohort. For that strategy, the proportional shortfall would be too low for the strategy to be eligible for reimbursement. For the strategies considered in this study there would thus be no difference between the threshold to apply for national prevention (fixed at €20,000) and for indicated prevention which would only include higher risk groups. The relatively small differences between the proportional shortfall in the strategies

with high- and/or medium-risk groups can be explained from the similar utility values that are used in the different risk groups. Would lower utility values have been used for higher risk groups, the proportional shortfall might have been higher which could have resulted in higher relevant thresholds.

**Table 2:** Impact future costs on the ICER, ICER before and after inclusion, and cost-effectiveness threshold based on proportional shortfall for different vaccination strategies (all in €)

| UMC | | Impact | | ICERs (ranking[a]) | | | Thresholds (proportional shortfall)[c] |
|---|---|---|---|---|---|---|---|
| | | NMC | Original[b] | Original + UMC | Original + UMC + NMC | | |
| Vaccination strategy | 65-74-all (base-case) | 19,383 | 17,151 | 9,157 (8) | 28,540 (7) | 45,691 (7) | 20,000 (0.15) |
| | 65-74-low | 7,519 | 13,347 | 53,142 (12) | 60,660 (12) | 74,008 (12) | 0 (0.02) |
| | 65-74-medium | 17,324 | 16,939 | 3,041 (5) | 20,365 (1) | 37,304 (1) | 20,000 (0.20) |
| | 65-74-high | 22,716 | 17,814 | -1,612 (1) | 21,104 (2) | 38,917 (3) | 20,000 (0.19) |
| | 65-74-at risk | 20,155 | 17,398 | 1,175 (2) | 21,331 (3) | 38,729 (2) | 20,000 (0.20) |
| | 65plus-at risk | 24,035 | 17,445 | 4,835 (6) | 28,870 (8) | 46,314 (8) | 20,000 (0.17) |
| | 65plus-all | 23,159 | 17,222 | 13,684 (10) | 36,842 (11) | 54,064 (11) | 20,000 (0.14) |
| | 50plus-at risk | 20,665 | 17,111 | 2,778 (4) | 23,442 (5) | 40,554 (5) | 20,000 (0.18) |
| | 50plus-all | 19,422 | 16,828 | 13,732 (11) | 33,154 (10) | 49,982 (10) | 20,000 (0.13) |
| | 18plus-at risk | 19,921 | 16,658 | 2,429 (3) | 22,350 (4) | 39,008 (4) | 20,000 (0.18) |
| | 65plus-all & 18-64-at risk | 19,594 | 16,564 | 7,968 (7) | 27,562 (6) | 44,126 (6) | 20,000 (0.14) |
| | 50plus-all & 18-49-at risk | 18,922 | 16,455 | 12,406 (9) | 31,328 (9) | 47,783 (9) | 20,000 (0.14) |

[a] Ranking of ICERs based on cost-effectiveness
[b] ICER from the original study adjusted to 2017 prices
[c] Proportional shortfall and corresponding threshold (0 for 0-0.09; 20,000 for 0.1-0.4; 50,000 for 0.41-0.7; 80,000 for >0.7)

In Table A.2 in section 6.3 in the appendix we also provide the impact of including UMC and NMC and the thresholds based on proportional shortfall for the different risk groups and age cohorts (compared to Table 2 with the information per *vaccination strategy*). Comparing this to Table 2, it clearly shows that the impact of the higher risk groups is limited by the smaller relative share of these groups within the strategies.

## Discussion and conclusion

Saving lives by preventing illnesses may lead to costs and benefits in added life-years from medical and non-medical consumption and increased productivity. This study showed that the additional medical and non-medical costs in the context of vaccination can be substantial, especially for people at higher risk of infection due to underlying health conditions for which medical treatment is needed. Considering these costs in CEA can lead to interventions no longer being cost-effective when judged against a relevant threshold. This threshold is typically relatively low in the Netherlands for national prevention, but also for indicated prevention when based on average severity of illness. While a higher threshold may apply for risk groups with a higher severity of illness, this could be offset by the related higher healthcare costs and lower quality of life in those groups. Hence, inclusion of future costs may also then indicate that these interventions are not cost-effective.

An important strength of this study is that we adjusted UMC based on the underlying health conditions for those at higher risk of infection. As the costs related to those conditions will be incurred only by those suffering from these conditions, this approach provides more realistic estimates of UMC for the different risk groups. In comparable research, typically the average per capita healthcare expenditures are used (e.g., (Ratushnyak et al., 2019; Meltzer et al., 2000c; Kruse et al., 2012)). We further discuss the impact of inclusion in relation to the relevant cost-effectiveness thresholds. While highlighting the impact on the ICER of including future UMC and NMC is already important, the potential effects of inclusion on final (reimbursement) decisions is also crucial, which in part depends on the thresholds applied in the decision-making process.

A limitation of our study is that we did not have access to the original models. We therefore estimated how QALYs gained would be distributed over time using a simplified replication of the original model based on the information provided in the original paper. This resulted in somewhat different numbers of total cases and QALYs gained for the different vaccination strategies, partly due to missing information on the transition to higher risk-groups. Although using the original models may change our results somewhat, it is not expected this would substantially affect our conclusions. Indeed, the costs for saving a life in the different age and risk groups already highlighted the large impact inclusion can have on results.

Another limitation is related to the prevalence for the risk groups in the original study, which was determined by age- and risk. When adjusting UMC from per capita to per patient costs, this led to discontinuities in costs by age around the bounds of the age-groups. A more gradual change in prevalence would have enabled more accurate estimates of per patient costs. However, given the information available, these per patient costs are presumably more accurate for these risk-groups than per capita estimates, given that the diseases for which those costs arise occur per definition within these risk-groups.

Further, the utility estimates in the original study were based on age-specific estimates in the general Dutch population, resulting in relatively high utility scores for all risk-groups. Since the people in higher risk-groups suffer from one or several medical conditions, it is likely that their quality of life is lower than for those in lower risk-groups. Lowering the denominator of the ICER, these QALY differences would (further) increase the differences in impact of including more future costs on the ICER between lower and higher risk groups. Different utility values for different risk groups also directly affect the severity of illness (expressed as proportional shortfall) calculations and might also affect the relevant thresholds when this approach would be followed.

Finally, we used point estimates from the original study in our analysis as no detailed information on distributions was available. Future research ideally would also consider uncertainty around the estimates for a more comprehensive analysis.  Finally

The results of this study have important implications for the CEA of vaccination. First, we demonstrated that obtaining risk group specific estimates of future costs is feasible. This study could be used as an aid for that purpose next to the practical guidance provided with PAID 3.0 (Kellerborg et al., 2020). Furthermore, as it was shown that the impact of future costs for vaccination strategies can be substantial, these costs cannot be simply ignored (even if inclusion poses important normative questions). This study showed that differences in the impact between risk groups can be large and considering these differences is important for studies where strategies are designed that include different risk groups based on their current health.



The potential of the inclusion of future costs to affect reimbursement decisions may have distributional consequences, not only across interventions, but also within. For instance, it could be that vaccination of people in the high-risk groups will not be cost-effective, while vaccination of people in lower risk groups is. This may result in and increase existing health inequalities. These results may reinforce ethical concerns related to the inclusion of future costs (and indeed other costs). One could argue that when including future costs, some people might no longer be eligible for treatment, which may be considered undesirable. Such concerns clearly need to be addressed. However, ignoring real costs may be considered an inappropriate strategy in dealing with these issues. Not only because this would ultimately harm other groups in society, but because ignoring costs would not even allow assessment of the extent to which this would be the case. Ignoring these costs would moreover endanger the quality and usefulness of CEA. Ethical concerns would preferably be explicitly incorporated in the evaluation and decision-making process (de Vries et al., 2018). For instance, if deemed appropriate, higher thresholds could be used for prevention or for specific high-risk groups when this accurately represents societal preferences and policy purposes.

Although including future costs may result in ICERs above the relevant threshold, this represents the relevant estimate of costs and effects of the intervention. Not including these costs does not mean they will not occur. Moreover, the ICER can be influenced by altering the price of the vaccine. As an example, the original study showed that lowering the price of the vaccination would make the base-case strategy cost-saving and cost-effective judged by the €20,000 threshold, also after including future UMC. Further price reductions would be required for the strategy to be cost-effective when including both future UMC and NMC. In that context patent status is also important, as average drug prices often drop after its expiration (Vondeling et al., 2018) (note that the patent of the studied vaccine has not yet expired (European Patent Office, n.d.)).

This study left several questions for further research. First, while we adjusted UMC for the different risk groups based on underlying health conditions in our study, we did not adjust NMC. However, it is not unlikely that illness also affects NMC to some extent (Finkelstein et al., 2013). As existing research reported different findings for the health state dependency of NMC, future research should further explore the impact of potential differences.

In our study, we further did not focus on future productivity costs as these were already included in the original analysis. These were estimated using the friction costs method (limiting added productivity to the friction period which is the period required to replace an absent worker) and could reach a maximum of €13,460 for persons between 15-49 and €15,605 for persons between 50-64. Previous studies, using the human capital method (not considering the possibility of replacement and counting all added productivity during the remaining lifetime) have shown that including future productivity costs could result in a lower ICER after including future costs for relatively young adults (during working ages) (e.g., (Meltzer et al., 2000c; Kruse et al., 2012)). Future research could investigate the differences between existing approaches to estimate productivity costs in the context of preventing mortality.

Finally, although this was not the focus of this paper, we want to note the ongoing discussion on what costs should be considered in CEA. The issue currently under debate is whether the benefits of future non-medical costs are fully captured in the QALY, and, if this is not the case, what this implies for including future non-medical costs (de Vries et al., 2018). It has been argued that, when benefits from NMC and losses from less leisure due to additional productivity in terms of utility are not fully captured in the QALY, the costs thereof should not be considered either (Nyman, 2004b). It is also unclear to what extent thresholds to which ICERs are compared include these benefits (de Vries et al., 2018). Further research into these issues is therefore recommended.

To conclude, in this paper we estimated the impact of including future UMC and NMC in the CEA of vaccination with PCV13 against pneumococcus disease. It was shown that the inclusion of these costs has a substantial effect on the ICER, especially when

people at higher risk with underlying health conditions are saved. Given this impact, interventions that were first projected to be cost-saving, were shown to be cost-ineffective after inclusion, when judged against relevant thresholds. Although this indicates the need to consider ethical considerations regarding how to deal with such situations, especially when they could exacerbate health inequalities, ignoring these real medical and societal costs does not solve the underlying issue and is not in line with optimizing outcomes with limited resources.

## Supplemental Material

*Per capita costs to per patient costs*

To consider different future unrelated medical costs (UMC) for the people in different risk groups, we needed to transform the per capita estimates from PAID 3.0 to per patient estimates for the costs for diseases indicating increased risk of pneumococcus infection. More specific, average costs as the division of healthcare costs for the entire population by the number of people in the population (per capita/unconditional) needed to be transformed into average costs as the division of total healthcare costs for the diseases by the number of patients suffering from the disease (per patient/ conditional). Equation A.1 shows this relation by presenting total healthcare expenditures for disease i at age a ($hce_i(a)$) as average costs for disease i at age a, conditional on having disease i (, multiplied by the number of patients having the disease at age a and as average costs for disease i at age a, multiplied by the entire population at age a.

$$total\ hce_i(a) = ac_i(a|i) * patients_i(a) = ac_i(a) * population(a) \quad \text{(eq.A.1)}$$

By writing patients/population as the prevalence (p), this can be rewritten into equation A.2, which shows average conditional costs as average unconditional costs for disease i at age a divided by the prevalence of disease i at age a.

$$ac_i(a|i) = \frac{ac_i(a)}{p_i(a)} \quad \text{(eq.A.2)}$$

Knowing both the prevalence of the diseases (from the percentages of the population in the risk groups) and per capita average costs (from PAID), we can derive average per patient costs for the diseases in the risk groups. However, PAID provides estimates not of average costs at age a, but as costs for decedents (dc) and survivors (sc), based on mortality. The relation between average costs and decedent and survivor costs is shown in equation A.3. for per capita costs and in equation A.4 for per patient costs.

$$ac_i(a) = [1 - m(a)] \times sc_i(a) + m(a) \times dc_i(a) \quad \text{(eq.A.3)}$$

$$ac_i(a|i) = [1 - m(a|i)] \times sc_i(a|i) + m(a|i) \times dc_i(a|i) \quad \text{(eq.A.4)}$$

Equation A.5 and A.6 show how we obtained age and disease specific per patient costs for decedents and survivors, based on the relations described in equation A.2, A.3, and A.4. For this, we used the survival information for the specific risk groups as used in the original study and the population mortality from Statistics Netherlands as used in PAID.

$$m(a) \times dc_i\,(a) = dc_i\,(a|i) \times p_i \times m(a|i) \qquad \text{(eq. A.5)}$$

=>

$$dc_i\,(a|i) = \frac{m(a)\ \times dc_i}{p_i(a) \times m(a|i)} = \frac{dc_i(a)}{p_i(a) \times \frac{m(a|i)}{m(a)}}$$

$$(1 - m(a)) \times sc_i\,(a) = sc_i\,(a|i) \times p_i \times (1 - m(a|i)) \qquad \text{(eq. A.6)}$$

=>

$$sc_i\,(a|i) = \frac{(1 - m(a))\ \times sc_i}{p_i(a) \times (1 - m(a|i))} = \frac{sc_i(a)}{p_i(a) \times \frac{(1 - m(a|i))}{(1 - m(a))}}$$

## *Matching ICD codes*

**Table A.1**: Matched diseases and ICD-10 codes from different sources

| Risk group | Condition original study | UK study | ICD-10 | PAID |
|---|---|---|---|---|
| Medium | Alcoholism | Not included | | Drug and Alcohol Dependence |
| | Cerebrospinal fluid leaks | Individuals with cerebrospinal fluid leaks | G96.0 | Other diseases of the nervous system and sense organs |
| | Chronic cardiovascular disease | Chronic heart disease | I05,I06,I07,I08,I09,I11,I12,I13, I20,I21,I22,I25,I27,I28,I3,I40,I 41,I42,I43,I44,I45,I47,I48,I49, I50,I51,I52,Q2 | Hypertension; coronary heart disease; heart failure, other heart disease, including pulmonary circulation; congenital anomalies of nervous system |
| | Chronic pulmonary disease | Chronic respiratory disease | J40,J41,J42,J43,J44,J47,J6,-J7,J80,J81,J82,J83,J84,Q30,-J31,Q32,Q33Q34,Q35,Q36,Q37 | Asthma and chronic obstructive pulmonary disease (COPD); other respiratory diseases; other congenital anomalies, excluding Down's syndrome |
| | DM with insulin DM | Diabetes | E10,E11,E12,E13,E14,E24,G59 .0,G63.2,G73.0,G99.0,N08.3 ,O24, P70.0,P70.1,P70.2 | Diabetes mellitus including diabetic complications; other endocrine, nutritional and metabolic diseases; other diseases of the nervous system and sense organs; pregnancy; other conditions originating in the perinatal period |
| | DM without insulin | Diabetes | E10,E11,E12,E13,E14,E24,G59 .0,G63.2,G73.0,G99.0,N08.3 ,O24, P70.0,P70.1,P70.2 | Diabetes mellitus including diabetic complications; other endocrine, nutritional and metabolic diseases; other diseases of the nervous system and sense organs; pregnancy; other conditions originating in the perinatal period |

| Risk group | Condition original study | UK study | ICD-10 | PAID |
|---|---|---|---|---|
| High | AIDS | not included | B20,B21,B22,B23,B24 | HIV/AIDS |
| | Functional or anatomic asplenia | Asplenia or dysfunction of the spleen | D73,D56.1,D57.8,D57.0,D57.1,K90.0 | Diseases of the blood and blood-forming organs; other diseases of the digestive system |
| | Chronic liver disease | Chronic liver disease | K70,K71,K72,K73,K74,K75,K76,K77,P78.8,Q44 | Chronic liver disease and cirrhosis; other liver diseases; other conditions originating in the perinatal period |
| | Chronic renal failure | Chronic kidney disease | N00,N01,N02,N03,N04,N05,N07,N08,N11,N12,N14,N15,N16,N18,N19,N25,Q60,Q61 | Nephritis and nephropathy; acute renal and urinary infections; other renal and urinary diseases; other congenital anomalies, excluding Down's syndrome |
| | Malignancy | Malignancies affecting the immune system: | C81,C82,C83,C84,C85,C88,C90,C91,C92,C93,C94, C95,C96 | Other lymphoid cancer and leukemia; non-Hodgkin's disease |
| | Bronchial obstruction due to primary lung cancer | | C34 | Lung cancer |
| | Hodgkin | | C81.90 | Other lymphoid cancer and leukemia |
| | Human immunodeficiency virus infection | | B20,B21,B22,B23,B24 | HIV/AIDS |
| | Leukemia | Malignancies affecting the immune system: | C81,C82,C83,C84,C85,C88,C90,C91,C92,C93,C94, C95,C96 | Other lymphoid cancer and leukemia; non-Hodgkin's disease |
| | Lymphoma | Malignancies affecting the immune system: | C81,C82,C83,C84,C85,C88,C90,C91,C92,C93,C94, C95,C96 | Other lymphoid cancer and leukemia; non-Hodgkin's disease |
| | Multiple myeloma | | C90 | Other lymphoid cancer and leukemia |
| | Receipt of immunosuppressive therapy | Conditions affecting the immune system: | D56.1,D57.8,D57.0,D57.D61,D70,D71,D72,D73,D76,D80,D81, D82D 83,D84, 1,K90.0 | Diseases of the blood and blood-forming organs; other endocrine, nutritional and metabolic diseases; other diseases of the digestive system |
| | Receipt of an organ/ bone marrow transplant | Transplanta-tions: | Z94,Z85, (Bone marrow transplants: Z94.8) | Not allocated |

# CHAPTER 8

General discussion

Investments aimed at preventing infectious diseases, or at mitigating their consequences, occur both within and outside the healthcare sector. Moreover, (preventing) infectious diseases can have consequences within and outside the health care sector as well as in both the short and the long run. Therefore, when evaluating the costs and benefits of interventions aimed at preventing or treating infectious diseases adopting a societal perspective is warranted. The COVID-19 outbreak and the measures taken to counter it may exemplify this. This dissertation aimed to apply the societal perspective in economic evaluations within the field of infectious diseases. First, the current practice of conducting economic evaluations of infectious diseases was explored. Then, some methodological challenges encountered when one aims to apply a societal perspective in practice were addressed. Finally, the consequences of the wider operationalization of the perspective on study results and related distributional issues were studied.

In this chapter, we present our main findings related to the research questions posed in the introduction and discuss the limitations and implications of our findings.

## Findings

### *Question 1: What is the current practice of inclusion of costs and benefits in economic evaluations of interventions aimed at infectious diseases?*

In chapter 2, we reviewed the literature to answer how the societal perspective is applied in cost-effectiveness analyses of interventions combatting and preventing pandemics. Here, we did not find a uniform approach to the operationalization of the societal perspective. The studies included in the review differed in the time horizon used, as well as the costs and benefits included. Although differences in national guidelines on economic evaluations might explain some of these differences, we also observed differences between studies conducted in the same country. Besides issues of standardization, the perspective was often operationalized in a way that was considered to be too narrow to capture all relevant costs and effects of an outbreak. This could lead to biased estimates of cost-effectiveness. Furthermore, the time horizon chosen was often too short to fully capture the full societal costs and effects of an intervention. Studies that used a longer time horizon did capture the future health gains of the interventions studied but did not balance these effects with the inclusion of future costs that would occur within the applied time horizon. When future costs were included, usually only production gains were included, while the costs of non-medical consumption were ignored. These results indicate that current economic evaluations may not capture all relevant societal costs and benefits, and therefore may misrepresent the desirability of policies aimed at preventing or mitigating outbreaks.

Using the common (incomplete) operationalization of the societal perspective and including only short-term medical costs and lifetime productivity gains, we conducted a cost-effectiveness study to explore the implications of that definition. In Chapter 3, we

therefore studied the timing of interventions against the West African Ebola outbreak. Here we found that the larger share of cost and effects were found in the long run from added life years and productivity gains. As these costs occur in the future they could only be captured within a broader definition of the societal perspective and would have been missed with a too narrow conceptualization and timeframe. This result was in line with the studies identified in the literature review. It also emphasized that using this incomplete operationalization of the societal perspective (i.e. only including future health and productivity gains), evaluations may misrepresent the actual cost-effectiveness of interventions and likely underestimate incremental cost-effectiveness ratios, especially of life-prolonging interventions.

### *Question 2: How can the current methods for the estimation and inclusion of broader costs in economic evaluations of infectious disease interventions be improved?*

The results from Chapter 2 suggested that the operationalization of the societal perspective in practice is often (too) narrow and does not account for costs and effects in the long term. This may be perceived as a shortcoming when trying to evaluate the full societal impact of an intervention since only a minority of the total costs occur in the short term. This latter point was confirmed in Chapter 3 where, using the example of interventions against the West African Ebola outbreak, we showed that the largest share of costs and effects are to be found in the longer term, i.e. in the added life-years resulting from an intervention. A common denominator of all studies included in the literature review was that they did not include future unrelated medical costs or the costs of non-medical consumption in life-years gained. However, these costs should be included if the aim underlying economic evaluations and subsequent decisions is to maximize social welfare (Meltzer, 1997a). Hence, decisions based on partial evidence can potentially lead to allocations not supporting the goal of maximizing welfare. We decided to add to the literature on the societal perspective by introducing practical methods that facilitate the inclusion of future costs in economic evaluations.



Within the broad category of future costs, the least studied cost category is the cost of non-medical consumption (de Vries et al., 2018). In Chapter 4, we borrowed methods from the economic literature on life-cycle consumption and estimated age-dependent costs of non-medical consumption adjusted for age-period-cohort effects (Alessie and Ree, 2009; Fernández-Villaverde and Krueger, 2007), and economies of scale related to consumption within households (Nelson, 1988). These effects have not previously been considered in estimates of these costs for use in economic evaluations. We found that in deriving these estimates, the role of cohort effects was limited while household economies of scale were quite influential. Previously published literature has disregarded the effect of household economies of scale and by doing so overestimated the impact of non-medical consumption on the ICER (Kruse et al., 2012; Manns et al.,

2003b; Meltzer, 1997a; Meltzer et al., 2000b). When estimating future non-medical costs we observed a clear age pattern where costs peaked at middle age and decreased at older age, which was also reported in previous studies (Alessie and Ree, 2009; Fernández-Villaverde and Krueger, 2007).

To facilitate the inclusion of future costs in practice, we updated existing tools aiming to standardize the inclusion of future costs in economic evaluations (van Baal et al., 2011c). Using recently published data, we produced ready-to-use Dutch estimates of future related and unrelated medical costs, adjusted for time to death which is of importance (Zweifel et al., 1999b), as well as estimates of non-medical consumption costs by age.

### *Question 3: What are the implications of broadening the perspective of economic evaluations of infectious disease interventions?*

We explored the implications of broadening the perspective in economic evaluations by assessing the consequences of including costs in life years gained. The exact size and direction of the impact on the ICER depend on the intervention studied, the type of costs included, as well as the population served with the intervention. Consequently, this can result in different reimbursement decisions being made. Although some interventions might be less cost-effective if future costs are included, other interventions will be relatively more cost-effective. On balance, decisions based on cost-effectiveness results including future costs will result in a higher level of social welfare (Meltzer, 1997a) which, ultimately, is the aim of applying the societal perspective in economic evaluations (Jönsson, 2009).

In Chapter 3 we found that as the interventions combating the Ebola outbreak would result in in life years gained at ages in which people are most productive including productivity gains would cause the interventions to even become cost saving. Here, it should be noted that we used the Human Capital approach which generally generates higher estimates of productivity gains than the Friction Cost Method (Krol et al., 2013; Pritchard and Sculpher, 2000). Including the costs of medical and non-medical consumption, in contrast, increased the estimated ICER as demonstrated in Chapters 4 to 7. In general, our results follow a pattern of increased ICERs by approximately €10,000 for the middle-aged and younger and approximately €20,000 for the older age groups. An important reason for this age pattern is that if life is extended at old age life years will generally be spent in a lower quality of life. We showed in Chapters 6 and 7 that this age effect is strengthened by the fact that costs of medical consumption increase strongly with age even if one accounts for the fact that most medical consumption is centered in the last phase of life. Furthermore, in Chapter 7 we showed that the impact of future medical costs on the ICER is much larger if life is extended in an already ill population. In Chapter 6, we investigated the impact

of including non-medical costs on the ICER across different socioeconomic groups. Although higher educated generally consume more they also enjoy a higher quality of life and are less often single at old age. On balance, these observations cause that the impact of including future non-medical costs is rather similar across different educational groups.

## Limitations

In each chapter of this thesis, we discussed the studies' individual limitations. In this section, we discuss the overall limitations of this thesis in relation to its overall aim. Many of the contributions included in this thesis have focused on the inclusion of future costs in economic evaluations which are of particular relevance when evaluating interventions aimed at preventing infectious diseases. However, we do note that these costs constitute only a part of the full societal impact of preventing infectious diseases and are only a small part of the full impact of a pandemic as has been illustrated by the Covid-19 pandemic. In itself this focus on particular aspects of economic evaluations can be seen as a limitation of this thesis. However, also specifically related to the topics addressed in the different chapters, several additional overarching limitations need to be discussed.

A first limitation concerns the generalizability of the presented results. Care must be taken when generalizing the results of Chapters 4, 5, and 6 since we only used Dutch data. Absolute values will often be difficult to translate to other settings, but trends may, arguably, be more generalizable to other (similar) countries and contexts. For instance, the age effect of consumption can be expected to be relatively similar in other high-income countries as previously has been indicated (Domeij and Johannesson, 2006; Fernández-Villaverde and Krueger, 2007). Similarly, the importance of household size when estimating non-medical consumption, which also has been observed previously and in other geographical settings (Nelson, 1988), is also likely to be relevant in other countries. In line with this, the methods we developed and employed could also be used to analyze data from other countries to produce comparable estimates. In a similar vein, the clustering of healthcare costs in the last phase of life is also well known internationally (Zweifel et al., 1999b). Notwithstanding this, other results presented in this thesis, such as the limited significance of elements such as educational attainment, may prove to be less transferable to other countries. This may, for instance, play a bigger role in countries with a system with less redistribution of wealth through taxes or subsidization of services and where the income inequality is larger.

Another limitation that needs to be highlighted relates to limitations of the data used in different chapters. In Chapter 3, we modeled the Ebola Virus disease epidemic using publicly available data on cases from the WHO weekly situation reports and gathered information regarding the available beds from various sources such as news

media, notification reports, and UN situation reports. The case data may be a source of uncertainty as these were collected during an intense epidemic in a country with an already strained healthcare system and limited monitoring capacity. Moreover, we had to make several strong assumptions to model the long-term costs and effects of preventing the spread of Ebola. In Chapters 4,5 and 6, we used a rich dataset spanning multiple years allowing us to adjust for potential biases such as age, cohort, and period effects when estimating non-medical consumption. However, our findings suggested that consumption has increased with time. In that context it is important to stress that the latest available data in our study was from 2005, which may have resulted in an underestimation of the current consumption levels even though we adjusted for increases in price levels. Moreover, the global economy has experienced two large recessions which may not only affect an otherwise monotonous positive trend but also have distributional consequences if socioeconomic groups were affected differently by the recessions. This is especially relevant for our findings in Chapter 5 with respect to the differences in consumption between educational groups.

While we have tried to explore the role of future costs in a broad sense, still we did not investigate all relevant aspects. Productivity costs are one of the aspects we did not explore in much detail but may, nonetheless, have a substantial impact on the ICER when including future costs. The estimation and inclusion of productivity costs in economic evaluation do however receive relatively much attention in the literature compared the types of future costs more prominently addressed in this thesis, and are also more commonly included in economic (de Vries et al., 2018; Krol et al., 2013). In Chapter 7 we updated a study that already included productivity costs estimated using the Friction Cost Method. The inclusion of future non-medical consumption resulted in an increase of the ICER, as the costs of non-medical consumption in life years gained were larger than the productivity gains for all age groups. It could be the case that if the human capital method was used to estimate production costs, this would not have been the case. Indeed, the human capital method usually results in much higher estimates of production gains than the friction cost method (as also was illustrated in Chapter 3).

## Implications

### *Research implications*

In this thesis, we have provided methods for estimating and including future costs in economic evaluations and explored some of the implications of including these costs. While our estimates of future medical costs build on a large empirical literature investigating the relation between age, health and health care use, this is not the case for our estimates of non-medical costs. The relation between health and non-medical consumption has remained relatively underexplored. Here, we see important areas for future research. First of all, there is a large literature on the relation between age, time

to death and health care use indicating that time to death is relevant when explaining health care use (Weaver et al., 2009; Werblow et al., 2007; Wong et al., 2011a; Zweifel et al., 1999b). It could be the case that in explaining non-medical consumption time to death could be a useful proxy for health as it has been argued that poor health might explain the decrease in non-medical consumption at old age (Finkelstein et al., 2013). More generally, the impact of health on non-medical consumption is relevant for economic evaluation. Until now, the debate regarding the inclusion of non-medical consumption costs has focused solely on these type of costs in added life years. What was not explored in this thesis, is the relationship between health state and non-medical consumption. This may be relevant for interventions that extend life but result in different levels of quality of life (Finkelstein et al., 2009; Gyrd-Hansen, 2016). Empirical studies on the impact of health on non-medical consumption have been inconclusive and the question whether non-medical consumption is positively or negatively associated with health remains to be answered (Finkelstein et al., 2009; Gyrd-Hansen, 2016).

The approach in this thesis has been more practical than theoretical. However, there are also theoretical issues that need that need to be addressed in relation to the inclusion of future costs. One of the arguments against including future non-medical costs is that the benefits of this consumption are not included in the QALY, as common instruments to measure health-related quality of life do not contain domains that (explicitly) deal with the benefits of consumption (Nyman, 2004a). In a response to this reasoning, Gandjour (Gandjour, 2006a), among others, argued that there is an implicit inclusion when valuing health states. Furthermore, it is hard to disagree with the fact that when life is prolonged also food needs to be consumed. Moreover, when valuing future health, people will (implicitly) assume a particular standard of living in terms of housing and social activities. The associated costs would then need to be captured as non-medical consumption. Nonetheless, it is important to acknowledge that is remains unclear at this stage whether the utility derived from non-medical consumption is adequately accounted for in economic evaluation. Studies aimed at investigating whether and to what extent the utility from non-medical consumption is included in health state valuations would be beneficial to this debate and could contribute to the further optimization of economic evaluation methodology.



### *Policy implications*

This thesis has contributed to removing practical barriers for including future costs in economic evaluations. The work that we have performed, can also further the debate about the inclusion of future costs. Even among the countries in which a societal perspective is recommended, currently few guidelines explicitly recommend the inclusion of future costs (de Vries et al., 2018). The second US Panel on Cost-Effectiveness in Health and Medicine in 2016 did recommend the inclusion of all future

costs, related and unrelated medical costs as well as future production and consumption (Sanders et al., 2016). Moreover, the Dutch guidelines changed in 2016 to prescribe the inclusion of a broader set of costs and the mandatory inclusion of future unrelated medical costs (Zorginstituut Nederland, 2016b). In contrast, the Swedish guidelines changed from inclusion of future costs to not prescribing mandatory inclusion of future costs (TLV, 2018). In the case of infectious diseases, recommendations regarding the type of models suitable to capture the transmission effects of the communicable nature of the diseases already exist (Pitman et al., 2012; Ultsch et al., 2016). However, when evaluating interventions targeted at infectious diseases costs and benefits can accumulate for a long period after the intervention and transmission phase if lives are saved (e.g. childhood vaccination programs). As these costs and benefits not only fall within the healthcare sector the need for a broad societal perspective to capture these costs and effects has also been acknowledged (Christensen et al., 2020; Ultsch et al., 2016) (Annemans et al., 2021). Therefore, more specific attention needs to be given to the role of future costs when developing guidance for the economic evaluation of interventions targeted at infectious diseases.

If future costs are to be included in economic evaluations, several equity implications need to be considered. Inclusion of future costs will have a greater impact on the results of economic evaluations of life-saving interventions than on those of interventions that only improve quality of life. This may result in relatively less favorable ICERs of interventions that extend life and therefore in relative terms promote interventions aimed at improving quality of life. The discussion about including future costs in economic evaluations also fueled ethical debates on the distributional consequences of doing so. Interventions that extend lives of the elderly (and especially those who are already ill and have high unrelated medical spending) are most heavily impacted by the inclusion of future costs. Some have argued that because of this impact, these costs should be excluded from economic evaluations (Grima et al., 2012). However, rather than ignoring these real societal costs, it would be better, also in dealing with distributional consequences, to deal with them openly and explicitly. If interventions cause high future costs in certain patient groups, the question is whether society is willing to sacrifice more resources to yield health gains in that particular group, as these costs represent resources that only be consumed once and could otherwise lead to (more) health in others. Put it another way, estimates of future costs are a required input for an informed discussion on efficiency-equity trade-offs and in that context especially ignoring future costs might be viewed as unethical. Additionally, increased ICERs as a result of including future costs, might also result in a downward pressure on prices of medical interventions.

Our results show that there is no commonly accepted or applied standard of which costs to include when adopting a societal perspective. For studies that are intended to inform HTA submissions, this may not be surprising as national guidelines on

economic evaluations differ in this respect. Initiatives for further standardization and harmonization of these guidelines have been taken, but these did not result in a broad practical consensus yet (Vella Bonanno et al., 2019) and hence remain important. Furthermore, especially for the type of diseases studied in this thesis country borders and local approaches to countering them less are less relevant and effective, as has become clear during the Covid-19 outbreak. Infectious diseases and outbreaks can quickly spread from country to country and continent to continent. This reduces the value of separate studies on a national scale as the consequences of larger outbreaks will often extend beyond the borders of specific countries. Therefore, attempting to reach international consensus on a clear set of core recommendations regarding how to evaluate interventions and diseases that have an impact across different countries, would be of great value. It could result in improved comparability and more practical use of the results of studies as well as improving the quality of separate studies.

## Conclusion

In this thesis I explored the current operationalization of the societal perspective in the field of infectious diseases and added to the literature by focusing on the estimation and inclusion of future costs. These costs are relevant in the context of life-prolonging interventions which will often be the case when evaluating the prevention and mitigation of outbreaks of infectious diseases. While much work remains to be done and numerous knowledge gaps to fill, I hope this thesis has contributed to the further development of economic evaluations in this context by addressing several practical issues related to the estimation and inclusion of future costs, and hence facilitating their inclusion in practice.

## Summary

Communicable diseases have caused a large disease burden throughout history. Improvements in disease surveillance, public health campaigns, and medical technologies have mitigated the impact of this burden in recent decades. However, the COVID-19 pandemic has shown that infectious outbreaks still pose a threat to population health and can cause large economic losses. To combat such threats, further investments in interventions that prevent and treat infectious diseases are needed. Such interventions will need to compete with other spending opportunities for finite (healthcare) resources. Cost-effectiveness analysis (CEA), where the incremental costs and benefits of healthcare interventions are estimated, can be used to support this prioritization and ensure efficient use of the healthcare budget. However, which costs are to be included in CEAs of interventions aiming to combat communicable disease is still a topic for debate. The focus of this thesis is to explore the methods used in the CEA of interventions against infectious diseases and to better understand which costs should be included and how these costs should be estimated.

Chapter 2 of the thesis reviewed the published literature of economic evaluations of interventions in major outbreaks of infectious diseases. This study described the current methods used and which costs and benefits are included. Of the 34 studies selected for review, a majority evaluated pharmaceutical interventions in high-income countries. The findings in this chapter show that methods used vary substantially between studies, as do the different costs and health benefits included. Furthermore, studies employing a societal perspective rarely estimated costs and/or benefits over a lifetime horizon.

In chapter 3, we evaluated the effect of early interventions in Sierra Leone during the Ebola virus disease outbreak from 2014 to 2016. A deterministic and stochastic compartment model, aiming to capture transmission on a district level, incorporating setting-specific effects – such as bed availability in treatment centers and underreporting of cases – was estimated using publicly available data. The start date of the early-intervention scenario was implemented fourweeks earlier than a comparator scenario. DALYs and costs were attached to the model compartments. The effect of earlier interventions was found to greatly decrease the health losses and resulted in productivity gains by preventing premature deaths due to Ebola.

In chapters 4 to 7, we estimated the future costs that occur if interventions prolong life. These costs are of particular relevance in the context of preventing and treating infectious diseases. Future costs can be broadly divided into three categories: related medical costs, unrelated medical costs, and non-medical costs.

In chapter 4, we estimated non-medical costs to be included in economic evaluations. Using Dutch household consumption data spanning multiple decades, we decomposed age, period, and cohort effects using P-splines. By using the same model specifications, we also estimated household size and combined the predictions of consumption and household size, to calculate the impact on the ICER by including non-medical consumption using life-table techniques. We found that the inclusion of non-medical consumption costs increased the ICER, but that the effect varied by age. Here, we showed the importance of economies of scale of consumption within households and that ignoring this effect leads to an overestimation of costs.

In chapter 5, we provided updated estimates of future non-medical consumption and future medical consumption costs, adjusting for time to death, in the Netherlands. We also showed how to adjust these costs to populations that differ from the average population in terms of underlying illnesses. The inclusion of future costs increased the ICER and may affect choices by decision-makers.

In chapter 6, we explored the distributional consequences of including future non-medical consumption costs in economic evaluations by estimating the impact on the ICER for specific socioeconomic groups. The results showed that the impact was the largest for interventions aimed involving higher socioeconomic groups. However, after adjusting for household size and quality of life, the differences were mitigated.

In chapter 7, we updated a previously published study evaluating vaccination against pneumococcus disease with the 13-valent pneumococcal conjugate vaccine. We recalculated the ICER after including future medical costs. The inclusion of future medical costs increased the ICER substantially, as did the inclusion of future non-medical consumption costs. The impact varied greatly by risk groups, defined by the types of underlying diseases, and the age at which death was averted.

In conclusion, this thesis has explored the methods used to evaluate interventions against infectious diseases and provided standardized estimates for including future costs in economic evaluations. For evaluations adopting a societal perspective and for interventions that prolong life, these costs may be of particular relevance. Theoretical and practical issues persist, but this thesis has clarified some key components of economic evaluations in the field of infectious diseases.

## Samenvatting

Infectieziekten hebben in de loop van de geschiedenis een grote ziektelast veroorzaakt. Verbeteringen in de surveillance, volksgezondheidscampagnes en medische behandelingen hebben de ziektelast de laatste decennia sterk verminderd. De COVID-19-pandemie heeft echter aangetoond dat uitbraken van infectieziekten nog steeds een bedreiging vormen voor de volksgezondheid en grote economische schade kunnen veroorzaken. Investeringen in maatregelen ter preventie en behandeling van infectieziekten blijven dus noodzakelijk. Een belangrijke vraag is echter welke investeringen prioriteit behoeven. Kosteneffectiviteitsanalyses (KEA's), waarbij de incrementele kosten en baten van interventies in de gezondheidszorg worden ingeschat, kunnen worden gebruikt om deze prioritering te ondersteunen en te zorgen voor een efficiënt gebruik van het gezondheidszorgbudget. Welke kosten moeten worden meegenomen in KEA's is echter nog steeds onderwerp van discussie. Dit proefschrift is erop gericht om de methoden die gebruikt worden in KEA's van interventies tegen infectieziekten te onderzoeken, en beter te begrijpen welke kosten moeten worden meegenomen en hoe deze kosten moeten worden geschat.

In hoofdstuk 2 van het proefschrift is de gepubliceerde literatuur over economische evaluaties van interventies bij grote uitbraken van infectieziekten op een rij gezet. Van de 34 studies die voor dit onderzoek werden geselecteerd, analyseerde een meerderheid farmaceutische interventies in hoge inkomenslanden. De bevindingen in dit hoofdstuk tonen aan dat de gebruikte methoden evenals de kosten en baten voor de gezondheid die zijn meegenomen aanzienlijk verschillen tussen de studies. Bovendien hebben studies met een maatschappelijk perspectief zelden een schatting gemaakt van de kosten en/of baten op de lange termijn.

In hoofdstuk 3 evalueerden wij het effect van vroegtijdige interventies in Sierra Leone tijdens de uitbraak van het Ebolavirus van 2014 tot 2016. Een deterministisch en stochastisch compartimentenmodel, gericht op het modelleren van transmissie op districtsniveau, rekening houdend met de beschikbaarheid van bedden in behandelcentra en onderrapportage van gevallen, werd geschat met behulp van publiek beschikbare gegevens. Disability Adjusted Life Years (DALYs) en kosten werden aan de modelcompartimenten gekoppeld. Modelanalyses lieten zien dat vroegtijdige interventies resulteerden in grote gezondheidswinst en productiviteitswinst door het voorkomen van vroegtijdige sterfgevallen als gevolg van Ebola.

In de hoofdstukken 4 tot en met 7 hebben wij een schatting gemaakt van de kosten die ontstaan wanneer interventies het leven verlengen. Deze kosten zijn van bijzonder belang in het kader van de preventie en behandeling van infectieziekten. De kosten kunnen grofweg in drie categorieën worden ingedeeld: gerelateerde medische kosten in gewonnen levensjaren, niet-gerelateerde medische kosten in gewonnen levensjaren, en niet-medische kosten in gewonnen levensjaren.

In hoofdstuk 4 hebben wij een schatting gemaakt van het effect van het meenemen van niet-medische kosten in gewonnen levensjaren in economische evaluaties. Met behulp van data over consumptiegegevens van Nederlandse huishoudens hebben wij leeftijdspatronen van kosten van niet-medische consumptie geschat rekening houdend met periode- en cohorteffecten. De analyses in dit hoofstuk lieten zien dat het meenemen van niet-medische consumptiekosten de kosteneffectiveitsratio verhoogde, maar dat het effect sterk afhangt van leeftijd. Tevens toonden wij het belang aan van schaalvoordelen met betrekking tot consumptie binnen huishoudens en dat het negeren hiervan leidt tot een overschatting van de niet-medische kosten in gewonnen levensjaren.

In hoofdstuk 5 presenteren we schattingen van kosten in gewonnen levensjaren van medische en niet-medische consumptie naar leeftijd in Nederland. Wij lieten ook zien hoe deze kosten kunnen worden meegenomen in economische evaluaties voor uiteenlopende interventies in verschillende doelgroepen.

In hoofdstuk 6 onderzochten wij de distributieve gevolgen van het opnemen van niet-medische kosten in gewonnen levensjaren in economische evaluaties door het effect op de kosteneffectiviteitsratio voor verschillende sociaaleconomische groepen te schatten. Uit de resultaten bleek dat het effect het grootst was voor interventies gericht op hogere sociaaleconomische groepen. Na correctie voor huishoudgrootte en kwaliteit van leven werden de verschillen in de kosteneffectiviteitsratio tussen sociaaleconomische groepen echter kleiner.

In hoofdstuk 7 hebben wij een eerder gepubliceerde studie geactualiseerd waarin vaccinatie tegen pneumokokkenziekte met het 13-valent pneumokokkenconjugaat vaccin werd geëvalueerd. Wij hebben de kosteneffectiviteitsratio herberekend na het meenemen van (niet) medische kosten in gewonnen levensjaren. Het meenemen van medische kosten in gewonnen levensjaren verhoogde de kosteneffectiviteitsratio aanzienlijk, net als het meenemen van niet-medische kosten in gewonnen levensjaren. Het effect varieerde echter sterk per risicogroep en leeftijd.

Concluderend kan worden gesteld dat dit proefschrift methoden heeft verkend die worden gebruikt om interventies tegen infectieziekten te evalueren en dat het gestandaardiseerde schattingen heeft opgeleverd voor het meenemen van kosten in gewonnen levensjaren in economische evaluaties. Voor evaluaties met een maatschappelijk perspectief en voor interventies die het leven verlengen, kunnen deze kosten van groot belang zijn.

# PhD Portfolio

## Training

| | |
|---|---|
| 2016 | Introduction to Infectious Disease Modeling. London School of Hygiene and Tropical Medicine. |
| 2018 | Bayesian Methods in Health Economics. University College London. |
| 2019 | Decision Analytic Modelling Methods for Economic Evaluation – Advanced Course. University of Glasgow. |

## Teaching

| | |
|---|---|
| 2017-2019 | Quantitative research in healthcare. Pre-master program in Health Policy and Management |
| 2016-2018 | Advanced research methods. Master programs in Health economics, Policy and Law, Health Care management |
| 2018 | Public health economics. Master programs in Health economics, Policy and Law, Health Care management |
| 2018-2019 | Thesis supervision. Master programs in Health economics, Policy and Law, Health Care management |

## Presentations

| | |
|---|---|
| 2017 | Lowlands Health Economics Study Group |
| 2017 | COMPARE General Meeting |
| 2018 | COMPARE Young Researchers Annual Meeting |
| 2018 | Lowlands Health Economics Study Group |
| 2019 | International Health Economics Association |
| 2019 | Lowlands Health Economics Study Group |

## Publications in this thesis

Kellerborg K, Brouwer W, van Baal P. Costs and benefits of interventions aimed at major infectious disease threats: lessons from the literature. Eur J Health Econ. 2020 Dec;21(9):1329-1350

Kellerborg K, Brouwer W, van Baal P. Costs and benefits of early response in the Ebola virus disease outbreak in Sierra Leone. Cost Eff Resour Alloc. 2020 Mar 16;18:13

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