Reconsidering the Scope of Cost-Effectiveness Analyses in Healthcare

Views on what and how costs and benefits should be included in economic evaluations of healthcare interventions

Linda de Vries

Reconsidering the Scope of Cost-Effectiveness Analyses in Healthcare

Views on what and how costs and benefits should be included in economic evaluations of healthcare interventions

Linda de Vries

Reconsidering the Scope of Cost-Effectiveness Analyses in Healthcare. Views on what and how costs and benefits should be included in economic evaluations of healthcare interventions

Author: Linda de Vries
Printing: Ridderprint, www.ridderprint.nl
Layout and design: Dagmar Versmoren, persoonlijkproefschrift.nl

Reconsidering the Scope of Cost-Effectiveness Analyses in Healthcare

Views on what and how costs and benefits should be included in economic evaluations of healthcare interventions

Het heroverwegen van de reikwijdte van kosteneffectiviteitsanalyses in de gezondheidszorg

Opvattingen over welke en hoe kosten en baten moeten worden meegenomen in economische evaluaties van gezondheidszorginterventies

Thesis

to obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the
rector magnificus

Prof.dr. A.L. Bredenoord

and in accordance with the decision of the Doctorate Board.
The public defence shall be held on

Friday 26 April 2024 at 10.30 hrs
by

Linda Michelle de Vries
born in Reeuwijk, the Netherlands.

Erasmus University Rotterdam

Doctoral Committee:

Promotors:	Prof.dr. P.H.M. van Baal Prof.dr. W.B.F. Brouwer
Other members:	Prof.dr. L. Hakkaart - Van Roijen Prof.dr.ir. H. Koffijberg Prof.dr. T.L. Feenstra

Table of contents

Chapter 1

Introduction

Several factors currently put pressure on the sustainability of healthcare systems, including the ageing of populations, a larger share of people being chronically ill, and growing medical technological opportunities (1). As there are only limited resources available, not all interventions that improve health can also actually be provided. This means that choices must be made on what healthcare to provide and reimburse (and what not) (2). For those who must make such sensitive and impactful decisions, it is important that information is available on the relevant costs and benefits of different options to enable (better) informed decision making. Although it is impossible to have full information available on all relevant aspects of interventions and to consider all that is relevant for those affected, methods have been developed and improved over the years to inform decision makers in healthcare on the effects of different options to support the decision-making process. Cost-effectiveness analysis (CEA) is a type of economic evaluation which has increasingly been used in this context (3). In CEA the costs and benefits of different healthcare interventions are compared to inform on which interventions offer most value for money (4). Using CEA, decision makers can choose to fund those interventions that contribute most to their objectives, given the available resources.

Several countries use CEA in their decision-making processes on the funding and provision of interventions in healthcare (3). Examples are Canada, the Netherlands, Sweden, and the UK (5). What costs and benefits are considered in CEAs and how these are measured and valued depends, among others, on the perspective chosen for the evaluation (4). For instance, when a healthcare perspective is applied, generally only costs and benefits within the healthcare sector are included. When a societal perspective is adopted, all relevant costs and benefits for society are generally considered. In such analyses, also broader welfare implications of healthcare interventions are captured, such as productivity costs and costs of informal care (6). Although the practice of applying the different perspectives is described as including all relevant costs and benefits within that perspective, differences exist in the practical application within as well as between perspectives (5). Which perspective to apply as well as which and how costs and benefits should be included is often prescribed in country-specific pharmacoeconomic guidelines. These are basically step-by-step guides to perform CEAs. Of the previous examples, a healthcare perspective is prescribed in Canada and the UK, while in the Netherlands and Sweden a societal perspective is prescribed (5).

Although costs in CEA are generally measured in monetary units, how health benefits are quantified varies in different sub-types of CEA. In cost-utility analysis, the most often applied approach, outcomes are typically quantified in quality-adjusted life-years (QALYs), life-years corrected for health-related quality of life (4). The results from CEAs are typically summarized in an incremental cost-effectiveness ratio (ICER), the ratio of additional costs to additional benefits from an intervention in comparison to its alternative (4). The general decision rule related to CEA states that interventions should only be provided (and collectively financed) when their total benefits outweigh their total costs. That is, when the ICER is below a threshold value representing the value of health (2). The nature of what the threshold for ICERs represents differs

between the perspectives; it represents the health losses due to displaced healthcare spending for the healthcare perspective and the consumption value of health for the societal perspective (2,7).

For the healthcare perspective, assuming a fixed healthcare budget, the decision rule related to CEA can be written as follows:

$$k_Q \Delta Q - \Delta c_h > 0 \quad (1)$$

Here, k_Q represents the opportunity costs of displaced healthcare spending (the marginal cost-effectiveness of current spending in the healthcare system), ΔQ are the incremental health gains (in QALYs), and Δc_h are the incremental healthcare costs. This rule can be rewritten into its more practical form, stating that the ICER (left side of the equation) should not exceed the threshold value k_Q (right side of the equation):

$$\frac{\Delta c_h}{\Delta Q} < k_Q \quad (2)$$

For the societal perspective, the decision rule related to CEA can be written as follows:

$$v_Q \Delta Q - \Delta c_t > 0 \quad (3)$$

Here, v_Q represents the consumption or monetary value of health and c_t comprises total costs, capturing both healthcare and costs outside the healthcare sector. In its more practical form, it states that the ICER (left side of the equation) should not exceed the threshold value v_Q (right side of the equation):

$$\frac{\Delta c_t}{\Delta Q} < v_Q \quad (4)$$

From the start, there has been discussion on what and how costs and benefits should be included in CEA within the different perspectives. For instance, there has been a debate on whether (when taking the societal perspective) productivity costs should be included in the cost or benefits side of the analysis (8). Another debate has been on the extent to which future costs, the costs that arise during the life-years that would not have been lived without a life-extending intervention, should be included in CEAs (9–11). Within this latter discussion, separate attention has been paid to future medical costs and future non-medical costs. For medical costs, there is little discussion regarding the inclusion of those costs that are related to the condition on which the intervention focused, so-called future *related* medical costs (e.g., costs for yearly checkups at the cardiologist when evaluating an intervention that saves someone from dying from a heart attack). However, the inclusion of medical costs in life-years gained that result from the intervention only through its life-extending effect (future *unrelated* medical costs, e.g., the costs for treating a broken arm for the person saved from dying from a heart attack) has been disputed. For

future non-medical costs (defined as costs of future non-medical consumption minus additional productivity in life-years gained), productivity costs are generally included, while the inclusion of costs for non-medical consumption (e.g., the costs of food and housing in life-years gained from an intervention) has been disputed.

Currently, both future unrelated medical costs and future non-medical consumption costs are often excluded in practice, and sometimes even prescribed to be excluded in pharmacoeconomic guidelines, regardless of the perspective applied. This is the case, even though it has been shown that inclusion of all future medical costs for both the societal and the healthcare perspective, and the inclusion of all future costs for the societal perspective is required to come to optimal decisions (9,12). An important aim of this thesis is therefore to improve the practice of including and estimating future costs in CEA, with careful consideration of past and present discussions around the inclusion for the different perspectives.

Another important aim of this thesis is to obtain more insight into what benefits beyond health are (implicitly) captured in CEA. More specifically, which benefits are included in the monetary or threshold value of the QALY when adopting a societal perspective. In this thesis, we focus on the Willingness to Pay method for estimating the monetary value of health, one of the applied approaches for determining the value of (changes in) health (13). The second aim of this thesis is closely related to the first aim, since an important argument against the inclusion of future non-medical costs has been that the benefits related to these costs are presumably not, or at least fully and consistently captured in the evaluation (it has been argued that its costs should therefore also be excluded to be consistent) (14). However, the implications of the extent to which benefits beyond health are captured in CEA go beyond the issues around the inclusion of future costs (costs in life-years gained from interventions). The extent to which CEA captures benefits beyond health is also relevant for interventions which are only quality of life-improving and not life-extending. In this, it is specifically important to investigate how such elements beyond health vary with health status. For instance, if benefits beyond health are captured in CEA and vary with health status, this may imply that inclusion of costs of non-medical consumption could be relevant both for normal life-years and life-years gained. This would also have implications for the estimation of these costs, as these would presumably need adjustment based on health status.

The last aim of this thesis is to improve CEA in the context of infectious disease surveillance. CEA has mainly been applied and developed for analyzing well-defined interventions for clearly defined target groups (e.g., medication to lower blood pressure in patients with cardiovascular disease). As evidenced by the recent COVID-19 pandemic, however, system level interventions such as improvements in infectious disease surveillance, are also important to protect and improve population health (15). However, for CEA of such interventions, different analytical approaches may be needed than those traditionally applied and other types of costs might be relevant to include (16). This makes it important to consider to what extent the CEA framework is applicable for system level interventions such as infectious disease surveillance and to indicate ways in which such evaluations could be improved.

Overall, this thesis aims to contribute to discussions related to and improvements of the methodology of CEA in healthcare. In doing so, the thesis focuses on the scope of CEA in terms of what and how costs and benefits should be included in CEA. The main research questions addressed in the different chapters of this thesis are as follows:

1. How can methods for the estimation and inclusion of future costs in cost-effectiveness analysis be improved?
2. Which benefits beyond health are captured in monetary estimates of the value of a QALY?
3. How can cost-effectiveness analysis of infectious disease surveillance be improved?

The structure of the thesis is as follows. Chapter 2 provides an overview of the debate on the inclusion of future costs in CEA and highlights which related issues are currently under debate. This chapter provides the general rationale to answer the first research question of how methods for the estimation and inclusion of future costs in CEA can be improved. It also gives insight into the current state of affairs and schools of thought around these issues. In Chapter 3, the first research question is approached more practically. This chapter presents an update of the tool developed for the inclusion of future costs in CEA, improving and further enabling the practical inclusion of these costs in CEA. Chapter 3 also includes case-studies in which the methods for and impact of inclusion of future costs is demonstrated. In this, it provides practical guidance to improve the inclusion of future costs in practice. In the same line, Chapter 4 demonstrates the impact of inclusion of future costs in the CEA of a vaccination program in different risk groups. In this chapter, future unrelated medical costs are adjusted based on underlying health of people in the program. Where the focus of chapters 2, 3, and 4 is on costs in CEA, Chapter 5 focuses on benefits captured in CEA. This chapter aims to answer the second research question of this thesis on what benefits are captured in the monetary value of a QALY when using a Willingness to Pay study. Chapter 6 describes several economic considerations for infectious disease surveillance. In this context, it also describes how CEA for interventions in the context of infectious disease surveillance can be improved, thereby answering the last research question of this thesis. Finally, Chapter 7 provides an overall discussion of this thesis.

Chapter 2

Future costs in cost-effectiveness analyses

Past, present, future

Based on: de Vries LM, van Baal PHM, Brouwer WBF. Future Costs in Cost-Effectiveness Analyses: Past, Present, Future. *Pharmacoeconomics. 2019;37(2):119–30.*

Abstract

There has been considerable debate on the extent to which future costs should be included in cost-effectiveness analyses of health technologies. In this chapter, we summarize the theoretical debates and empirical research in this area and highlight the conclusions that can be drawn for current practice. For future related and future unrelated medical costs, the literature suggests that inclusion is required to obtain optimal outcomes from available resources. This conclusion does not depend on the perspective adopted by the decision maker. Future non-medical costs are only relevant when adopting a societal perspective; these should be included if the benefits of non-medical consumption and production are also included in the evaluation. Whether this is the case currently remains unclear, given that benefits are typically quantified in quality-adjusted life-years and only limited research has been performed on the extent to which these (implicitly) capture benefits beyond health. Empirical research has shown that the impact of including future costs can be large, and that estimation of such costs is feasible. In practice, however, future unrelated medical costs and future unrelated non-medical consumption costs are typically excluded from economic evaluations. This is explicitly prescribed in some pharmacoeconomic guidelines. Further research is warranted on the development and improvement of methods for the estimation of future costs. Standardization of methods is needed to enhance the practical applicability of inclusion for the analyst and the comparability of the outcomes of different studies. For future non-medical costs, further research is also needed on the extent to which benefits related to this spending are captured in the measurement and valuation of health benefits, and how to broaden the scope of the evaluation if they are not sufficiently captured.

Key Points for Decision Makers

When an intervention prolongs life, this leads to additional costs in added life-years. Including the additional medical costs in economic evaluations is required, under reasonable assumptions, to allow optimal decisions, both from a healthcare and societal perspective.

Knowledge on how to estimate future (unrelated) medical costs has improved. Important challenges for their systematic inclusion in economic evaluations are changing pharmacoeconomic guidelines to allow or prescribe inclusion (rather than exclusion) and lowering the practical difficulties for doing so.

The inclusion of future non-medical costs is hampered by both theoretical and empirical challenges. The benefits of future non-medical consumption and productivity may currently not be comprehensively and systematically included in cost-effectiveness analyses. This is a requirement for including these costs.

Introduction

Cost-effectiveness analyses are increasingly used to guide pricing and reimbursement decisions in healthcare (3). The analytical approach most frequently applied is a cost-utility analysis, wherein outcomes are quantified in quality-adjusted life-years (QALYs). The results of the analysis are typically summarized in an incremental cost-effectiveness ratio (ICER), the ratio of additional costs to additional benefits of a new intervention compared to an appropriate alternative. A fundamental issue within a cost-effectiveness analysis, which is unresolved to date, is the extent to which future costs should be included in the ICER (11,17). Future costs (also referred to as 'survivor costs') are the costs that arise during the life-years that would not have been lived without a life-extending intervention. These costs are typically classified into future related medical costs, future unrelated medical costs, and future non-medical costs.[1]

Future related medical costs are costs for treatments in life-years gained that are directly related to the disease that is being treated with the life-extending treatment. When, for instance, an intervention to treat a heart-attack successfully extends life, costs for routinely visiting a cardiologist thereafter would count as future related medical costs. Future unrelated medical costs are only a consequence of the life-extending intervention through its effect on life expectancy. Costs for treating a broken leg or severe influenza after surviving a heart attack would be examples of these costs. Future non-medical costs comprise future net non-medical resource use. These future non-medical costs can be obtained by subtracting productivity gains as a result of the ability to work longer when life is extended from the costs of non-medical consumption during the life-years gained. Examples of such future non-medical consumption costs are travel expenditures and costs for housing and food during the life-years gained.

Although none of the future costs would arise without the life-saving intervention, not all of these costs would generally be included in cost-effectiveness analyses of life-prolonging interventions. The exclusion of some of the costs can be justified by the perspective adopted by the decision maker. The aim of a decision maker adopting a healthcare perspective, for example, is typically assumed to be the maximization of health or health-related utility under the constraint of the healthcare budget. Broader welfare implications including future non-medical costs are then generally ignored. In contrast, a decision maker adopting a societal perspective is typically assumed to aim to maximize social welfare, often described as some (weighted) aggregation of individual welfare, under the constraint of total societal resources.[2]

---

1 Future non-medical costs could also be categorized into future related and unrelated costs, to the same degree as future medical costs. However, in concordance with previous literature, we will not make this distinction and label all these costs here as future non-medical costs.

2 Note that adopting a societal perspective is not synonymous with taking a welfarist approach, which restricts welfare information to solely (individual) utilities. Extra-welfarism, allowing broader definitions of welfare including for example capabilities, is fully compatible with taking a societal perspective (149). Hence, the issues addressed in this chapter are relevant for both approaches.

For such a decision maker, broader welfare economic implications beyond healthcare are relevant, and are generally taken into account in an economic evaluation (4).

The extent to which future costs should be included in a cost-effectiveness analysis, considering the decision maker's perspective, has been frequently debated (9–12,14,18–30). Although progress has been made, diverging approaches and viewpoints continue to exist in both theoretical and practical contributions in this area. To contribute to appropriate methods, to increase validity, consistency, and comparability of results, our aims in this chapter are threefold. First, to highlight past theoretical debates and empirical research on the inclusion of future costs in a cost-effectiveness analysis; second, to clarify which issues within these debates are unresolved to date; and third, to indicate future research needed in this area.

Future Medical Costs

In this section, we discuss the inclusion of future medical costs. We start with the discussion of the theoretical debates and then elaborate on the empirical research.

Theoretical Debates

In the development of methodological guidance for cost-effectiveness analyses, mathematical models have played an important role. For instance, the decision rule to adopt an intervention only when the ICER is lower than a cost-effectiveness threshold has been derived from a mathematical model with a clearly defined objective and several constraints (31). Such models have also been developed and used to address the question whether future costs should be included in cost-effectiveness analyses.[3]

Van Baal and colleagues (12), for instance, set up a mathematical model describing a decision maker who wants to maximize QALYs given a fixed healthcare budget. They concluded that both future related medical costs and future unrelated medical costs should be included in a cost-effectiveness analysis to maximize the number of QALYs gained from available resources. The explanation is that given a fixed healthcare budget, life-prolonging interventions necessarily result in a lower budget per person for healthcare in the future. Hence, life-prolonging interventions have real health opportunity costs by leaving less budget for others. Excluding future unrelated medical costs therefore leads to an underestimation of the opportunity costs of life-extending interventions. As a consequence, ignoring these costs could result in care being adopted that is actually less cost effective than the care that it displaces or prevents from being funded. Hence, inclusion of future unrelated medical costs can lead to different decisions and ultimately leads to more (health) benefits.

3 In these models, future medical costs are specified as related or unrelated on a cost level (expenditures conditional on survival, which do not change with an increase in the quantities of the intervention consumed, are unrelated). In practice, future medical costs are typically specified as related or unrelated on the level of the disease to be treated.

For decision making from the societal perspective, several competing mathematical models have been proposed that have implications for the inclusion of future medical costs. The assumptions underlying these models are typically of major importance for the interpretation and real-world relevance of the results. For instance, Garber and Phelps (10) developed a model from which the welfare-optimizing decision rule included future related and unrelated medical costs in the ICER. However, according to their model, future unrelated medical costs could be excluded without affecting the relative ranking of cost effectiveness of alternatives. This makes exclusion possible provided practice is consistent and the value of the cost-effectiveness threshold appropriately adjusted (10). Crucial assumptions in their model that were required to arrive at these conclusions were that earnings and consumption profiles (both medical and non-medical) do not vary by age and that at every age, individuals exactly consume what they produce. These assumptions are difficult to justify, given the observed age patterns in healthcare use and net resource use (9,32). Furthermore, the trade-off between improvement of quality of life and improvement of length of life was not properly accounted for in this model. This is relevant because interventions that only increase quality of life are not affected by the inclusion or exclusion of costs in life-years gained (as survival is unaffected). Ignoring future costs for life-prolonging interventions thus distorts their comparison to interventions that improve quality of life. This leads to biased decisions in favor of life-prolonging interventions.

Meltzer (9) constructed a more general model with less restrictive assumptions, and, based on that, concluded that the welfare-optimizing decision rule necessarily includes both future related medical costs and future unrelated medical costs in the ICER. As future unrelated medical costs can vary under different conditions, excluding these may affect the relative ranking of cost effectiveness of alternatives, and consequently lead to different decisions on the care to provide.

Later, Lee presented a model implying that the welfare-optimizing decision rule need not include future unrelated medical costs. Furthermore, including these costs would, according to this model, lead to suboptimal outcomes for society (24). His model was subsequently criticized because it employed similar assumptions as Garber and Phelps by ignoring survival probabilities in the budget constraint. Therefore, ignoring this essentially implies that these costs were not meaningfully included in the model to begin with (25). Feenstra and colleagues (26), in response to Lee, showed that proper inclusion of the probability of survival in the budget constraint, and thereby capturing the increase in future unrelated medical expenditures as a necessary consequence of increased life expectancy, leads to the conclusion that future unrelated medical costs should be included in a cost-effectiveness analysis. These results support the results earlier found by Meltzer (9,25).

Conversely, some have argued that new treatments should be evaluated in isolation (excluding both costs and benefits of unrelated care) (4,33). In this line of reasoning, it is claimed that future unrelated medical care is not a necessary consequence of the life-prolonging intervention because no irreversible commitment to obtain future unrelated care is made when adopting it (4). Although intuitively appealing, the commitment argument does not provide a rationale why we

should include lifetime consequences of a decision in terms of healthcare use for related diseases (like the cardiologist's visits in the introduction) but not for unrelated diseases (like the broken leg). For both disease categories, it is often unclear what the exact commitments will be in the future (although it is likely that there will be commitments). More importantly, van Baal and colleagues demonstrated that consistently excluding the costs and benefits of unrelated care in general pushes the ICER upwards and results in suboptimal decisions (22). The reason for this is that unrelated medical care is usually a mix of different interventions, and the cost effectiveness of unrelated medical care will then be some sort of average return to healthcare expenditures, which on average is lower than the threshold. If indeed future unrelated medical care is cost effective, the inclusion of both costs and benefits can never push an ICER above the threshold.

It should also be emphasized that although the inclusion of future unrelated medical costs has been disputed, the benefits related to this spending are generally already included in cost-effectiveness analyses. The quality of life and life expectancy upon which estimates of benefits of life-prolonging interventions are based are typically observed in patients also receiving unrelated medical care. This implies that the benefits of unrelated medical costs are projected in the estimations of the QALY gains of a life-extending intervention. Childhood vaccination may, for example, prevent early death. However, quality of life and expected survival in added life-years depend on the provision of unrelated healthcare during these years and estimates thereof typically obtained in people receiving unrelated care. To exclude costs but include benefits of unrelated future medical care would of course be inconsistent.

In that context, Nyman developed rules for internal consistency to determine which costs should be included in a cost-effectiveness analysis given the benefits included. These rules require that all costs required to produce projected benefits should be included, as well as those that are causally related to the intervention, even when they do not yield additional benefits. Given current practice, internal consistency thus requires that future unrelated medical costs should be included because benefits thereof are captured in the projected QALY gains (14,22).

It needs to be noted that internal consistency could also be achieved by excluding both costs and benefits of unrelated care. Doing so however requires disentangling related and unrelated costs and benefits, which is practically difficult, if not impossible (22,29). Benefits from interventions would then for example need to be estimated under the assumption that patients would not receive any unrelated care. It appears highly difficult to practically estimate the quality of life of patients under such assumptions. Furthermore, it is not always clear or known which costs are actually related or unrelated (34,35). Additionally, if the aim of an economic evaluation is to meaningfully inform healthcare decision makers, inclusion of future unrelated medical costs and their benefits seems most appropriate (also referred to as the external consistency argument) (11,22,29). To illustrate this, take the example of childhood vaccination. It seems rather inconceivable that people who live longer because of childhood vaccination would be denied standard future care on that ground. Nor is it clear how one would estimate their life

expectancy and quality of life without future care, or what the practical relevance would be of doing so.

Summarizing, the theoretical work in this area suggests that under the most reasonable assumptions it is necessary to include both future related medical costs and future unrelated medical costs in the ICER to obtain optimal decisions, in line with the decision maker's objectives. This conclusion holds, regardless of the perspective that is adopted by the decision maker. Inclusion is optimal as well as internally and externally consistent.

Empirical Research

Practical difficulties in the estimation of future unrelated medical costs and the burden that having to include these costs may place on analysts have been mentioned as arguments not to include these costs in a cost-effectiveness analysis (17,33,36). However, methods have been developed to facilitate the estimation of future medical costs, which was possible given the knowledge on the effect of aging on healthcare expenditures (37). It would be an unsurmountable task to predict the risk of all unrelated diseases and link these predictions to costs to estimate future unrelated medical costs. Therefore, rather than modeling all these individual diseases explicitly, the starting point for the estimation of future unrelated medical costs is typically estimates of medical spending by age, which comprise spending on all sorts of diseases (9). Such an approach is similar to how economic modeling studies usually deal with other causes of death, as well as estimates of quality of life by age (which are included to deal with the fact that mortality risk increases with age and quality of life generally decreases) (38). Age- and sex-specific per-capita medical spending can then be linked to survival curves to estimate future unrelated medical costs. In general, there is no correction for the fact that per-capita spending includes spending for related diseases unless the related disease(s) represent a large part of health spending. For instance, several modeling studies focusing on smoking and obesity do correct per-capita spending for the cost of related diseases when estimating future unrelated medical costs (39–41).

Further refinements in estimating future medical consumption have been made by taking into account the observation that healthcare spending is usually concentrated in the last phase of life (42,43). This also typically affects how age influences medical expenditures because part of the effect of aging may be owing to the costs of dying (and older people have higher probabilities of dying) (44). Given that everybody only dies once, the impact of unrelated medical costs on the ICER is less strong when one accounts for the higher spending in the last year of life (42,45).

In the Netherlands, a tool was developed that facilitates the inclusion of unrelated medical costs in a standardized manner, accounting for the high spending in the last year of life and allowing for the correction for costs of related diseases (43). For other countries, such tools do not yet exist but estimates of spending by age, sex, and disease have been produced for several countries, which would allow the creation of such a tool or other comparable guidance, also for

those countries. For instance, several studies have illustrated how to estimate future unrelated medical costs for the UK (12,46–48).

Of course, the exact nature and height of future healthcare spending is uncertain, and increasingly so when it is further ahead in the future. A common assumption in studies addressing future unrelated medical costs is that future spending patterns resemble current healthcare spending patterns. While this is an assumption that need not completely hold, it seems a reasonable starting point for estimation (and better than estimates of zero) and is consistent with the types of assumptions commonly made in practical economic evaluations. In these evaluations, for instance, the estimates of the impact of individual interventions on future health and healthcare also assume the current standard of care (29).

Estimates of the impact of including future unrelated medical costs for specific patients and treatments have revealed that the inclusion of future unrelated medical costs can significantly affect the cost effectiveness of interventions (12,22,34,49–53). These findings refute the argument that future unrelated medical costs are negligible and can therefore be ignored (33,36). Moreover, these studies revealed large differences in the changes in ICERs as a result of inclusion depending on the age of the patients, following from the pattern that healthcare consumption is typically higher for people at higher ages. As a result, including the future unrelated medical costs has more impact when people reach higher ages.

Textbox 1 describes an example of a Dutch study in which including future unrelated medical costs significantly affected cost-effectiveness estimates. During the submission process of the new intervention, Dutch pharmacoeconomic guidelines were updated and future unrelated medical costs had to be included. Because of this, a full analysis was performed both including and excluding future unrelated medical costs (54), highlighting the impact of inclusion.

Textbox 1: Future unrelated medical costs and the cost effectiveness of LCZ696

Most patients with chronic symptomatic heart failure with reduced ejection fraction are treated with angiotensin-converting enzyme inhibitors (ACEI) and betablockers. When ACEI are not tolerated, patients may receive angiotensin receptor blockers. However, if patients remain symptomatic, ACEI should be replaced by the angiotensin receptor neprilysin inhibitor sacubitril/valsartan (LCZ696). A global health economic model was adopted to reflect the Dutch societal perspective, to determine the cost effectiveness of LCZ696 in comparison to treatment with ACEI in adult patients with chronic heart failure with reduced left ventricular ejection fraction in the Netherlands, based on an average age of 75 years.

The analysis displayed a quality-adjusted life-year (QALY) gain from LCZ696 compared to ACEI of 0.33. With total incremental costs (excluding future unrelated medical costs) of €5,839 the incremental cost-effectiveness ratio (ICER) was estimated on €17,600 per QALY. The increased

longevity of 0.39 life-year because of LCZ696 caused additional discounted medical costs, unrelated to heart failure, of €2,950. The inclusion of future unrelated medical costs increased the ICER with €8,891 (€2,950/0.33) to €26,491 per QALY gained.

In the Netherlands, cost effectiveness is judged against a threshold ranging from €20,000 to €80,000, for which the height depends on the principle of proportional shortfall. For this treatment, a threshold of €50,000 applied. The intervention was thus cost effective both before and after inclusion of future unrelated medical costs. However, the increase of the ICER with over 50% shows that the effect can be large. (See (54) for more details.)

Future Non-Medical Costs

In this section, we discuss future non-medical costs. As already mentioned in the introduction of this chapter, these costs are only relevant for the societal perspective. We follow the same structure here as for the previous section, starting with the theoretical debates, following with empirical research.

Theoretical Debates

Some of the mathematical models highlighted above in the discussion of the inclusion of future medical costs have also played a key role in the debate on the inclusion of future non-medical costs. Generally, comparable conclusions were drawn regarding the inclusion. For instance, in the welfare-optimizing decision rule derived from the model by Garber and Phelps (10), future non-medical costs could be included or excluded without affecting the relative ranking of cost effectiveness. This conclusion strongly depended on the restrictive assumptions underlying the model. Using less restrictive assumptions, Meltzer (9) found that the welfare-optimizing decision rule necessarily includes future non-medical costs. Leaving these out would affect the relative ranking of cost effectiveness of alternatives, which could consequently lead to suboptimal decisions and outcomes.

In terms of internal consistency, it should be noted that Meltzer implicitly assumed that in cost-effectiveness analyses, utility measures are used that capture the full welfare benefits, also those of non-medical consumption and productivity (leisure). However, QALYs are intended to measure health-related quality of life. The internal consistency rules, proposed by Nyman, specify that the ICER should only include costs for which the related benefits are also captured (or when these are causally related though do not yield additional benefits) (14). One may wonder whether QALYs capture the benefits related to non-medical consumption.

From a theoretical point of view, QALY optimization would only be compatible with welfare maximization (with broader costs and benefits beyond health also implicitly considered) under strict assumptions rarely met in practice (55). Empirically, different views exist on what actual benefits are captured in the quality-of-life weights that are assigned to the health states. Standard

gamble and time-trade-off exercises are typically used to derive these weights. Although the most frequently used questionnaires used do not explicitly mention non-medical consumption (14), it is not clear what consumption level the respondents implicitly assume when answering the questions.

Some argue that people expect non-medical resource use to remain unaffected to the current level (19,21). Another view is that people at least consider the non-medical resource use needed to stay alive, such as daily food intake. Such assumptions have not been empirically verified. It is also good to emphasize that even if minimal consumption levels to stay alive are not considered by respondents in health-state valuations, they are still required to obtain the quality of life that is measured from the questionnaires and should thus be counted as a cost (20,49). This could also be stated for other non-medical consumption, which to a certain extent produces health in the same manner as medical care. Considerable gains in life expectancy in many Western countries were for example the result of interventions outside the healthcare sector (clean water, sewerage, healthier and safer foods, road safety) (56).

Available experiments suggest that respondents inconsistently include impacts on productivity and leisure in health-state valuations, if not explicitly requested to do so. The latter is uncommon in practice. The influence of spontaneous inclusion of these impacts on health-state valuations varied (57), although it was typically small and often insignificant, especially on average valuations, suggesting that these impacts would better be valued separately. Explicit instructions (to exclude these effects) could improve consistency in terms of what respondents include in health-state valuations.

Adarkwah and colleagues investigated the impact of instructions on including the impact of ill health on the utility of consumption and leisure in health-state valuations (58). Explicit instruction to consider this utility did not influence valuations. In contrast, spontaneous consideration in the group without explicit instruction led to significantly lower valuations. From this, one could derive that currently the non-health benefits of interventions are not systematically captured through common health-state valuations. However, because relatively few studies have been performed in this area, with varying results, further research is needed to gain more insight into the extent to which people consider the broader welfare implications that result from ill health.

Besides being internally consistent, the information a cost-effectiveness analysis provides to decision makers should also be externally consistent; the information should entail the policy-relevant consequences of adopting an intervention. In line with this, Lundin and Ramsberg argue that rather than following the QALY, which costs (and benefits) to include should be determined by the welfare theoretic foundations underlying a cost-effectiveness analysis (21). This is related to the argument by Richardson and Olsen that the scope of the analysis should be consistent with the aims of the decision maker and preferences of society (19). According to Nyman, because the aim of healthcare interventions is mainly to increase health, a focus on

health-related quality of life as an outcome would be sufficient (59). These arguments, however, are more related to the issue of how to conceptualize the societal perspective appropriately (60) than to the specific issue of inclusion of future costs.

Nyman has later argued that the welfare implications of non-medical consumption and productivity (leisure) are already known to be positive and can therefore be safely ignored. He argues that, unlike for medical consumption, people can and do weigh benefits of non-medical consumption and production against its costs, and make deliberate and appropriate decisions whether to consume, and to work or enjoy leisure instead (27,59). Whether this is a sufficient argument to exclude these costs from evaluations remains to be seen, as the welfare effects may still differ between interventions (even if often positive). Meltzer also demonstrated that decisions will be affected when consumption or productivity are excluded when having an effect on welfare.

Empirical Research

Several studies have estimated net non-medical resource use, for inclusion in cost-effectiveness analyses (9,49–53,61). For this, productivity costs were estimated using the human capital approach (in economic evaluations, the friction cost approach sometimes is also used to calculate productivity costs in 'normal' life-years (4)). For consumption, these studies used either data from household expenditure surveys (52,61) or data on earnings to extract consumption costs as disposable income minus savings (50). Age patterns of per-capita consumption and average earnings (as a proxy for productivity) were used for these estimates (9,51–53).

Different views exist regarding how to handle transfer payments when estimating future consumption costs and productivity. Lee (24) argued that net resource use should be calculated by net dissavings, implying that not only earnings from productivity should be included, but also other sources of income such as private and public pension payments and asset income. This argument was refuted by Meltzer (25), explaining that transfer payments are not relevant when analyses are performed from a societal perspective. This is consistent with how transfer payments are treated in a traditional cost-effectiveness analysis from a societal perspective (as transfers not costs) (62).

Net resource use (consumption minus production) is typically positive in younger ages, negative in middle ages, and again positive in older ages. This means that only in people of 'working ages' does production normally exceed consumption. For example, it was shown that for the Danish population, production exceeded consumption from ages 24–62 years (50). Other research found comparable patterns (49,51–53). The difference between age groups is typically owing to higher (paid) work force participation among younger people. Note that in these studies, data on household consumption were used to derive per-capita consumption but economies of scale within households were not addressed. Economies of scale can be important when the goal is to estimate the costs of non-medical consumption resulting from living longer because preventing death in a multi-person household would result in less additional consumption than preventing

death in a single-person household. Additionally, to date, studies have not yet used the friction cost method when estimating production gains in life-years gained. This would likely result in lower productivity gains at a societal level from the prolonged life of patients (owing to the possibility of replacement), hence a less often negative net resource use. It needs to be noted that unpaid work is not accounted for in these calculations.

More generally, in comparison with the inclusion of the future medical costs, there is less experience with the inclusion of future non-medical costs. An example of the difference in cost effectiveness when future non-medical costs are either included or excluded based on a Swedish study can be found in Textbox 2. Because of a change in the Swedish pharmacoeconomic guidelines, this study obtained ICERs both including and excluding future non-medical costs (63).[4]

Textbox 2: Future non-medical costs and the cost effectiveness of pomalidomide

Patients with multiple myeloma who have progressed following treatment with both bortezomib and lenalidomide have a poor prognosis. In this late stage, patients are often left with best supportive care. Pomalidomide is an anti-angiogenic and immunomodulatory drug for the treatment of multiple myeloma. The cost-effectiveness was estimated of pomalidomide as an add-on to best supportive care in patients with relapsed and refractory multiple myeloma in Sweden, based on an average age of patients of 64 years. The analysis displayed a quality-adjusted life-year (QALY) gain from pomalidomide of 0.74 and increased longevity of 1.21 life-year.

The incremental cost-effectiveness ratio (ICER) [without future non-medical costs] was estimated to be €56,682 per QALY. Including future productivity gains (which were negligible owing to the fact that most life-years are spent in retirement in this patient group) lowered the ICER with €457 to €56,225 per QALY. When consumption costs in added life-years were included, this increased the ICER with €28,642 to €84,867 per QALY gained.

Despite the relatively high ICER, the treatment was granted reimbursement by the Swedish authorities. (For more details see (63).)

4 Numbers are based on table IV in (63) and in euros. Consumption costs in this study comprised both medical and non-medical consumption. Using the proportions from the original estimates (61), it can be derived that of the €28,642, the increase as a result of future non-medical consumption costs would be approximately €25,896 ((1-(13,623/142,074))*28,642), and the increase as a result of future non-medical costs would be €2,746.

Practical Relevance

Pharmacoeconomic Guidelines

Which costs are actually considered in a cost-effectiveness analysis largely depends on the requirements in country-specific pharmacoeconomic guidelines.[5] These guidelines generally prescribe the inclusion of future related medical costs (typically referring to these as 'direct medical costs') in the reference case, the standard format for a cost-effectiveness analysis. However, they often pay no further attention to the inclusion of future unrelated medical costs or explicitly require the exclusion of these costs. In jurisdictions in which a societal perspective is adopted, it is generally required to include future productivity costs (or gains) and the future costs of non-medical consumption related to the intervention (such as informal care and traveling expenditures). Other non-medical consumption is rarely mentioned in the guidelines. Consistent with these prescriptions, empirical studies found that in practice, future unrelated medical costs and future non-medical consumption costs not related to the intervention are rarely included in economic evaluations (49,64).

Some countries recently changed their guidelines regarding the inclusion of future costs. For instance, Dutch guidelines, which prescribe adopting a societal perspective, traditionally did not require the inclusion of future unrelated medical costs. This changed in 2016, when inclusion of these costs became mandatory. However, still no specific attention is paid to future non-medical consumption that is not related to the intervention (65). In 2013, Swedish guidelines, adopting a societal perspective, were changed to specifically (and uniquely) prescribe the inclusion of future costs as total consumption (medical and non-medical) minus production in life-years gained (66). However, the guidelines were changed after criticism was voiced from the public and patient advocacy groups on the inclusion of future costs (67). It was stated that it would be investigated how these costs should be handled in the future (68,69). In the revised versions from 2015 (70) and 2017 (71), only the inclusion of future related medical costs and additional productivity in life-years gained is required and not future unrelated medical and consumption costs. In contrast, the second US Panel on Cost-Effectiveness in Health and Medicine in 2016 (72) recommended the inclusion of all future costs, contrary to the first US Panel in 1996 (36). While the recommendations of the Panel are not official requirements, they have shown to be influential (73).

In the debates on the inclusion of future unrelated medical costs, the influential National Institute for Health and Care Excellence guidelines (74), which apply in England and Wales, are often discussed. These prescribe taking a healthcare perspective. To date, however, National Institute for Health and Care Excellence guidelines exclude future unrelated medical costs from the analysis. It has been argued that National Institute for Health and Care Excellence should change its guidelines in this context because the exclusion of future unrelated medical costs is

5 For an overview of country-specific pharmacoeconomic guidelines, see https://tools.ispor.org/peguidelines/.

inconsistent with the aims of the analysis (11,29,30,35,37). Counterarguments mainly relate to ethical concerns regarding the potential distributional impact of including these costs (34,37).

Summarizing, in general, guidelines still typically are silent or prescribe the exclusion of future unrelated medical costs and future non-medical costs not directly related to the treatment. However, first signs of adjustment towards inclusion of, at least, future unrelated medical costs appear to be showing. The inclusion of future non-medical costs not directly related to the treatment may follow but seems more contested.

Ethical Concerns

As illustrated by the examples in the textboxes, the inclusion of future unrelated medical costs and future non-medical costs can have a substantial impact on final ICERs. Consequently, including these costs in cost-effectiveness analyses in practice may affect funding decisions. In general, the impact of the inclusion of these costs is larger when life-years gained are spent in relatively poor health (implying a lower denominator and thereby increasing the ICER). Note that while the total number of life-years gained is relevant in terms of budget impact, it typically has a limited impact on the ICER. Further, even if the number of life-years gained is small, the impact of future costs can still be substantial.

Additionally, including future unrelated medical costs and future non-medical costs results in different decisions on what care to provide, and thus has distributional consequences.

Including future unrelated medical costs may, for instance, disfavor interventions targeted at the elderly (because non-medical expenditures are typically higher at higher ages, which increases the impact of including future unrelated medical costs) and people already in ill health or with already higher healthcare expenditures. On the ground of such ethical concerns, it has been argued to exclude future costs from a cost-effectiveness analysis (4,34,37,75). Acknowledging the relevance of these issues, it has also been argued that ignoring real costs is not an appropriate or useful answer to ethical questions (17,35,76). One may even wonder whether ignoring real opportunity costs, that will have consequences on others, is an ethical strategy. Furthermore, ignoring real costs endangers the credibility and usefulness of outcomes from a cost-effectiveness analysis (35). Equity issues need to be dealt with, preferably based on all relevant information in deliberative decision-making processes. In light of the information provided, decision makers may for instance wish to use a higher threshold for care focused on specific groups of patients (77).

The question of how to appropriately incorporate ethical concerns into the decision-making process is an important matter in this context. One method is through an appraisal phase in which ethical concerns are dealt with explicitly, while being fully informed on all relevant costs and effects (35). This may also be facilitated by incorporating societal distributional preferences into the ICER or threshold, by assigning higher weights or values to health gains for specific groups in the population (73). Another option is to use a multi-criterion decision analysis. In this approach, formal methods are used to identify and score the various factors considered

relevant to a decision (3). All such methods do require initial inclusion of information on all relevant costs and benefits.

Discussion

Future Medical Costs

The theory and practical possibility of including future medical costs in a cost-effectiveness analysis has significantly developed over the past years. Most (relevant) economic models revealed that optimal outcomes require considering all current and future medical costs, regardless of whether these are related or unrelated (9,12,25,26). Although some models yielded opposite results (10,24), the assumptions underlying these models are too restrictive to be relevant in practice. Furthermore, other arguments against the inclusion of future unrelated medical costs (e.g., future unrelated medical costs are not a necessary consequence of an intervention or that future unrelated treatments should be evaluated on their own) have been refuted (12,29).

It has also been explained that projected benefits from interventions require the provision of future unrelated care and that costs thereof should also be considered in economic evaluations to be internally consistent (14,22). Furthermore, external consistency requires both the benefits and costs of future unrelated care to be included for the analysis to be most informative for the decision maker. It has additionally been argued that ethical issues (e.g., inclusion may disadvantage specific patient groups) should be dealt with explicitly and informedly and cannot justify systematically ignoring real costs.

Most pharmacoeconomic guidelines nevertheless still do not require the inclusion of future unrelated medical costs. This may be because of some 'status quo bias', wish for intertemporal comparability of results, and practical concerns about difficulties of estimating these costs. It may also simply reflect the fact that guidelines are normally based on well-established and accepted viewpoints, which implies they follow (with some lag) on from theoretical developments.

It must also be noted that it is not only the cost effectiveness of the new intervention for which additional inclusion of future unrelated medical costs would be relevant. Additionally, this issue matters for the determination of the threshold against which the cost effectiveness is judged. For instance, within a system with a fixed healthcare budget, when funding a new healthcare intervention implies displacing health sector activity elsewhere, the threshold represents the cost effectiveness of displaced care. The future unrelated medical costs should also be considered in the estimates of the threshold to represent the opportunity costs more accurately. Recent estimates of such a threshold in the Netherlands illustrated how this can be achieved (78).

Future Non-Medical Costs

For jurisdictions adopting a societal perspective in economic evaluations, with the aim to optimize societal welfare, future non-medical costs are relevant to consider as well (9). This is typically not done in practice nor prescribed or encouraged in guidelines. Concerns about

the benefits captured when quantifying outcomes in QALYs reiterated the debate on the appropriateness of including these costs because internal consistency requires that only costs are included when benefits thereof are also included (14). Several authors discussed the extent to which welfare implications beyond health are measured and valued in QALYs (57,58).

A point that has not yet received any attention in the discussion in this context is to what extent people take into account the non-medical benefits when they provide monetary valuations of QALY gains. These valuations are usually obtained using willingness-to-pay exercises and are one possible source of determining the threshold value at which health technologies are considered too expensive (2). Further research in this area is needed. If such research shows that relevant aspects of benefits beyond health are indeed not systematically and comprehensively measured and valued in current economic evaluations, one could take this to imply that the associated costs can also be ignored. However, if the aim is to improve overall societal welfare, a more appropriate response might be to investigate how the scope of economic evaluations can be broadened to include the relevant benefits as well as costs.

Although internal consistency is a fundamental premise (considering that all transactions have both a cost side and benefit side) (27), internal consistency is not a sufficient criterion. The information a cost-effectiveness analysis provides should also be externally consistent. It needs to inform the relevant decision maker by providing information on all relevant consequences of adopting an intervention. It can be argued that interventions in healthcare primarily aim to improve health-related quality of life. However, welfare implications beyond health (care budgets) can also be relevant for decision makers. This is, by definition, true for decision makers who aim to optimize societal welfare, defined in a relevant welfarist or extra-welfarist approach (9).

One might also argue that decision makers in principle taking a healthcare perspective would not wish to be left completely ignorant about the 'welfare externalities' their decisions might have. In such cases, a separate account of broader societal impacts may be provided. In either case, the inclusion of future non-medical costs would be warranted. A two-perspective approach could facilitate a full account of impacts, while indicating where these impacts fall. Recently, the second US Panel on Cost-Effectiveness in Health and Medicine argued in favor of using such a two-perspective approach, detailing impacts from both a healthcare perspective and from a broader societal perspective (72), as was proposed before (79). With such an approach as standard, non-medical costs could systematically be included in economic evaluations in healthcare. This leaves open the possibility for decision makers to weight certain impacts more than others and to explicitly address distributional consequences related to the inclusion of specific elements.

However, given the questions regarding whether, how, and to what extent the benefits beyond health related to future non-medical costs are adequately captured in current economic evaluations, it would be premature to advise to simply include these costs. For now, it might

be advisable to include these costs separately in a cost-effectiveness analysis. Then, at least the decision maker is provided with more comprehensive information regarding societal costs that follow from a new intervention.

Future Research

Regarding future unrelated medical costs, further research could be aimed at reducing practical objections in terms of difficulties in estimating future unrelated medial costs, by standardizing methods and estimates across and within jurisdictions. This will improve both the applicability of inclusion and the comparability of outcomes. Translating the large body of research on the economics of aging into tools and reference tables that can be used by practitioners of a cost-effectiveness analysis seems one clear way forward. Furthermore, estimates of future unrelated medical costs could be improved by taking into account changes in healthcare expenditures over time as presently these estimates are typically based on the current standard of care.

For future non-medical costs, further research should be conducted regarding the question of whether relevant benefits are already captured in current outcome measures, and, if not, how this could be assured. To facilitate inclusion, research is also required on the development and improvement of methods for the estimation of future non-medical consumption costs. For instance, by accounting for economies of scale in household consumption and by investigating the relation between non-medical consumption and health status. Furthermore, research should focus on how to standardize estimation methods across jurisdictions applying the societal perspective, to broaden the applicability and comparability of outcomes.

Conclusion

When an intervention prolongs life, additional costs in the added life-years are incurred. To allow optimal decisions, both from a healthcare and societal perspective, including the additional related and unrelated medical costs in economic evaluations is required. Knowledge on how to estimate future (unrelated) medical costs has improved, also allowing inclusion in practice. Inclusion of these costs would presumably benefit most from lowering the practical difficulties and the burden on the analyst of including these costs in a cost-effectiveness analysis, as well as guidelines prescribing or at least encouraging inclusion rather than prescribing exclusion.

For future non-medical costs, the conclusion is less clear. The benefits of future non-medical consumption and productivity may currently not be comprehensively and systematically included in a cost-effectiveness analysis. Therefore, the appropriate technique to include future non-medical costs requires further attention, both theoretically and empirically. Research in this area is encouraged. Ultimately, this should contribute to optimal decision making in healthcare to obtain the most favorable outcomes for society.

Chapter 3

Practical guidance for including future costs in economic evaluations in the Netherlands

Introducing and applying PAID 3.0

Based on: Kellerborg*, K, Perry-Duxbury*, M, de Vries*, L, van Baal, P. Practical Guidance for Including Future Costs in Economic Evaluations in The Netherlands: Introducing and Applying PAID 3.0.
Value in Health. 2020;23(11):1453–61.

**These authors contributed equally to this work*

Abstract

Objectives: A consensus has been reached in The Netherlands that all 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 chapter are twofold: (1) 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 (2) 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 2 additional cases where published studies are updated by including future costs.

Methods: Using the latest published cost of illness data from the year 2017, we model future unrelated medical costs as a function of age, sex, 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.

Results: 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.

Conclusion: This chapter improves upon previous work and provides the first tool for the inclusion of future non-medical consumption in The Netherlands.

Introduction

Although cost-utility analysis (CUA) is increasingly used to assess whether new interventions in healthcare yield sufficient value for money (3), there are still several methodological issues that require attention. One such issue is the extent to which future costs should be included in CUAs (11,80), 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). Nonmedical costs here refer to consumption (eg, costs for housing and food) minus production (benefits from additional work in LYG). For medical costs, a distinction is made between related (eg, costs for check-ups by a cardiologist after a heart attack) and unrelated costs (eg, costs for treating pneumonia after said heart attack). Future related medical costs are typically included in CUAs. Including future unrelated medical costs, however, 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 (9,10), the most compelling being that all future costs and benefits should be considered (9). Later, the discussion was extended with the more practical view that because future unrelated medical consumption benefits are generally included, the costs thereof should be included to be consistent (14). 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 Quality Adjusted Life-Year (QALY) (27). There are different views, however, on the extent to which the benefits from non-medical consumption and production are actually included (19,20,49), and there is so far no compelling (empirical) evidence regarding this (80). The inclusion of future unrelated medical costs in CUA is now required in The Netherlands (65) and recommended in the United States (72). Although 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 (72).

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 (43) and updated in 2016 (PAID 1.1). This tool provides age and sex-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 the 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 healthcare costs are often higher in the last period of life (44). Since older people are more likely to die, not correcting for this leads to an overestimation of the impact of age on medical expenditures (44) and ignores the fact that saving a life at a given age leads to the postponement of this high-cost last period of life (42). Future related medical costs of specific diseases already included in the analysis can be excluded to prevent double-counting.

This chapter provides an extensive update of PAID to PAID 3.0. First, it uses most recent available cost of illness (COI) data (2017). Second, and the largest difference from PAID 1.1,

future costs of non-medical consumption are included. We provide guidance, supported by 3 case studies, on how to use PAID 3. 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 (9), 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:

$$ICER = \frac{\Delta\ [LY \times (RMC + PC)]}{\Delta\ QALY} + \frac{\Delta\, LY \times UMC}{\Delta\ QALY} + \frac{\Delta\, LY \times NMC}{\Delta\ QALY} \quad (1)$$

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 3 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 $LY \times [UMC + NMC]$ for an individual aged a dying at age n, can be written as shown in Equation (2):

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

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 sex as a starting point for estimating unrelated medical costs. Using methods identical to those of van Baal and colleagues (43), 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 (43). Disease-specific per capita healthcare costs were estimated using data from the Dutch COI from 2017 (81). Rather than using the system of health accounts (82) perspective (used in PAID 1.1), we use the classification from the National Institute for Public Health and the Environment (RIVM). Although the system of health accounts is internationally recognized, the RIVM definition includes more healthcare costs, such as international care. Whereas 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 sex and 21 age-classes, which we interpolated using cubic splines to obtain age-year-specific per capita expenditures, and which 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 these are also included in our definition of unrelated medical costs. Because healthcare costs are strongly determined by both age and time to death (83), individual lifetime healthcare costs can be estimated as shown in the first 2 parts of Equation (2). To obtain estimates for survivors and decedents, average per capita expenditures are divided into 1 part attributable to those dying and 1 part to those surviving at that particular age, assuming average costs are a weighted average of costs for survivors and decedents (age and sex indices are left out here for notational purposes):

$$ac_i = (1 - m) \times sc_i + m \times dc_i \tag{3}$$

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 sex- and age-dependent ratios between costs for decedents and survivors (r_i):

$$dc_i = r_i \times sc_i \tag{4}$$

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

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

Mortality rates from 2017 were obtained from Statistics Netherlands (84). We used the same disease-specific ratios for costs between decedents and survivors for the hospital sector 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 (85). 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 (83–86).

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 (87,88), implying lower per person consumption costs when household size is larger. For instance, spending on housing can be divided among 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 because preventing a death in a single-person household will result in more future non-medical consumption than preventing a death in a multiperson household (89). To estimate costs of non-medical consumption for an average household by age, we fit 2 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 Organisation for Economic Co-operation and Development modified equivalence scale (90). The Organisation for Economic Co-operation and Development modified equivalence scale assigns a weighting factor of 0.5 to each additional adult household member and 0.3 to each child in a multiperson household. The second model estimates the probability of a household having more than 1 adult; we are interested in making predictions for an average household. Using this equivalence scale implies that preventing a death in a singleperson household results in twice as much non-medical consumption as compared with a multiperson household with two adults. Details on these models and testing of assumptions can be found elsewhere (88).

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):

$$nmc(a) = \left[hh\,equiv(a) \times h(a) \times w\right] + \left[hh\,equiv(a) \times \left(1 - h(a)\right)\right] \quad (5)$$

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 an adult and .3 for a child.

Case Studies

We demonstrate the impact of including future costs on the ICER via 3 case studies. Benefits are discounted at 1.5% per year and costs at 4% per year, in adherence with Dutch guidelines(65). For the first case study, a life is hypothetically saved at ages 0 to 100, whereas 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 data from Gheorghe and colleagues (91).

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 3 colon cancer (92), wherein oxaliplatin showed an incremental QALY gain of 1.02 and 0.68 LYG, incremental costs of V9961, and a corresponding ICER of V9766. The sample consisted of patients previously diagnosed with stage 3 colon cancer who were 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 lung cancer (93). The paper from which the survival curves are extracted does not perform a CEA, and therefore there are no "baseline" ICER or QALY gains. In this clinical trial, the median age at baseline was 64 years of age, and 71% of patients were male. This case study demonstrates how to use PAID when survival is short. We recommend using estimates of living 1 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 because 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 1 year longer at a particular age can be calculated as follows:

$$c(a,g) = sc(a,g) + dc(a+1,g) - dc(a,g) \quad (6)$$

where

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

Furthermore, although the approach discussed earlier 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 healthcare 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:

$$sc(a)_i = p(i \mid a) \times sc(a \mid i)_i \quad (7)$$

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

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 patients with lung cancer (94). 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 (94) and adding these back to the sum of unrelated medical costs, as shown in the equations below.

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

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

where

- j = unrelated disease with higher costs (e.g. stroke);
- λ = multiplier.

To demonstrate how to use PAID with survival data on an individual level, we fitted 2 parametric survival models, assuming a Weibull distribution to overall survival results presented in the Kaplan–Meier plot (93) 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, whereas per capita non-medical consumption shows a less strong age pattern but decreases at old age and peaks at middle age (identical numbers for males and females because estimates are not sex specific). These graphs show that up until around age 75, people have higher non-medical costs than healthcare consumption, whereas afterward, healthcare exceeds non-medical consumption.

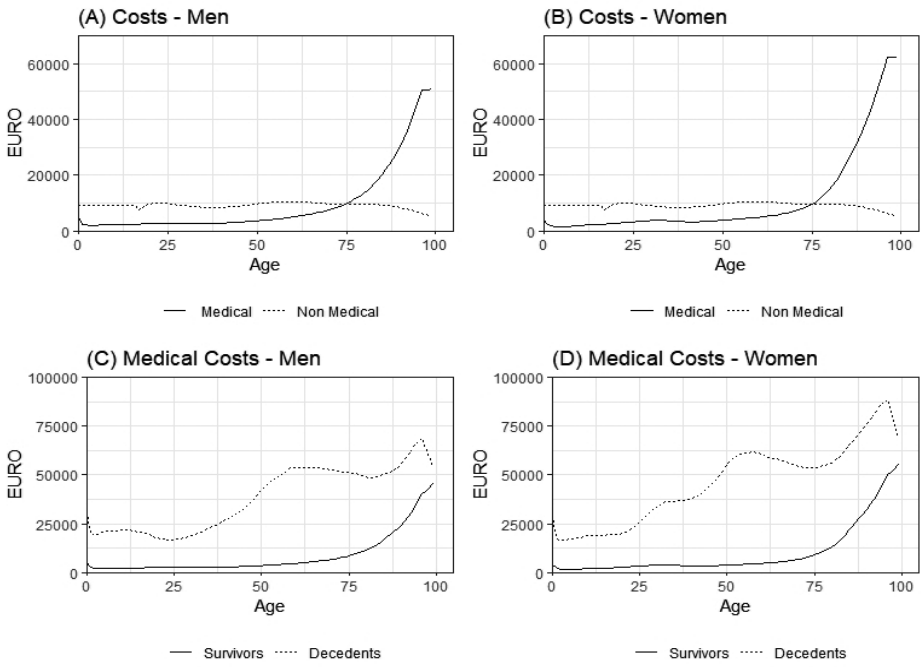


Figure 1: (A and B) Average per capita medical costs and nonmedical consumption by age. (C and D) Medical costs, split into survivor and decedent costs by age.

Age-specific per capita medical costs for survivors and decedents are presented in graphs C and D, showing comparable patterns in spending by sex, 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 and decedents typically incur higher healthcare expenditures, narrowing the difference in costs.

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 save them.

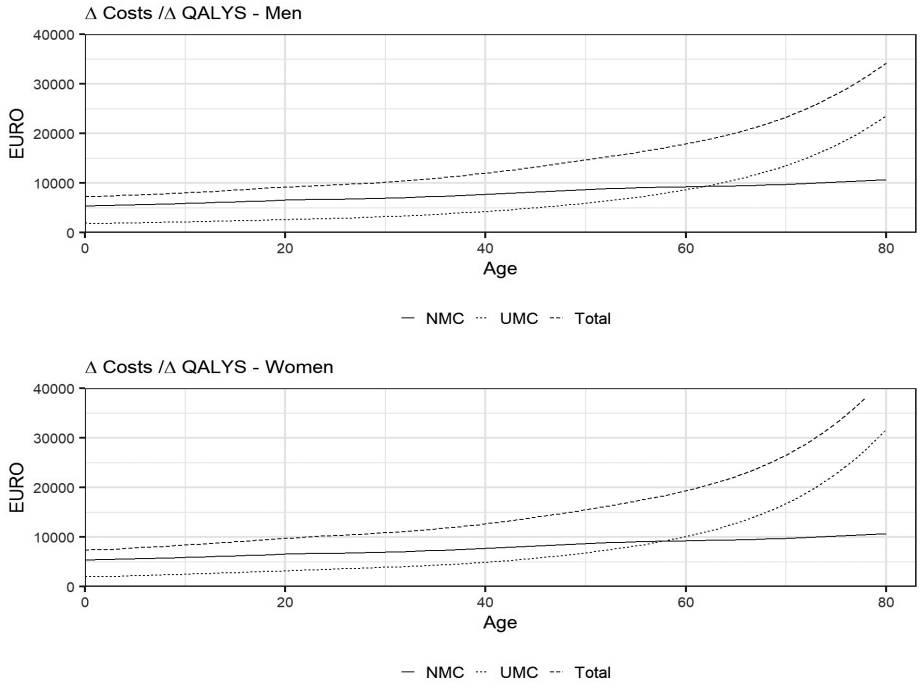


Figure 2: Case study 1. The hypothetical impact of including future unrelated medical costs and future nonmedical consumption (NMC) on the ICER when death is prevented (for free) at a certain age.

The results of the second and third case study are summarized in Table 1. Figures 3 and 4 show 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

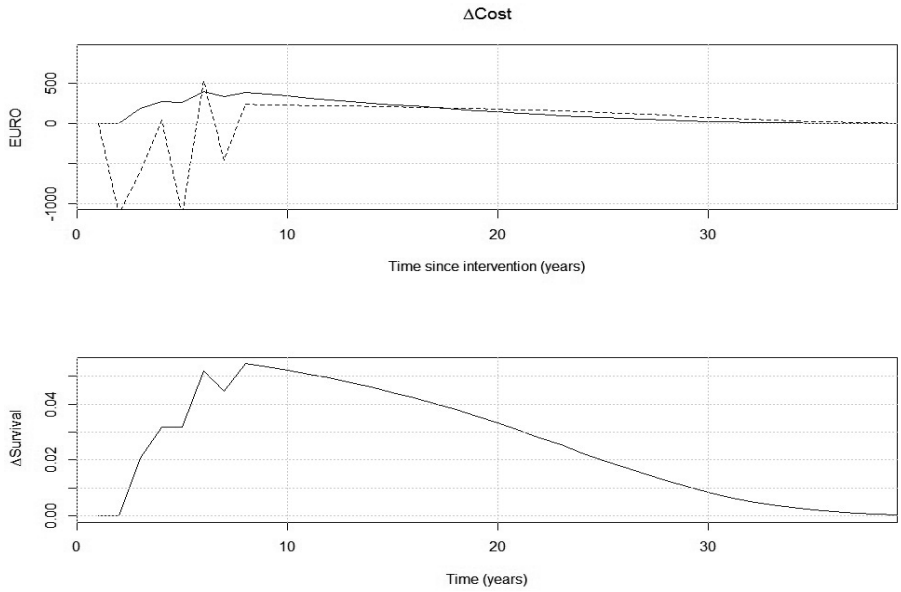


Figure 3: Case study 2. The added costs for including unrelated medical consumption and non-medical consumption (top), and the difference in survival between intervention and comparator group (bottom).

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 4 (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 to €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.

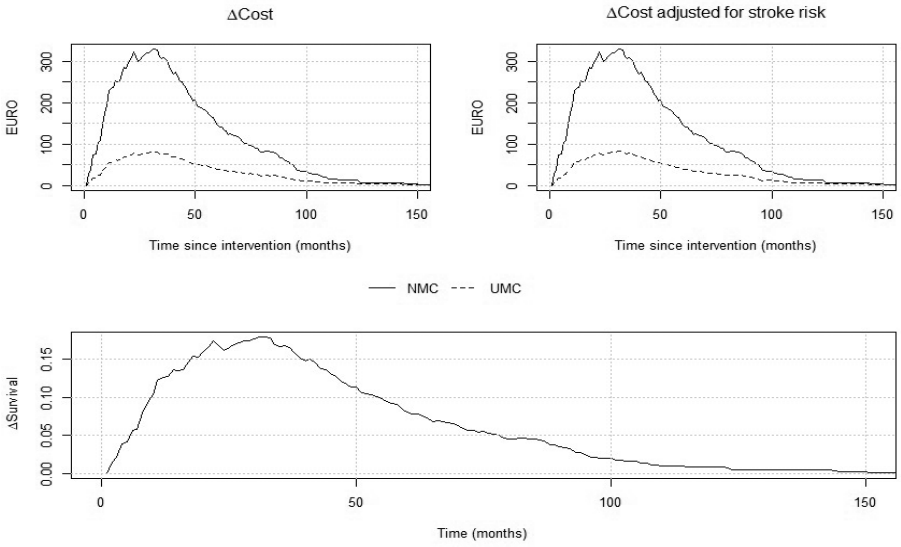


Figure 4: Case study 3. The additional costs by time for the lung cancer intervention (top left), and the additional costs by time when adjusted for increased stroke risk (top right). Difference in survival between intervention and comparator group (bottom).

Discussion and conclusion

In 2011, a practical tool to include future unrelated medical costs in a standardized manner was introduced (43). In this chapter, we updated the tool with the most recent data on medical costs and included estimates for future non-medical consumption. Recent COI data were 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. Using case studies, this chapter further demonstrated how to use the tool in practice.

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 owing to rising healthcare expenditures with age, whereas 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 (87,95); 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. When estimating the impact of including future unrelated medical costs on saving a life at different ages, however, we consider time to death. 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%, 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 (2,77). Using the iMTA Disease Burden Calculator (96), 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 (77). Including future costs in this study could thus make this intervention not cost-effective because 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 show that PAID estimates can easily be applied to several forms of models. Furthermore, we show how to adjust estimates when costs for unrelated diseases in the studied population are suspected to differ from the costs for 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, whether adjusted or unadjusted, is relatively small. 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 (52).

An important limitation to the study 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 (97), more detailed estimates may show different patterns. An update of these ratios would be useful for future research. A further limitation with regard to decedent–survivor cost ratios is that we did not have estimates for all providers, and disease-specific estimates for 3 providers were derived by combining hospital estimates with provider-specific sector estimates. In a similar vein, the classification of costs among 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. Although 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, although this is unlikely in the Dutch context, given that almost all healthcare spending is publicly financed (98).The findings that non-medical consumption decreases from a certain age (87,95,99), however, 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 chapter. Uncertainty could stem from the 2 key elements of our estimates: survival and costs. The original costs in this case are averages provided by Statistics Netherlands and are therefore with little surrounding uncertainty. However, there are still sources of uncertainty, such as decedent-survivor cost ratios; the larger the time to death effect (larger ratios), the smaller the impact of future costs on the ICER (9).

In general, including future costs may have a systematic effect on reimbursement decisions because 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 (9).

In this chapter, no specific attention is paid to future related medical costs and future productivity because 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 (100). 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 are 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 (14). Furthermore, it is also unclear to what extent thresholds to which ICERs are compared include these benefits (80). The impact of including future non-medical consumption and the comparison with existing thresholds should thus be interpreted with caution.

To conclude, this chapter provides an update and extension of PAID and demonstrates 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.

Appendices

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 Illness study)

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	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)
	Infectious and parasitic disease				1.72
1	Intestinal infectious diseases	A00-A09	001-009	- r001 (001-008) - r002 (009)	12.50
2	Tuberculosis	A10-A19, B90	010-018, 137	- r003 (010-018, 137)	1.14
3	Meningitis	A39, A87, G00-G03	036, 047, 320-322	- r006 (remainder of 001-139, except 0340, 0993, 0994, 135, 1361)	2.27
4	Septicemia	A40-A41	038	- r004 (038)	5.68
5	HIV/AIDS	B20	042-044	- r005 (042-044 or 2795, 2796)	15.91
6	Sexually transmitted diseases	A60, A50-A58 A63, B00, B07, B08	054, 078, 090-099	- r006 (remainder of 001-139, except 0340, 0993, 0994, 135, 1361)	4.55
7	Hepatitis	B15-B19, K77	070, 573.1	- r006 (remainder of 001-139, except 0340, 0993, 0994, 135, 1361) - r072 (570, 571.4-573)	13.64
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	- r006 (remainder of 001-139, except 0340, 0993, 0994, 135, 1361) - r130 (remainder of V01-V82)	43.18

Table B1: Summary of disease categories in PAID 3.0 (based on the categories distinguished in the Dutch Costs of Illness study) *(continued)*

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	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)
	Neoplasms				6.69
9	Esophagus cancer	C15	150	- r015 (remainder of 140-208)	1.46
10	Stomach cancer	C16	151	- r015 (remainder of 140-208)	0.58
11	Colorectal cancer	C18-C21	153-154	- r007 (153, 154)	10.20
12	Pancreas cancer	C25	157	- r015 (remainder of 140-208)	1.75
13	Lung cancer	C33-C34	162	- r008 (162)	7.87
14	Breast cancer	C50	174	- r010 (174,175)**	14.87
15	Cervical cancer	C53-C55	180	- r011 (179,180,182)**	2.33
16	Ovary cancer	C56-C57	183	- r012 (183)**	1.46
17	Prostate cancer	C61	185	- r013 (185)*	6.71
18	Bladder and kidney cancer	C64-C68	188-189	- r014 (188) - r015 (remainder of 140-208)	4.66
19	Non-Hodgkin's disease	C82- C83	200, 202	- r015 (remainder of 140-208)	3.79
20	Other lymphoid cancer and leukemia	C81, C90-C95	201, 203-208	- r015 (remainder of 140-208)	12.14
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	- r015 (remainder of 140-208) - r010 (174,175)** - r130 (remainder of V01-V82)	21.57
22	Other benign neoplasms	C44, D03, D10-D23, D30-D36	173, 210-216, 223-239	- r009 (172,173) - r016 (230-234) - r017 (2113,2114) - r019 (remainder of 210-239)	10.79

Table B1: Summary of disease categories in PAID 3.0 (based on the categories distinguished in the Dutch Costs of Illness study) *(continued)*

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	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)
	Endocrine, nutritional and metabolic diseases				2.85
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	- r022 (250) - r034 (remainder of 320-359) - r036 (remainder of 360-379) - r090 (580-5834, 5838, 5839, 5900-5902, 5908, 5909, 591, 5933-5935, 5937, 5996) - r099 (remainder of 580-629 except 5997)	63.70
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	- r023 (remainder of 240-278) - r130 (remainder of V01-V82)	36.30
	Diseases of the blood and the blood-forming organs				0.51
25	Diseases of the blood and blood-forming organs	D50, D51, D56-D59, D61, D63-D75, Z13	280-289, V78	- r020 (280-285) - r021 (135, 2790-2793, 2798, 286-288, 2890, 2894-2899) - r130 (remainder of V01-V82)	100.00
	Mental and behavioral disorders				28.60
26	Dementia	F01-F05, F329	290, 311	- r024 (2900-2902, 2904-2909, 2941) - r028 (296, 2980, 3004, 3011, 311)	35.99

Table B1: Summary of disease categories in PAID 3.0 (based on the categories distinguished in the Dutch Costs of Illness study) *(continued)*

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	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)
27	Schizophrenia	F20	295	- r027 (295, 2970-2973, 2978-2979, 2983-2989)	1.64
28	Depression	F30, F341	296, 300.4	- r028 (296, 2980, 3004, 3011, 311)	4.50
29	Anxiety	F40-F42, F449, F488, F43, F438	300.0, 300.10-300.15, 300.2-300.3, 300.5, 308, 309.8	- r029 (remainder of 290-319)	3.07
30	Personality disorders	F431, F6811, F688, F60	300.16-300.19, 301	- r028 (296, 2980, 3004, 3011, 311) - r029 (remainder of 290-319)	2.73
31	Dependency on alcohol and drugs	F10-F16, F18-F19,	291-292, 303-305	- r025 (291, 303, 3050) - r026 (292, 2940, 304, 3051-3059)	3.27
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	- r024 (2900-2902, 2904-2909, 2941) - r026 (292, 2940, 304, 3051-3059) - r029 (remainder of 290-319) - r130 (remainder of V01-V82)	16.02
33	Mental retardation, including Down's syndrome	F70-F73, F79, Q909	317-319, 758.0	- r029 (remainder of 290-319) - r110 (740-759)	32.86
	Diseases of the nervous system				6.71
34	Parkinson's disease	G20-G21	332	- r034 (remainder of 320-359)	3.49
35	Multiple sclerosis	G35	340	- r031 (340)	3.49
36	Epilepsy	G40	345	- r032 (345)	5.23
37	Cataract	H26	366	- r035 (366)	5.23
38	Disorders of accommodation and refraction	H52	367	- r036 (remainder of 360-379)	15.41

Table B1: Summary of disease categories in PAID 3.0 (based on the categories distinguished in the Dutch Costs of Illness study) *(continued)*

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	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)
39	Blindness and low vision	H54	369	- r036 (remainder of 360-379)	7.56
40	Conjunctivitis	H00-H02	373-374	- r036 (remainder of 360-379)	1.74
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	- r036 (remainder of 360-379)	6.98
42	Ear disorders	H60-H95	380-389	- r037 (380-389)	22.97
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	- r030 (3310) - r034 (remainder of 320-359) - r130 (remainder of V01-V82)	27.91
	Diseases of the circulatory system				11.66
44	Hypertension	I10-I15	401-405	- r038 (401-405)	6.35
45	Coronary heart disease	I21-125	410-414	- r039 (413; ICD-9-CM: 4111, 413) - r040 (410) - r041 (411-412, 414; ICD-9-CM: 4110, 4118, 412, 414)	22.24
46	Heart failure	I50-I51	428-429	- r044 (428) - r048 (2891-2893, remainder of 390-459 except 435, 446 and 4590)	8.03
47	Other heart disease, including pulmonary circulation	I30-I49	390-398, 415-427	- r048 (2891-2893, remainder of 390-459 except 435, 446 and 4590) - r042 (415-417) - r043 (426, 427)	19.40

Table B1: Summary of disease categories in PAID 3.0 (based on the categories distinguished in the Dutch Costs of Illness study) *(continued)*

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	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)
48	Stroke	I60-I69	430-438	- r033 (435) - r045 (430-434, 436-438)	14.38
49	Diseases of arteries	I70-I79	440-448	- r046 (440) - r048 (2891-2893, remainder of 390-459 except 435, 446 and 4590)	9.36
50	Other circulatory diseases	I80-I99	451-459	- r048 (2891-2893, remainder of 390-459 except 435, 446 and 4590)	20.23
	Diseases of the respiratory system				3.39
51	Acute upper respiratory infections	J00-J06	460-466	- r049 (0340, 460-465, 487; ICD-9-CM: 340, 460-465, 487, 488) - 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
52	Pneumonia and influenza	J09-J18	480-487	- r050 (480-486) - r049 (0340, 460-465, 487; ICD-9-CM: 340, 460-465, 487, 488)	16.67
53	Asthma and chronic obstructive pulmonary disease (COPD)	J40-J47	490-496	- r054 (490-492, 494, 496) - r055 (493) - r056 (remainder of 460-519)	14.37

Table B1: Summary of disease categories in PAID 3.0 (based on the categories distinguished in the Dutch Costs of Illness study) *(continued)*

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	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)
54	Other respiratory diseases	J30-J39, J60-J99	467-479, 488-489, 497-519	- r049 (0340, 460-465, 487; ICD-9-CM: 340, 460-465, 487, 488) - r053 (470-473, 475-478) - r056 (remainder of 460-519)	57.47
	Diseases of the digestive system				6.84
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	- r057 (520-525) - r058 (526-529)	62.11
56	Gastroduodenal ulcers	K25-K28	531-534	- r060 (531-534)	0.57
57	Appendicitis	K35-K38	540-543	- r062 (540-543)	1.42
58	Abdominal hernia	K40-K46	550-553	- r063 (550) - r064 (551-553)	2.85
59	Inflammatory intestinal disease	K50-K52	555-556	- r065(555, 556)	6.84
60	Other intestinal diseases	K55-K64	557-569	- r066 (558) - r067 (560) - r068 (562) - r069 (565, 566, 5690-5694) - r070 (557, 564, 5695, 5698, 5699)	1.71
61	Chronic liver disease and cirrhosis	K70	571	- r071 (5710-5713) - r072 (570, 5714-573)	1.42

Table B1: Summary of disease categories in PAID 3.0 (based on the categories distinguished in the Dutch Costs of Illness study) *(continued)*

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	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)
62	Other liver diseases	K72, K75, K763-K769, K77	570, 572, 573.0, 573.2-573.9	- r072 (570, 5714-573) - r076 (remainder of 520-579)	0.00
63	Gallbladder diseases	K80-K83	574-576	- r073 (574) - r074 (575, 576)	3.70
64	Other diseases of the digestive system	K20, K29-K31, K86-K90	530, 535-537, 577-579	- r059 (530) - r061 (535-537) - r075 (577) - r076 (remainder of 520-579)	19.37
65	**Diseases of the genitourinary system**				3.16
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	- r090 (580-5834, 5838, 5839, 5900-5902, 5908, 5909, 591, 5933-5935, 5937, 5996) - r091 (5836, 5837, 584-586) - r093 (0994, 587-589, 5903, 5930-5932, 5936, 5938, 5939, 595- 597, 5980, 5981, 5988, 5989, 5990-5995, 5998, 5999, 6256)	27.78
67	Acute renal and urinary infections	N11, N30, N34, N390	590, 595, 597, 599.0	- r090 (580-5834, 5838, 5839, 5900-5902, 5908, 5909, 591, 5933-5935, 5937, 5996) - r093 (0994, 587-589, 5903, 5930-5932, 5936, 5938, 5939, 595- 597, 5980, 5981, 5988, 5989,5990-5995, 5998, 5999, 6256)	8.64

Table B1: Summary of disease categories in PAID 3.0 (based on the categories distinguished in the Dutch Costs of Illness study) *(continued)*

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	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)
68	Other renal and urinary diseases	N13-521, N32, N35, N360-N369	591-594, 596, 598, 599.1-599.9	- r090 (580-5834, 5838, 5839, 5900-5902, 5908, 5909, 591, 5933-5935, 5937, 5996) - r092 (592, 594, 7880) - r093 (0994, 587-589, 5903, 5930-5932, 5936, 5938, 5939, 595- 597, 5980, 5981, 5988, 5989, 5990-5995, 5998, 5999, 6256)	28.40
69	Hyperplasia of prostate	N40	600	- r094 (600)*	4.94
70	Other disorders of male genital organs	N41-N51	601-608	No estimates***	4.94
71	Disorders of female genital organs	N60-N92, N94	610-627, 629	No estimates	18.52
72	Female infertility	N97, Z31	628, v26	No estimates	6.79
	Pregnancy, childbirth and the puerperium				2.07
73	Pregnancy	O00-O48, Z34	630-648, V22-V23	No estimates	34.91
74	Childbirth	O60-O84, Z76, Z37, Z38	650-669, V20, V27, V30-V39	No estimates	37.74
75	Puerperium	O85-O92, Z39	670-676, V24	No estimates	20.75
76	Contraception	Z30	V25	No estimates	7.55
	Diseases of the skin and subcutaneous tissue				1.64
77	Eczema	L22-L25	691-692	- r078 (690-693, 6943, 696-6983, 6988, 6989)	13.10
78	Decubitus	L89	707	- r079 (remainder of 680-709)	13.10

Table B1: Summary of disease categories in PAID 3.0 (based on the categories distinguished in the Dutch Costs of Illness study) *(continued)*

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	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)
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	- r077 (680-686) - r078 (690-693, 6943, 696-6983, 6988, 6989) - r079 (remainder of 680-709)	75.00
	Diseases of the musculoskeletal system and connective tissue				7.47
80	Rheumatoid arthritis	M05-M08	714	- r083 (0993, 711-716, 718, 719, 7271, 7284)	9.92
81	Osteoarthrosis	M15	715	- 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) - 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) - r083 (0993, 711-716, 718, 719, 7271, 7284)	
82	Dorsopathy	M40-M54	720-724	- r085 (720, 721, 7230, 7235, 7240, 737) - r086 (7220-7227, 7229) - r087 (7231, 7234, 7236, 7241-7243, 7245)	14.36
83	Osteoporosis	M810, M844	733.0-733.1	- r089 (remainder of 710-739)	1.83

Table B1: Summary of disease categories in PAID 3.0 (based on the categories distinguished in the Dutch Costs of Illness study) *(continued)*

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	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)
84	Internal derangement of the knee	M23	717	- r082 (717)	5.74
85	Unspecified musculoskeletal diseases or conditions	M35, M75, M60, M61, M65, M79	725-729	- r083 (0993, 711-716, 718, 719, 7271, 7284) - r084 (1361, 2794, 446, 710, 725, 7285) - r086 (7220-7227, 7229) - r088 (726, 7270, 7272-7279) - r089 (7280-7283, 7286-7289, 729)	37.08
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	- r083 (0993, 711-716, 718, 719, 7271, 7284) - r084 (1361, 2794, 446, 710, 725, 7285) - r089 (remainder of 710-739)	31.33
	Congenital malformations				0.58
87	Congenital anomalies of nervous system	Q00-Q05	740-742	No estimate	3.33
88	Congenital anomalies of circulatory system	Q20-Q25	745-747	No estimate	26.67
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	No estimate	70.00

Table B1: Summary of disease categories in PAID 3.0 (based on the categories distinguished in the Dutch Costs of Illness study) *(continued)*

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	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)
	Certain conditions originating in the perinatal period				0.23
90	Disorders relating to premature birth	P07	765	No estimate	75.00
91	Other conditions originating in the perinatal period	P00-P04, P08-P15, P22-P28, P50-P90	760-763, 766-767, 769-770, 772-779	No estimate	16.67
	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified				1.91
92	Symptoms, signs and ill-defined conditions	R40-R99	780-799	No estimate	100
	Injury, poison and certain other consequences of external causes				3.28
93	Skull-brain injury	S02, S04- S06	800-801, 803-804, 850-854, 950-951	No estimates	12.50
94	Fractures of upper extremities	S42-S52	810-819	No estimate	7.14
95	Hip fracture	S72	820-821	No estimate	16.07
96	Other lower extremity fracture	S82, S92	822-829	No estimate	14.29
97	Superficial injury	S00, S05, S09-S10, S20, S30, S40, S60, S70, S80, S90, T07	910-924	No estimates	2.38

Table B1: Summary of disease categories in PAID 3.0 (based on the categories distinguished in the Dutch Costs of Illness study) *(continued)*

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	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)
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	No estimates	48.21
	Not allocated/ Not disease related				10.68
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	No estimates	91.97
100	Not disease-related	Z00, Z02, Z52, Z56, Z59, Z60, Z69, Z71, Z74, Z75, Z76	V59-V62, V65, V70	No estimates	8.03

* 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

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).

$$r_{i,j>1} = r_{i,j=1}^{x_j>1} \tag{C1}$$

Where:

- j = index denoting the healthcare provider;
- j = 1 implies hospital care;
- $r_{i,j}>1$ = ratio for disease i for healthcare provider j other than hospital care;
- $x_j>1$ = 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:

$$r_{i=1,j>1} = r_{i=1,j=1}^{x_{j>1}} \rightarrow \log(r_{i=1,j>1}) = x_{j>1}\log\left(r_{i=1,j=1}\right) \rightarrow x_{j>1} = \frac{\log(r_{i=1,j>1})}{\log\left(r_{i=1,j=1}\right)} \tag{C2}$$

We assume that the scaling factor $x_{j>1}$ is equal for all diseases, which leads to Equation C.3:

$$x_{j>1} = \frac{\log(r_{i=1,j>1})}{\log\left(r_{i=1,j=1}\right)} = \frac{\log(r_{i>1,j>1})}{\log\left(r_{i>1,j=1}\right)} for\ all\ values\ of\ i \tag{C3}$$

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):

$$\left(sc_{tot,j>1} - \sum_i \frac{a c_{i,j>1}}{1 + \left(r_{i,j=1}^{x} - 1\right) \times m}\right)^2 \tag{C4}$$

Chapter 4

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

Based on: de Vries LM, Kellerborg KM, Brouwer WBF, van Baal PHM. 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.
Vaccine. 2021;39(29).

Abstract

Background: 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.

Methods: 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.

Results: 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.

Discussion and conclusion: 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 (101). 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) (4). 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 (4). The cost-effectiveness of an intervention can then be evaluated by comparing the ICER to a predefined cost-effectiveness threshold (2). 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 (4).

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 (102). 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 (9). 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 (11,80). It was shown, using theoretical models, that including all future medical costs would be required for optimal decisions from a healthcare perspective (12). From a broad societal perspective, the analysis should include future medical as well as non-medical consumption and productivity costs (9). 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, often measured using the EQ-5D questionnaire and related country-specific value sets) (80). 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) (103) and was recently recommended in the US by the Second Panel on Cost Effectiveness in Health and Medicine (104). The inclusion of all future non-medical costs, defined as NMC minus productivity costs, is currently only recommended in the US by the aforementioned Panel (104).

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') (83), and NMC and productivity are typically higher in middle ages (87,105). Healthcare costs are also generally higher for people with underlying health conditions for which medical treatment is needed (35), 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.

The empirical literature on the impact of including additional future costs in CEA is growing. For instance, it was shown that ICERs of cancer screening in the US were underestimated by between $10,300 and $13,700 when future UMC would be excluded and utility losses for competing diseases would not be considered (106). Also, for the UK, it was shown that including future UMC led to an increase in the ICER of between 7% and 13% (103). A last example is from the Netherlands, where a tool was developed and updated to include both future NMC and UMC (104). Nevertheless, 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 (107) 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 (108). 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):

$$Total\,ICER = \underbrace{\frac{\Delta\,[LY \times (RMC + PC)]}{\Delta\,QALY}}_{Original\ ICER} + \underbrace{\frac{\Delta\,LY \times UMC}{\Delta\,QALY}}_{Impact.\ UMC} + \underbrace{\frac{\Delta\,LY \times NMC}{\Delta\,QALY}}_{Impact\ NMC} \quad (1)$$

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 (109) 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. In the next sub-section, we discuss how these costs were estimated. QALYs used from the original study were obtained from general population utilities and EQ-5D questionnaires from disease-specific studies. As mentioned in the background section, it is under discussion to what extent QALYs capture benefits beyond health – and related to what extent the costs thereof should be considered. However, since the focus of this chapter is on the cost-side, we focus on these here and pay some more attention to the issue in the discussion and suggestions for further research.

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 (65). We combined these estimates and the QALYs gained from preventing non-fatal cases with cases prevented over time by age- and risk group. For this, we multiplied these costs and QALYs by the cases prevented for the different years. 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 (107).

Since not all details from the original model were available, 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 (104). 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 from the Dutch Cost of Illness study and separated into costs for decedents and survivors using mortality information from Statistics Netherlands 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 Dutch Household Consumption surveys. Economies of scale within households were considered in these estimates as these have been found important when estimating NMC (89). To do so, consumption for the average household was estimated using the Organisation for Economic Co-operation and Development modified 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 Appendix A and B, we explain in more detail how we derive per patient estimates.

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 (110). 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) (111). 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, stemming from a guideline for primary prevention for cardiovascular disease with cholesterol-lowering statins (112). 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 (110). 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 (77,110). The €20,000 is based on the threshold for primary prevention. The €50,000 and €80,000 are mainly based on research into the willingness to pay for treatment in others and themselves or loved ones, respectively (110).

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 (113,114). 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 (114). 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). 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. The relation between age and costs for different risks are somewhat different for decedent costs. For medium- and low-risk groups, decedents costs do still increase with age, but at a slower pace. Decedents costs in the high-risk group show a hump-shaped pattern, for which an important factor is the large share of costs for cancers for this risk group, for which per capita costs increase until approximately age 60 and then decrease. 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. 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. An important reason for this is that for medium-risk, costs for cardiovascular diseases comprise a large share of the costs, which rapidly increase with age for both survivors and decedents. This, while costs for cancers are a large share of the costs in the high-risk group and these costs are much more centered in the last year of life compared to the costs for cardiovascular diseases. The estimates of NMC by age for all risk groups show a hump-shaped pattern, 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

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. *(continued)*

		Age				
Cost category	**Risk group**	**18**	**50**	**65**	**75**	**85**
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 of 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. In Figure A.1 in Appendix C, an additional graph is shown only including UMC. 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.

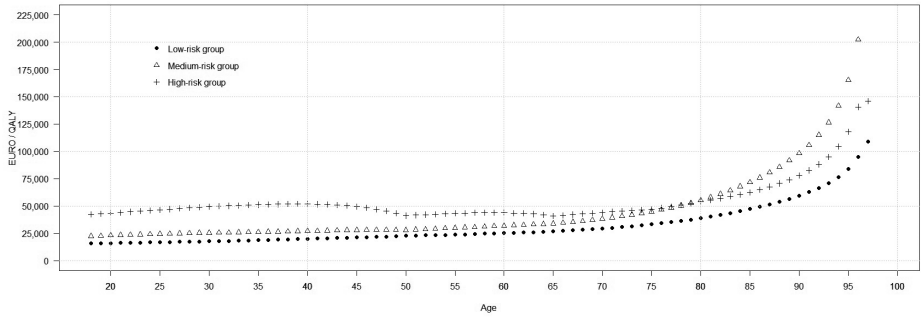


Figure 1: Impact future unrelated medical costs and non-medical consumption on ICER for saving a life by age and risk group

Impact of future costs on cost-effectiveness of 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 5th 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.

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 €)

		Impact		ICERs (ranking[a])			Thresholds (proportional shortfall)[c]
		UMC	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)

The last column in Table 2 shows the cost-effectiveness thresholds based on the average proportional shortfall ((average) health lost in the population treated) 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.

In Table A.2 in Appendix C 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. For instance, the impact of including UMC and NMC for the strategy 18plus-at risk is €36,579, whereas the impact for the subpopulation aged 85+ with medium-risk of infection is €77,260. This emphasizes that how the different strategies are constructed highly affects the outcomes of the impact, and presumably the analyses in general, and careful construction of these strategies is warranted.

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., (50,53,106)). 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. In general, the accuracy of future CEA could presumably be improved by using utility values measured in the specific risk groups.

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.

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 (104). 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 (since excluding costs just like including costs has distributional consequences), 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 (80). 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. An accurate and complete estimate of all costs and benefits is a prerequisite for such an (and any other) exchange between efficiency and equity.

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 (115) (note that the patent of the studied vaccine has not yet expired (116)).

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 (117). 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 and 49 and €15,605 for persons between 50 and 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 (or gains) could result in a lower ICER after including future costs for relatively young adults (during working ages) (e.g., (50,53)). Future

research could investigate the differences between existing approaches to estimate productivity costs in the context of preventing mortality. It would be relevant to then also consider potential differences in productivity based on different risk groups. People with underlying conditions could, for instance, be less productive during their lifetime, potentially lowering the impact of these costs.

Finally, although this was not the focus of this study, 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 (80). 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 (14). It is also unclear to what extent thresholds to which ICERs are compared include these benefits (80). Further research into these issues is therefore recommended.

To conclude, in this chapter 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.

Appendices

Appendix A: 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 (hcei (a)) as average costs for disease i at age a, conditional on having disease i ($ac_i(a|i)$), 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.

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

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.

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

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.

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

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

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.

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

=>

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

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

=>

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

Appendix B: Matching ICD codes

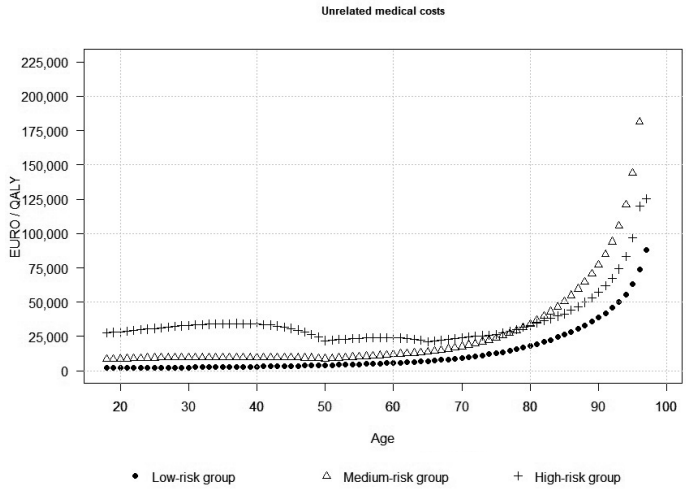
Table A.1: Matched diseases and ICD-10 codes from different sources

Risk group	Condition original study	UK study	ICD-10	PAID
	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,I41,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
Medium				
	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

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

Risk group	Condition original study	UK study	ICD-10	PAID
	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
High	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,Dw57.0,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	Transplantations:	Z94,Z85, (Bone marrow transplants: Z94.8)	Not allocated

Appendix C: Results



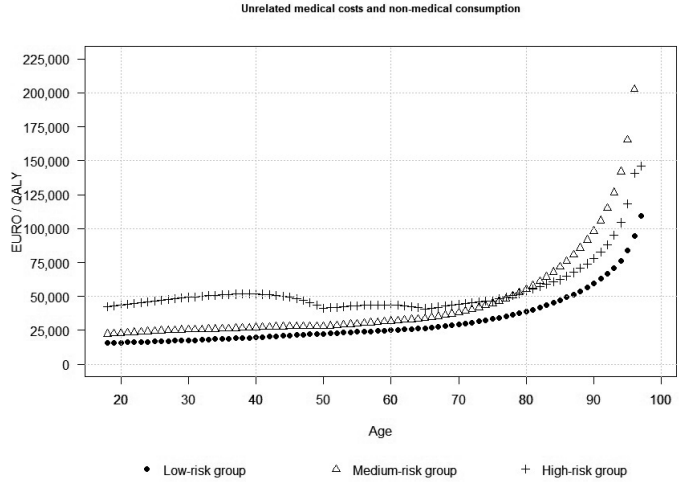


Figure A.1: Impact future costs on incremental cost-effectiveness ratio for saving a life by age and risk group

Table A.2: Impact future unrelated medical costs (UMC) and non-medical consumption (NMC) on the ICERs and cost-effectiveness threshold based on proportional shortfall for different age- and risk groups (all in €).

		Impact			Thresholds
Age	**Risk**	**UMC**	**NMC**	**UMC + NMC**	**(proportional shortfall)[a]**
18-49	Low-risk	1,805	9,636	11,441	0 (0,01)
	Medium-risk	7,700	13,792	21,492	20,000 (0,15)
	High-risk	26,107	14,850	40,956	20,000 (0,34)
50-64	Low-risk	4,546	14,109	18,655	0 (0,02)
	Medium-risk	10,086	16,207	26,293	20,000 (0,19)
	High-risk	20,006	16,854	36,860	20,000 (0,24)
65-74	Low-risk	7,519	13,347	20,866	0 (0,02)
	Medium-risk	17,324	16,939	34,263	20,000 (0,20)
	High-risk	22,716	17,814	40,529	20,000 (0,19)
75-84	Low-risk	15,530	15,680	31,210	0 (0,01)
	Medium-risk	31,260	17,238	48,498	20,000 (0,19)
	High-risk	31,550	18,233	49,783	0 (0,04)
> 84	Low-risk	30,312	16,921	47,234	0 (-0,01)
	Medium-risk	59,871	17,389	77,260	20,000 (0,17)
	High-risk	47,981	17,984	65,965	0 (-0,04)

[a] 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)

Chapter 5

Benefits beyond health in the willingness to pay for a quality-adjusted life-year

Based on: de Vries LM, Brouwer WBF, van Baal PHM. Benefits beyond Health in the Willingness to Pay for a Quality-Adjusted Life Year. *Submitted manuscript.*

Chapter 6

The economics of improving global infectious disease surveillance

Based on: de Vries L, Koopmans M, Morton A, van Baal P. The economics of improving global infectious disease surveillance.
BMJ Glob Health. 2021;6(9).

Abstract

The threat of new emerging infectious diseases demands improvements in infectious disease surveillance, which crucially depends on (real-time) data sharing and new technologies.

Infectious disease surveillance can be typified as global public good, and related important obstacles are financing and removing barriers for producing and sharing information.

Public financing and provision are important to enable cost-effective disease surveillance, since otherwise optimal levels for society are unlikely to be reached.

Additional investments in infectious disease surveillance are preferably based on sound economic evaluations considering the specific characteristics of infectious disease surveillance, however, a framework for cost-effectiveness analyses capturing the specific characteristics is yet non-existent.

Introduction

With the global increase in population density, urbanization, and global travel and trade, the threat of widespread outbreaks of infectious diseases has increased relentlessly (129) as evidenced by recent examples of COVID-19 and Ebola. Further, although the most important causes of death shifted to noncommunicable diseases, in some poorer parts of the world, communicable diseases remain the most important cause of death (130). Crucial in the prevention of and reaction to these threats is early detection, which demands an infectious disease surveillance system that can signal unusual events. How to set up and improve surveillance and how to prioritize investments are questions that need input from different scientific disciplines. Here, we focus on some economic considerations.

The benefits of improving infectious disease surveillance

The best recognized purpose of disease surveillance is the (early) detection of epidemics and other health threats. New diagnostic tools such as unbiased and targeted next-generation sequencing (NGS) are being explored as options to improve surveillance as these allow to determine causes of unexplained disease outbreaks, trace and link sources of disease transmission, and facilitate a better understanding of how viruses and bacteria pass from animal to humans. With NGS, the same platforms and sometimes even the same protocols can be used for the analysis of viruses, bacteria, genes and parasites with the potential for cost saving through economies of scale (economies of scale occur when the costs per unit decrease when produced quantities increase, as total costs can be divided among more units), improving its affordability also for lower income countries (131,132). As most emerging infectious diseases are zoonotic, further improvements could come from incorporating concepts from 'One Health', integrating capacities across human and animal health sectors. In general, sharing data in a timely manner, both within and between sectors and countries, is expected to greatly enhance and accelerate the understanding of diseases and their patterning and reduce unit costs. Improved collaboration and data sharing could further help to reduce barriers for the adaption of new technologies through reducing current human capital constraints. For instance, limited access to the specific expertise is an important barrier for the adoption of technologies such as NGS for various countries (133). A last example of how surveillance could be improved is by limiting current workforce constraints. This was evidenced during the COVID-19 pandemic where, for instance, testing capacities were falling short at some points. Indeed, many of such improvements could also improve the effectiveness and efficiency of healthcare systems in general (134,135).

Incentives for research and data sharing

Currently, there are limited incentives and a lack of appropriate infrastructure for data sharing, which requires a clear governance structure that ensures a balance between privacy and access and adheres to (inter)national ethical and legal requirements. Solutions have been proposed for many of the issues limiting timely sharing of data in genomics research (133). An example of

an initiative to enhance data sharing is the model for improving disease surveillance set by the Collaborative Management Platform for detection and Analyses of (Re-)emerging and foodborne outbreaks (COMPARE) and its sequel Versatile Emerging infectious disease Observator (VEO) (https://www.compareeurope.eu; https://www.compare-europe.eu/VEO). The project aims to develop a global platform for sharing and analyzing NGS data that are customizable so groups of users can share data rapidly when needed while retaining ownership (131).

Financing disease surveillance and the 'global public good' concept

Hossain and colleagues (136) found that low-income and middle-income countries spend an annual median of $0.04 per capita on vaccine-preventable disease surveillance. The Organization for Economic Cooperation and Development provides estimates of spending on epidemiological surveillance and risk and disease control programs for 2018 ranging from 0.002% (Luxembourg) to 0.9% (Switzerland) of total healthcare expenditures. Recent research on the willingness to pay for surveillance in the EU found that, on average, people are willing to spend €264/year, which roughly translates into 5% of total health spending (137). Based on this, it could be argued that within the EU currently too little is spent on disease surveillance.

An important characteristic of surveillance and interventions around infectious diseases is externalities, outcomes beyond the scope of those pursuing the activity. (That is, preventing the spread in one country may also prevent the spread to other countries. Although externalities might be an opportunity for collaboration, the risk is that actors consider only their own costs and benefits, leading to underprovision of surveillance activities). Public goods are a special case where externalities exist, and goods are non-rivalrous and nonexcludable. Infectious disease surveillance is sometimes described as a (global) public good (e.g., people cannot be excluded from benefiting from a reduction in risk of infectious disease when its incidence is reduced (non-excludability), and one person benefiting from this reduction does not prevent anyone else from benefiting as well (non-rivalry)) (138). Although the purity of the public good characteristics can be questioned (139), the concept can be useful to promote and justify public interference and funding. Non-excludability and thereby inability to demand payment eliminates commercial incentives for producing public goods in the private market. Consequently, the market fails to provide quantities optimal for society: an argument for governmental interference and financing. As no global government exists, global public goods are often financed by international organizations, national governments or transnational corporations (139). Such organization of governmental and donor financing is a complex task, which requires attention for, among others, constraints related to fragmented financing within and across sectors and governmental levels (140).

Investments in surveillance in developing countries are often initiated as development aid. From the global public good perspective, however, one could argue that financing by more developed countries is actually in those countries' own interest. (One of the difficulties, however, is that countries typically have different priority diseases and thereby different surveillance priorities

due to the various threats to different population groups. Where rich countries may fear the importation of new viruses, poor countries suffer from common infections which give rise to diarrhea and respiratory diseases. Improved affordability of newer catch-all tools that can provide diagnosis for most common diseases and rule out emerging diseases would reduce these differences and stimulate international collaboration.) A recent example is the Access to COVID-19 Tools Accelerator (https:// www.who.int/initiatives/act-accelerator), a global collaboration to produce and provide equitable access to tests, treatments, and vaccines against COVID-19, which initially aids poorer countries though eventually helps to protect the entire world. Morton and colleagues addressed this perspective in a model based on which could be decided how development aid in global health should be spent (141). However, absence of hard evidence on cost-effectiveness of disease surveillance complicates the use of such analytical models.

The cost-effectiveness of disease surveillance

Methods of economic evaluation have been applied in cost-effectiveness analyses of clinical interventions with a clear link between costs of an intervention and health benefits of the target patient group (4). Such evaluations are more complex in case of surveillance systems. In general, surveillance results in health improvements only when combined with other programs as effective policy responses require a well-functioning health system and intragovernmental coordination. In case of healthcare emergencies, outbreaks further not only influence human health, health spending and labor market participation but also general security, animal health, and have broader disruptive effects on international trade and tourism. Furthermore, behavioral responses with respect to policies play a crucial role, making outcomes less predictable (142). Some issues regarding cost estimation are that costs from detected cases (including false positives) should be considered and that costs for the development of incentive structures for data sharing and facilitation of data sharing can be difficult to quantify and attribute to separate surveillance systems and activities. The latter relates to seeking an optimal balance between funding disease-specific (vertical) interventions and (horizontal) health system strengthening. Models were built (e.g., previous works (16,135)) to address this, which take into account that investments in health systems will increase benefits of other programs.

Another bottleneck is the absence of a methodological framework capturing the unique characteristics of surveillance. Earlier estimates of costs of surveillance and response activities were mainly restricted to predefined preparedness or response activities for endemic diseases and single pathogen models (see Textbox 1 for an example).

Textbox 1: The economic evaluation of PulseNet

PulseNet is a surveillance system designed to identify and facilitate investigation of foodborne illness outbreaks. This molecular subtyping network of public health and food regulatory agency laboratories provides stakeholders information to improve decision-making and provides powerful incentives for the industry. It furthermore enhances the focus of regulatory agencies and limits the impact of outbreaks. The health and economic impacts associated with PulseNet were studied in an economic evaluation (150). Effectiveness was measured as a reduction of reported illness due to improved information, enhanced accountability of the industry and more rapid recalls. Economic costs comprised program costs and medical costs and productivity costs averted due to reduced illness. Based on data collected between 1994 and 2009, it was estimated that the system reduced the number of illnesses from Salmonella by 266,522, from Escherichia coli (E. coli) by 9,489, and from Listeria monocytogenes by 56. This reduced medical and productivity costs by $507million. Direct effects from improved recalls additionally reduced illnesses from E. coli by 2,819 and Salmonella by 16,994, which further reduced costs with $37million. Annual costs for PulseNet to public health agencies were $7.3million, representing a more than fivefold return on investment.

Uncertainty is an important characteristic of infectious diseases that should be considered in evaluations, for instance, by using the 'value of information' and 'real option' concepts. Value of information focuses on uncertainty surrounding decisions and the role additional information can play in reducing uncertainty (143). In Textbox 2, we explain this concept using an example. The example shows how information can aid policy makers to optimize outcomes, which we partly illustrate using a decision tree (Figure 1) and simplified sensitivity analysis (Figure 2), though also reveals other practical difficulties as how to get the industry to cooperate and how to divide the burden and consequences. Pooling of risks through insurance could be an option here. Although incentives for prevention and control in the market will be limited when it is known that potential losses will be reimbursed, such moral hazard is inherent to insurance and options to limit this, such as the deductible, can be applied. The real option approach focuses on the dynamic character of uncertainty by valuing the option to postpone an investment provided that some initial investment is made to ensure such options are available (144). This is important in the case of disease surveillance as appropriate timing of information provision and other actions is crucial.

Other issues in the context of economic evaluations of surveillance are the choice of the appropriate perspective and decision rules. (Two main perspectives used are the healthcare perspective (where only costs and benefits, the latter typically quantified in quality-adjusted life years (QALYs), within the healthcare sector are considered relevant) and the societal perspective (where all costs and benefits in society are considered).) A societal perspective appears to be most appropriate, recognizing the broad impact of disease surveillance and facilitating comparisons across interventions (both in different sectors). Obtaining the value or decision rules for investments in surveillance is complex. In terms of the value of health, a recent review indicated an average value of a QALY of around €75,000 (13). This figure only captures the

value of health gains, and furthermore requires health gains to be specified in QALYs to be useful. The aforementioned study covering several countries within the EU into the valuation of an improved surveillance system indicated an average willingness to pay of around €22/ month per household (137). Figures like this suggest that truly effective surveillance systems may well offer value for money from a societal perspective, given the broad range of benefits they potentially offer.

Textbox 2: Value of information and the closure of mink farms

We demonstrate the concept of value of information using a recent example of with COVID-19-infected farmed minks in the Netherlands (151). We perform a simplified analysis for a policy maker facing the decision of whether to close the approximately 125 mink farms.* Immediate permanent closure of a mink farm is assumed to cost approximately €4 million per farm, based on earlier research (152). Not closing a farm while infected is assumed to cost €10 million,† a combination of the monetary value of lost life-years after transmission to humans and economic consequences in the industry. It is assumed that 10%† of the farms is likely to be infected. With no further information available the expected value of not closing a farm would be -€1 million (10%*-€10million). With the expected value of closing a farm of -€4million, the expected value of not closing the farm would be higher (-€1 million> -€4 million) and that option would be economically preferred. This is presented in the decision tree in Figure 1.‡ For 125 farms, this decision would lead to an expected loss of €125million.

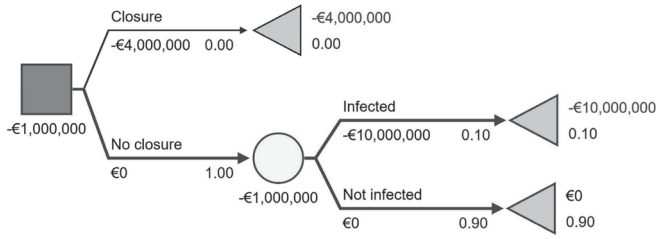


Figure 1: Decision tree

Now, suppose sequencing and sequence analysis can be introduced to trace the origin and transmission of the infection. With this information and monitoring, it is possible to detect new cases quickly and monitor actual statuses in the farms. This would enable a policy maker to close only farms that are infected or where there is high risk of infection. In that situation, only 10% of the farms will be closed with an expected loss of €50 million. The value of perfect information is the expected value with perfect information (-€50 million) minus the expected value with only probabilistic information (-€125 million), which is €75 million. A policy maker would be willing to pay a maximum of €75 million for sequencing and sequence analysis in this scenario.

In this example, we made assumptions on (among others) the values of input parameters. In real life decision-making, however, there is often uncertainty about the value of these parameters, which can be demonstrated through various types of sensitivity analyses. In Figure 2, we show simple example of a sensitivity analysis, where we present the expected value of perfect information (and thereby investment in sequencing) for different values of the probability of infection, costs of closing a farm and infection in an open farm, where we use earlier presented numbers for the base case and the highest and lowest values as presented in the figure.†

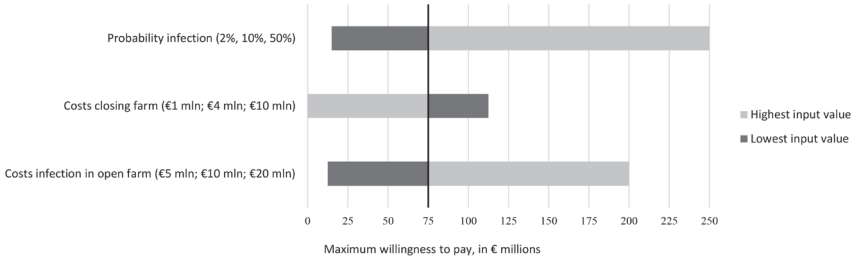


Figure 2: Sensitivity analysis

*We assume closed farms will not reopen since permanent closure of mink farms is planned for 2024.
†These numbers are hypothetical and generated solely to illustrate the principle of value of information in the context of infectious diseases.
‡Decision tree was prepared with freeware Silver decisions from the website (http://silverdecisions.pl/SilverDecisions.html?lang=en).

Conclusion

The threat of new emerging infectious diseases creates a need to continuously improve disease surveillance systems to prevent and control outbreaks. The key mechanism by which surveillance creates value is by producing information. Generally, the cost of sharing information is much less than the cost of producing it, and so from an economic point of view, it is desirable to share information as widely as possible. Unfortunately, incentive structures to ensure the production of information typically hinder sharing—as once information is shared, it is harder for the generator to capture the value for himself. Reward and regulatory mechanisms are critical to the creation and diffusion of innovative technologies for surveillance, and for the optimal use of the information which these products will generate. Economists have experience with such mechanisms in other settings and could contribute to the design of such mechanisms for surveillance technologies such as NGS. Considering substantial positive externalities of disease surveillance, market failure and consequently underprovision are likely. Hence, we argue for public interference in surveillance. The extent of such public involvement is an important area for further research; however, public financing and provision in itself is presumably required to enable cost-effective disease surveillance, since otherwise optimal levels for society are unlikely

to be reached. Higher prevalence and burden of infectious diseases in low-income and middle-income countries, combined with less financial resources available for disease surveillance in these countries, furthermore, demand financial support by higher-income countries. Additionally, considering current spending on surveillance, there is potential for substantial additional investments. For optimal use of scarce resources, further investments are preferably based on sound economic evaluations. Assessing cost-effectiveness of disease surveillance not only requires estimates of costs and effectiveness, which are difficult to estimate, but also a different analytical framework, which is yet non-existent. We highlighted methods, which, together with current practice of economic evaluation of individual interventions, could form the basis of such a framework.

Chapter 7

Discussion

Cost-effectiveness analysis (CEA) has increasingly been used to inform decision makers in healthcare on the incremental costs and benefits of different interventions, aiming to support the decision-making process around resource allocation in healthcare. From the start, there have been practical and methodological issues associated with performing CEA (e.g., (9,10,145,146)). This thesis aimed to contribute to some of the methodological discussions in the field of CEA in healthcare and to improve methods used in CEA. In doing so, the thesis focused on the scope of CEA in terms of what and how costs and benefits should be included in CEA. In this chapter, the main findings related to the three research questions posed in the introduction are presented and the limitations and implications of the findings are discussed. Furthermore, a summarizing answer to the research questions and concluding statement in relation to the overall aim of this thesis are presented.

Findings

Question 1: How can methods for the estimation and inclusion of future costs in cost-effectiveness analysis be improved?

In Chapter 2, we performed a critical review of how the debate on the inclusion of future costs in economic evaluations has developed over the years. In line with how the debates on inclusion of these costs evolved over time, we discussed future medical and future non-medical costs separately. There has been little debate on the inclusion of future related medical costs (medical costs in life-years gained that are related to the condition on which the intervention is focused). In contrast, the inclusion of future unrelated medical costs (medical costs in life-years gained that are only related to the intervention through its result of extending life) has been debated more frequently. Chapter 2 showed that the arguments against the inclusion of unrelated medical costs in life-years gained generally are invalid. This holds for both conceptual arguments (e.g., around whether benefits related to these costs are included and whether it can be assumed that these costs will take place) and practical arguments (e.g., around whether it is feasible to estimate these costs and whether inclusion makes a difference).

For future non-medical costs (defined as non-medical consumption minus production in life-years gained from an intervention, both generally only relevant when adopting a societal perspective) Chapter 2 showed that the literature is less conclusive. Although previous research has shown that including the costs and benefits of non-medical consumption would lead to welfare improving choices from a societal perspective, unclarities in and disagreement about which related benefits are captured in CEA led to debates on which costs should consequently be included. A frequently encountered argument for not including non-medical consumption costs is that the related benefits (i.e., utility gains from more consumption) are presumably not, not fully, or not consistently captured in the evaluation.

Chapters 3 and 4, in line with previous literature, confirm that estimating and adjusting future unrelated medical costs is feasible and that inclusion is practically possible. Moreover, inclusion can make a significant difference, that is, inclusion may lead to different (reimbursement)

decisions. In Chapter 3, we updated standardized estimates of future unrelated medical costs and provided estimates of future non-medical consumption for the Netherlands. For the estimates of unrelated medical costs, Chapter 4 showed that it is also important to consider potential differences in use of healthcare by the groups on which the intervention is focused. Although previous estimates and the standardized estimates in Chapter 3 of future unrelated medical care were typically based on average healthcare spending within an entire population, in some cases it may be more reasonable to assume that the targeted group has higher or lower healthcare expenditures than the average person. Chapter 4 showed that the impact of including future costs indeed differed substantially between risk groups.

Question 2: Which benefits beyond health are captured in monetary estimates of the value of a QALY?

Chapter 5 focused on this question and investigated the extent to which benefits beyond health are captured in the monetary value of the QALY (which can be used to set a cost-effectiveness threshold when adopting a societal perspective). We asked respondents which elements beyond health they considered during the valuation exercises in which they were asked what they would be willing to pay for improvements in health. It was found that most respondents, without instructions to consider these broader elements beyond health, did consider them. Furthermore, it was found that higher quality of life was related to higher stated utility of consumption. However, the results also suggest that considering these elements beyond health on average did not lead to significantly different monetary valuations of health gains. Given this, it can be argued that although people may (state to) consider elements beyond health, the impact on the valuation is negligible. In that context it would be inaccurate to conclude that the benefits of these elements are fully and consistently captured. For this to be the case their inclusion presumably should have resulted in different valuations, given the potentially large impact a change in these elements may have on people's lives. An alternative explanation would be that in relation to health, respondents attach little value to other elements, and therefore, the impact of considering these elements on the valuation is actually limited. While health is an important factor in overall welfare or wellbeing, the latter explanation is not in line with other types of research, which highlight the relative impact of different life domains on overall wellbeing (e.g., (147)).

Question 3: How can cost-effectiveness analysis of infectious disease surveillance be improved?

In Chapter 6, several economic issues related to infectious disease surveillance were described. We addressed that a decision regarding additional investments in infectious disease surveillance would preferably be based on CEA considering its specific characteristics. However, it was argued that a framework for cost-effectiveness analyses capturing these specific characteristics is not yet available. An example of such a characteristic is the large amount of uncertainty associated with the estimations of the impacts of infectious diseases and related interventions. Furthermore, interventions are more based on relatively small probabilities of infection in large samples, rather than scenarios in a more defined population in which it is more likely or even certain that the

targeted health event will occur or has occurred. The interventions are also more focused on improving a health system that facilitates the provision of healthcare, rather than on interventions targeting the conditions of a specific disease in individual patients. Several suggestions have been made in Chapter 6 for the improvement and extension of existing frameworks of CEA in order to facilitate application of CEA of infectious disease surveillance. An important example is dealing with uncertainty in CEA, which could be incorporated by using 'value of information' or 'real option' approaches. Sound CEA should, in general, consider all relevant costs and benefits of interventions, while aligning with the perspective prescribed by the decision maker. Given that the impact of (interventions in the area of) infectious diseases may have large impact on societies that reach beyond health, applying a broader societal perspective appears to be most appropriate.

Limitations

There are some limitations of this thesis that are important to highlight. A general limitation of this thesis is related to the focus of this research on the Netherlands. Although the applied methods and comparable methods can (and already have been, e.g., (103,148)) applied to other countries, this was not demonstrated within the scope of this thesis. Issues that may be relevant specifically within the context of decision-making frameworks used in other countries may therefore have been overlooked. For instance, as Chapters 3 and 4 demonstrated for the Netherlands, it is important to consider the entire decision-making framework to be able to determine the total impact of inclusion of additional costs in CEA. Also, the research on the inclusion of elements beyond health is focused on the Dutch population and therefore on how society and the health system are organized in the Netherlands. Different settings may also here lead to different findings and implications.

Another limitation is related to the methods applied to provide the standardized estimates of future unrelated medical costs and non-medical consumption costs. In several ways, this thesis has improved previous estimates and provided new estimates when these were not yet available. However, there are ways in which these estimates could be improved even further in the future. For instance, an important aspect of the estimates of unrelated medical costs in Chapter 3 was that a distinction was made between costs for people who will die (decedents) and those who will not (survivors). This was done given that people generally have higher healthcare expenditures in the last phase of their lives. To differentiate costs based on the last year of life and earlier years, we used decedent to survivor cost ratios for different cost-categories. However, (lacking more recent ones) relatively old decedent-survivor cost ratios were used. Furthermore, for some cost categories ratios were not available at all. Hence, estimates of these costs could be further improved by updating the existing ratios and deriving ratios for categories for which these are not yet derived. It is also worth noting that the data from the household survey, that was used to estimate non-medical consumption in this thesis, are relatively old. Although data were adjusted to 2017 prices, changes in spending patterns by age may not have been accurately captured.

An additional limitation is that we estimated non-medical consumption by age and assumed no correlation between non-medical consumption and health status. However, findings from Chapter 5 suggest that non-medical consumption may be affected by health status. People reported that they expected differences in (benefits from) consumption, leisure, and productivity in different health states. Also, people with higher health-related quality of life reported a higher utility of consumption. Standardized estimates of non-medical consumption provided in Chapter 3 do not take this potential variation into account. The accuracy of estimates of costs of non-medical consumption could further be improved by adjusting estimates of non-medical consumption based on health status. Note that this would not only affect non-medical consumption in life-years gained, but also in normal life-years.

Another noteworthy limitation, specifically related to Chapter 5, is that a new relatively simple scale was chosen to measure utility of consumption. In this context it is good to note that no comparisons with other scales or conceptualizations have been performed to date. Future research could provide more insight into how the applied scale relates to other ways of measuring the utility of consumption.

A final limitation highlighted here, specifically related to Chapter 6 which focused on the economics of infectious disease surveillance, was that this was a theoretical chapter. Although the chapter was based on previous research and included stylized examples tailored on the discussed topics, this chapter did not include new empirical studies to support its findings and recommendations. Further research could be performed for this purpose, for instance using the information available because of the COVID-19 pandemic.

Implications for policy and further research

The findings of this thesis have several implications for policy and future research. First, this thesis has shown that estimating and adjusting future unrelated medical costs is feasible and that inclusion is practically possible and makes a significant difference (that is, inclusion could alter reimbursement decisions). This is the case both for the general population and for specific target groups with different underlying healthcare needs. These results support the inclusion of these costs in CEA, regardless of the perspective taken for the analysis. Recommending and/or requiring this in guidelines for economic evaluations is an important way the inclusion of these costs can further be stimulated.

The inclusion of future unrelated medical costs is also relevant for the determination of the threshold against which the cost effectiveness is judged when this threshold should represent the marginal cost-effectiveness of current care. When adopting a healthcare perspective and assuming a fixed healthcare budget and the aim of maximizing healthcare from this budget, funding a new intervention means that current care gets displaced. The threshold then should represent the cost-effectiveness of that displaced care to ensure health maximizing choices.

Future unrelated medical costs should then not only be considered in the estimates of the ICER, but also in those of the threshold to represent the opportunity costs more accurately.

Given the remaining questions regarding the extent to which benefits beyond health related to future non-medical consumption costs are adequately captured in current CEA, it may be considered premature to advise to include these costs in standard CEA from a societal perspective. However, these costs can be shown separately in CEA (e.g., in a sensitivity analysis), which would provide decision makers with more comprehensive information regarding societal costs that occur due to implementing new interventions. This seems especially appropriate since, as was also shown in Chapter 3 and 4, the estimation of these costs is practically feasible, and their inclusion can make a significant difference on the ICER.

Improving knowledge on what is included in terms of benefits in current CEA, both in terms of QALYs and the monetary threshold, and working towards measures that capture all relevant benefits systematically and accurately, are important further steps towards gaining support for the inclusion of non-medical consumption costs. This would ultimately result in comprehensive CEA capturing all relevant costs and benefits. This area needs further investigation. Our research suggests that non-health benefits are, although often considered, presumably not fully and comprehensively valued, making CEA from a societal perspective including all relevant costs and benefits difficult to achieve at this point.

For the standardized estimates provided in this thesis to remain relevant, it is important to update these regularly, especially when significant changes occur in underlying data. It is also important to produce estimates of these costs for other countries. Next to regularly updating the estimates, several sources for improvement are found in this thesis for further improvement of estimates of future costs. For instance, by updating ratios of decedent to survivor medical consumption and by developing tools that quantify uncertainty in the estimates. Chapter 4 further showed that the impact of including future unrelated medical costs differed substantially between risk groups. Considering such differences is important for studies in which strategies are designed that include different risk groups based on their current health. It is important to stress that this also raises distributional questions.

An important topic for further research related to non-medical consumption is the potential variation of non-medical consumption with health status. An important finding in this thesis is that people expect elements beyond health such as utility of consumption and spending to vary with health. Also, people report higher utility of consumption in higher health-related quality of life. This has important implications for the inclusion of non-medical consumption costs. For instance, changing utility of consumption and spending implies that inclusion is relevant for both quality improving and life-extending interventions. This would imply an important change relative to current practice.

This thesis showed that it is important to take into account the specific characteristics of infectious disease surveillance when performing CEA for investments in this field. An important factor for improvement that was suggested is to construct an evaluation framework that adequately captures specific characteristics of disease surveillance, such as uncertainty. In general, it is important for these evaluations to be broad enough in scope to capture all relevant societal costs and benefits related to the intervention.

Conclusion

This thesis aimed to contribute to discussions related to and improvements of the methodology of CEA in healthcare, focusing on the scope of CEA in terms of what and how costs and benefits should be included in CEA. This was pursued by focusing on three related research questions.

The first question asked how methods for the estimation and inclusion of future costs in CEA can be improved. This thesis showed that including future unrelated medical costs is both methodologically sound and practically feasible, regardless of the perspective prescribed by the decision maker. Inclusion and estimation could be improved by recommending and/or requiring inclusion in pharmacoeconomic guidelines. Furthermore, costs should be adjusted when it is likely that different sub-populations in the target group have different underlying health profiles. Given unclarities regarding the extent to which benefits associated with non-medical consumption costs (which are only relevant when adopting a societal perspective) are currently captured in CEA, recommending highlighting the impact of including future non-medical costs on outcomes (e.g., in sensitivity analyses) separately appears more appropriate than including these in base case estimates at this point. For future costs in general, estimates can be improved by regularly updating standardized estimates of these costs for individual countries.

The second question of this thesis asked which benefits beyond health are captured in monetary estimates of the value of a QALY. It was found that although non-health elements were often considered by respondents in valuation exercises, this inclusion had limited impact on the resulting valuation. This suggests these benefits are not accurately valued in current CEA. For CEA from the societal perspective to fully capture all relevant consequences in costs and benefits, further research should also focus on accurately capturing these benefits. The positive relation between health and utility of consumption which was found in this research furthermore suggests that estimates of non-medical consumption could be improved by considering health status. It also suggests that these costs are relevant both for quality-improving and life-extending interventions.

The third and final research question of this thesis asked how cost-effectiveness analysis of infectious disease surveillance can be improved. In general, it is important for such evaluations to be broad enough to capture all relevant costs and benefits from the intervention. An important factor for improvement that was suggested is to construct an evaluation framework that captures specific characteristics of disease surveillance, such as uncertainty.

In conclusion, this thesis contributed to discussions and methodology related to what and how costs and benefits should be included in CEA of interventions in healthcare. In this, it focused on future costs, non-medical consumption, and infectious disease surveillance. Although this leaves many questions and topics unaddressed, and despite the limitations of this thesis, the practical and theoretical contributions in this thesis hope to have contributed to further improvement of economic evaluations of health interventions.

Appendices

Summary

Cost-effectiveness analysis (CEA) has been used increasingly in the context of allocating healthcare resources. Using CEA, decision makers can choose to fund those interventions that contribute most to their objectives, given the available resources. From the start, there have been practical and methodological issues around CEA. This thesis aimed to contribute to discussions related to CEA and improvements of the methodology of CEA in healthcare. In doing so, the thesis focused on the scope of CEA in terms of what and how costs and benefits should be included in CEA.

In Chapter 2, we performed a critical review of how the debate on the inclusion of future costs in economic evaluations developed over the years. It showed that both practical and theoretical arguments against the inclusion of future unrelated medical costs generally do not hold. This supports the inclusion of these costs in CEA and recommendation and/or prescription of inclusion in pharmacoeconomic guidelines, regardless of the perspective of the decision maker. The discussion around the inclusion of non-medical consumption costs is less determined. Although, from a theoretical viewpoint, most beneficial outcomes for society would be obtained when CEAs from a societal perspective include all relevant costs and benefits within the scope of the decision maker, current outcome measures presumably do not fully and consistently capture the benefits related to all benefits beyond health, such as utility of consumption. To be consistent in including both the cost and benefit side of elements, it has been argued that future non-medical consumption should therefore be excluded. Others argue that consistency should indeed be aimed for, albeit by finding or constructing measures that accurately capture all relevant benefits.

In Chapter 3, we provided practical guidance for the inclusion of future unrelated medical costs and future non-medical consumption costs for the Netherlands. Standardized estimates of these costs were updated for future unrelated medical costs and produced for future non-medical consumption costs and incorporated in PAID 3.0, a practical tool to aid the inclusion of future costs in CEA. Furthermore, case-studies were presented in which the inclusion of future unrelated medical costs and future non-medical costs was demonstrated. This chapter confirmed arguments in favor of the inclusion of these costs, presented in Chapter 2, by showing that estimation and inclusion of these costs is practically possible and does not have to put lot of additional burden on those performing CEA in practice and by showing that inclusion can have a substantial impact on the outcome of the analysis and may affect reimbursement decisions.

In Chapter 4, a case-study was performed in which future unrelated medical costs and future non-medical consumption costs were included in a previously performed CEA for vaccination, using the estimates provided in Chapter 3. In this chapter, specific attention was paid to the situation where it is likely that future unrelated medical costs (based on average yearly medical spending) are different for different groups in the study population. It showed that the impact of including future unrelated medical costs differed substantially between groups, with larger

impact (a larger increase of the Incremental Cost-Effectiveness Ratios (ICER)) for people in worse health.

Driven by the findings in Chapter 2, in Chapter 5 we studied the extent to which benefits beyond health are captured in the monetary value of a Quality-adjusted Life-year (QALY), using Willingness to Pay (WTP) methods. We found that although respondents generally consider elements beyond health while valuing the QALY, the impact of consideration on the valuation is limited. This raises the need for further research on how to achieve CEA that are consistent and include all relevant costs and benefits. Chapter 5 also showed that the utility of consumption is expected to vary with health. That is, people with better health reported higher (expected) utility of consumption. This suggest that estimates of non-medical consumption costs could be improved by considering health status. It also suggests that the inclusion of non-medical consumption costs is relevant for both life-extending and quality-improving treatments.

In Chapter 6, attention was paid to ways in which the economic evaluation of infectious disease surveillance could be improved. An important factor for improvement that was suggested is to construct an evaluation framework that captures specific characteristics of disease surveillance, such as uncertainty and the fact that disease surveillance influences the occurrence and treatment of multiple diseases. In general, it is important for evaluations to be broad enough to capture all relevant costs and benefits from the intervention.

In Chapter 7, the findings of the research in the chapters in this thesis were discussed in relation to the research questions posed in the introduction. Furthermore, limitations of the conducted research and implications for policy and further research were presented. In conclusion, this thesis provided contributions to discussions on, and methods related to what and how costs and benefits should be included in CEA of interventions in healthcare. Both practical and theoretical contributions were made and both past issues and new directions were explored. In this, the focus was on future costs, non-medical consumption, and infectious disease surveillance in relation to CEA.

Samenvatting

Kosteneffectiviteitsanalyses (KEAs) worden steeds vaker gebruikt om de beschikbare middelen voor de gezondheidszorg te verdelen. Met behulp van KEAs kunnen besluitvormers kiezen om die interventies te financieren die het meest bijdragen aan hun doelstellingen, gegeven de beschikbare middelen. Vanaf het begin van het gebruik zijn er praktische en methodologische problemen rond KEAs. Dit proefschrift had als doel een bijdrage te leveren aan de discussies gerelateerd aan KEAs en aan verbeteringen van de methodologie van KEAs in de gezondheidszorg. Daarbij concentreerde het proefschrift zich op de reikwijdte van KEAs en de vragen welke en hoe kosten en baten in KEAs moeten worden opgenomen.

In Hoofdstuk 2 hebben we kritisch gekeken naar hoe het debat over het meenemen van toekomstige kosten in economische evaluaties zich door de jaren heen heeft ontwikkeld. Hieruit bleek dat zowel praktische als theoretische argumenten tegen het opnemen van toekomstige indirecte medische kosten in het algemeen niet opgaan. Dit ondersteunt het opnemen van deze kosten in KEAs en het aanbevelen en/of voorschrijven van opname hiervan in farmaco-economische richtlijnen, ongeacht het perspectief van de beslisser. De discussie rond het meenemen van de kosten van toekomstige niet-medische consumptie is minder beslist. Er is gebleken dat, vanuit een theoretische invalshoek, de meest gunstige uitkomsten voor de samenleving kunnen worden verkregen als KEAs vanuit een maatschappelijk perspectief alle relevante kosten en baten omvatten binnen de reikwijdte van de beslisser. Echter, huidige uitkomstmaten omvatten vermoedelijk niet volledig en consistent alle niet-medische voordelen die voortkomen uit gezondheidszorg, zoals het nut van consumptie. Om consistent te zijn in het opnemen van zowel de kosten als de baten van elementen, is daarom in de literatuur betoogd dat de kosten van niet-medische consumptie zouden moeten worden uitgesloten. Een andere visie hierop is dat er inderdaad naar consistentie moet worden gestreefd, echter door instrumenten te vinden of ontwikkelen die alle relevante voordelen accuraat weergeven.

In Hoofdstuk 3 hebben we praktische richtlijnen gegeven voor het meenemen van toekomstige indirecte medische kosten en niet-medische consumptie kosten voor Nederland. Gestandaardiseerde schattingen zijn bijgewerkt voor indirecte medische kosten en geproduceerd voor niet-medische consumptie kosten en opgenomen in PAID 3.0, een praktisch hulpmiddel om de opname van toekomstige kosten in KEAs te vergemakkelijken. Bovendien werden casestudies gepresenteerd waarin indirecte medische kosten en niet-medische kosten werd opgenomen in bestaande KEAs. Dit hoofdstuk bevestigde de argumenten ten gunste van het opnemen van deze kosten, gepresenteerd in Hoofdstuk 2, door aan te tonen dat het schatten en opnemen van deze kosten praktisch mogelijk is en niet veel extra last hoeft te leggen op degenen die de KEAs in de praktijk uitvoeren, en door aan te tonen dat inclusie een substantiële impact kan hebben op de uitkomst van de analyse en van invloed kan zijn op vergoedingsbeslissingen.

In Hoofdstuk 4 werd een casestudy uitgevoerd waarin toekomstige indirecte medische kosten en niet-medische consumptie kosten werden opgenomen in een eerder uitgevoerde KEA voor

vaccinatie, waarbij gebruik werd gemaakt van de schattingen uit Hoofdstuk 3. In dit hoofdstuk werd specifieke aandacht besteed aan de situatie waarbij het waarschijnlijk is dat indirecte medische kosten (gebaseerd op de gemiddelde jaarlijkse medische uitgaven) verschillend zijn voor verschillende groepen in de onderzoekspopulatie. Hieruit bleek dat de impact van het meenemen van indirecte medische kosten substantieel verschilde tussen groepen, met een grotere impact (een grotere stijging van de incrementele kosteneffectiviteitsratio, IKER)) voor mensen met een slechtere gezondheid.

Gedreven door de bevindingen in Hoofdstuk 2, hebben we in Hoofdstuk 5 onderzocht in hoeverre de baten van niet-medische voordelen zijn opgenomen in de monetaire waarde van een Quality-adjusted Life-year (QALY), met behulp van Willingness to Pay (WTP) methoden. We constateerden dat, hoewel respondenten bij het waarderen van een QALY doorgaans rekening houden met elementen die gezondheid overstijgen, de impact van overweging op de waardering beperkt is. Dit vergroot de behoefte aan verder onderzoek naar methoden voor KEAs die consistent en accuraat alle relevante kosten en baten van interventies omvatten. Hoofdstuk 5 laat ook zien dat het nut van consumptie naar verwachting varieert afhankelijk van de gezondheid. Dat wil zeggen dat mensen met een betere gezondheid een hoger (verwacht) nut van consumptie rapporteerden. Dit suggereert dat schattingen van de kosten van niet-medische consumptie kunnen worden verbeterd door rekening te houden met gezondheidsstatus. Het suggereert ook dat het meenemen van niet-medische kosten relevant is voor zowel levensverlengende als kwaliteit verhogende behandelingen.

In Hoofdstuk 6 werd aandacht besteed aan manieren waarop de economische evaluatie van de surveillance van infectieziekten verbeterd zou kunnen worden. Een belangrijke factor voor verbetering die werd gesuggereerd, is het construeren van een evaluatiekader dat rekening houdt met de specifieke kenmerken van surveillance van infectieziekten, zoals onzekerheid en het feit dat surveillance het optreden en de behandeling van meerdere ziekten beïnvloedt. Over het algemeen is het belangrijk dat evaluaties breed genoeg zijn om alle relevante kosten en baten van de interventie in kaart te brengen.

In Hoofdstuk 7 werden de bevindingen van het onderzoek uit de hoofdstukken van dit proefschrift besproken in relatie tot de onderzoeksvragen die in de inleiding zijn gesteld. Bovendien werden de beperkingen van het uitgevoerde onderzoek en de implicaties voor beleid en verder onderzoek gepresenteerd. Concluderend, leverde dit proefschrift bijdragen aan discussies over en methoden gerelateerd aan welke en hoe kosten en baten moeten worden meegenomen in de KEAs van interventies in de gezondheidszorg. Er werden zowel praktische als theoretische bijdragen geleverd en zowel kwesties uit het verleden als nieuwe richtingen werden verkend. Hierbij lag de nadruk op toekomstige kosten, niet-medische consumptie en surveillance van infectieziekten in relatie tot KEAs.

PhD Portfolio

Training

- Academic writing (EGSH)
- Basic didactics and group dynamics (Risbo)
- Professionalism and integrity in research (EGSH)
- Self-presentation: confidence, focus, persuasion (EGSH)
- Data analysis with R (EGSH)
- Coach- en intervisievaardigheden (BVO)

Teaching

2018 - 2021 Kwantitatief leeronderzoek
2019 - 2021 Master thesis Health Economics
2019 - 2021 Master thesis HEPL
2020 - 2021 Bachelor Afstudeerproject

Presentations

2018 Lowlands Health Economics Study Group. Hoenderloo, Netherlands. Paper Presentation.
2018 European Health Economics Association. Maastricht, Netherlands. Paper Presentation.

Publications

1. de Vries LM, van Baal PHM, Brouwer WBF. Future Costs in Cost-Effectiveness Analyses: Past, Present, Future. Pharmacoeconomics. 2019;37(2):119–30.
2. Kellerborg, K, Perry-Duxbury, M, de Vries, L, van Baal, P. Practical Guidance for Including Future Costs in Economic Evaluations in The Netherlands: Introducing and Applying PAID 3.0. Value in Health. 2020;23(11):1453–61.
3. de Vries LM, Kellerborg KM, Brouwer WBF, van Baal PHM. 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. Vaccine. 2021;39(29).
4. de Vries L, Koopmans M, Morton A, van Baal P. The economics of improving global infectious disease surveillance. BMJ Glob Health. 2021;6(9).
5. Mokri H, Kvamme I, de Vries L, Versteegh M, van Baal P. Future medical and non-medical costs and their impact on the cost-effectiveness of life-prolonging interventions: a comparison of five European countries. The European Journal of Health Economics. 2023.

About the author

Linda de Vries was born in Reeuwijk, the Netherlands, on April 2nd, 1994. She finished her Bachelor studies in Economics and Business Economics at the Erasmus University of Rotterdam in 2015 and the Master specialization Health Economics at the same university in 2016. After her studies, Linda worked as a junior consultant in financial services and returned to Erasmus University in 2018 to start her PhD trajectory at the Erasmus School of Health Policy & Management.

Dankwoord

In dit dankwoord wil ik graag wat mensen bedanken zonder wie dit proefschrift niet had kunnen bestaan. Natuurlijk begin ik hierbij met het bedanken van mijn begeleiders.

Pieter, zonder jouw geduld, vertrouwen, en relativeringsvermogen had ik dit traject niet af kunnen ronden. Ik weet nog goed hoe je me tijdens het sollicitatiegesprek vroeg waarom ik aan een PhD traject wilde beginnen. Toen ik iets zei over de maatschappelijke relevantie, vroeg je me waarom ik dan niet gewoon bij het Leger des Heils ging werken (een vraag die ik mezelf de jaren erna nog vaak heb gesteld). Dit soort uitspraken maakte het voor mij leuk om met jou samen te werken en maakte het de moeite waard. Werner, misschien kun je je nog het etentje met de HE-groep herinneren waar jij met veel plezier het balletjesprobleem voorlegde aan de groep. De dynamiek tussen ons rond dit probleem (en alle problemen die daarna nog hebben gevolgd) heb ik altijd erg gewaardeerd. Ook jouw vertrouwen in mij en de ruimte die ik van je kreeg zijn erg belangrijk geweest. Jouw optimisme (realistisch of niet) was aanstekelijk en vaak ook net wat nodig was.

Pieter, Werner, beiden bedankt voor jullie steun en begrip. Bedankt dat jullie deze periode met me mee liepen en dat ik soms op jullie kon terugvallen. Dit traject is niet standaard geweest en ik heb veel bewondering voor jullie. Natuurlijk om jullie onderzoeks- en begeleidingsvaardigheden, maar vooral om wie jullie zijn als mens. Daarin heb ik misschien nog wel het meest van jullie mogen leren. Dat we daarnaast veel (zeer) belangrijke vragen hebben kunnen opwerpen is natuurlijk een mooie bonus.

Natuurlijk wil ik ook alle andere collega's bij HE bedanken voor de fijne werkplek de afgelopen jaren. Daarbij zijn er enkele collega's die ik hier graag specifiek wil noemen. Allereerst Arthur, bedankt voor je vertrouwen en aanmoediging om te solliciteren nadat ik je een tijdje na mijn scriptie bij jou had benaderd. Job, bedankt voor alle ruimte en steun achter de schermen. Judith en Vivian, bedankt voor jullie betrokkenheid en dat ik altijd bij jullie terecht kon. Sebastian en Charlotte, bedankt voor onze tijd als kamergenoten. Jullie gezelschap compenseerde een beetje het nare geluid in de kamer. Meg, Klas, bedankt voor de fijne samenwerking rond verschillende hoofdstukken in dit proefschrift (en in dat van jullie). Jawa, bedankt dat we het leed van Pieter als begeleider af en toe een beetje konden delen;). Marlies, bedankt voor je enthousiasme en dat we de 'laatste loodjes-fase' samen konden doorlopen. Stefan, bedankt dat ik af en toe voor wat advies bij je terecht kon.

Jawa en Ellen, bedankt dat jullie mijn paranimfen wilden zijn! Commissie, bedankt voor het lezen en beoordelen van mijn proefschrift en voor jullie aanwezigheid tijdens de verdediging.

Als laatste wil ik natuurlijk nog familie, vrienden, en alle anderen bedanken die er in deze periode voor mij zijn geweest. Hierbij in het bijzonder Judy, Hanneke, Suzan en Saskia: bedankt voor jullie vertrouwen in mij en jullie aanmoediging om vol te houden.

Fijn dat het proefschrift nu af is!

References

1. Thomson S, Foubister T, Figueras J, Kutzin J, Permanand G, Bryndová L. Addressing financial sustainability in health systems. World Health. 2009.
2. Brouwer W, van Baal P, van Exel J, Versteegh M. When is it too expensive? Cost-effectiveness thresholds and health care decision-making. European Journal of Health Economics. 2019;20(2):175–80.
3. Garber AM, Sculpher MJ. 08: Chapter Eight – Cost Effectiveness and Payment Policy. Handbook of Health Economics [Internet]. 2011;2:471–97. Available from: http://www.sciencedirect.com/science/article/pii/B9780444535924000086
4. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. Fourth Edi. Oxford University Press; 2015.
5. Zhao Y, Feng H, Qu J, Luo X, Ma W, Tian J. A systematic review of pharmacoeconomic guidelines. J Med Econ. 2018;85–96.
6. Claxton K, Walker S, Palmer S, Sculpher M. Appropriate Perspectives for Health Care Decisions. York: Centre for Health Economics [Internet]. 2010;1–86. Available from: www.york.ac.uk/inst/che/pubs
7. Wouterse B, Van Baal P, Versteegh M, Brouwer W. The Value of Health in a Cost-Effectiveness Analysis: Theory Versus Practice. Pharmacoeconomics. 2023;41:607–17.
8. Krol M, Brouwer W, Rutten F. Productivity costs in economic evaluations: Past, present, future. Pharmacoeconomics. 2013;31(7):537–49.
9. Meltzer D. Accounting for future costs in medical cost-effectiveness analysis. J Health Econ. 1997;16(1):33–64.
10. Garber, AM, Phelps C. Economic foundations of cost-effectiveness analysis. J Health Econ. 1997;16(1):1–31.
11. Rappange DR, Van Baal PHM, Van Exel NJA, Feenstra TL, Rutten FFH, Brouwer WBF. Unrelated medical costs in life-years gained: Should they be included in economic evaluations of healthcare interventions? Pharmacoeconomics. 2008;26(10):815–30.
12. van Baal P, Meltzer D, Brouwer W. Future Costs, Fixed Healthcare Budgets, and the Decision Rules of Cost-Effectiveness Analysis. Health Econ. 2016 Feb;25(2):237–48.
13. Ryen L, Svensson M. The willingness to pay for a quality adjusted life year: a review of the empirical literature. Health Econ. 2015;24(10):1289–301.
14. Nyman JA. Should the consumption of survivors be included as a cost in cost-utility analysis? Health Econ. 2004;13(5):417–27.
15. Aarestrup FM, Bonten M, Koopmans M. Pandemics– One Health preparedness for the next. The Lancet Regional Health - Europe. 2021;9.
16. Hauck K, Morton A, Chalkidou K, Chi YL, Culyer A, Levin C, et al. How can we evaluate the cost-effectiveness of health system strengthening? A typology and illustrations. Soc Sci Med. 2019;220:141–9.
17. van Lier LI, Bosmans JE, van Hout HPJ, Mokkink LB, van den Hout WB, de Wit GA, et al. Consensus-based cross-European recommendations for the identification, measurement and valuation of costs in health economic evaluations: a European Delphi study. European Journal of Health Economics. 2018;19(7).
18. Nyman JA. More on survival consumption costs in cost-utility analysis. Health Econ. 2006;15(3):319–22.
19. Richardson JRJ, Olsen JA. In defence of societal sovereignty: A comment on Nyman "the inclusion of survivor consumption in CUA." Health Econ. 2006;15(3):311–3.
20. Gandjour A. Consumption costs and earnings during added years of life - A reply to Nyman. Health Econ. 2006;15(3):315–7.

21. Lundin D, Ramsberg J. On survival consumption costs - A reply to Nyman. Health Econ. 2008;17(2):293–7.
22. van Baal PHM, Feenstra TL, Hoogenveen RT, de Wit GA, Brouwer WBF. Unrelated medical care in life years gained and the cost utility of primary prevention: In search of a "perfect" cost-utility ratio. Health Econ. 2007;16(4).
23. Liljas B, Karlsson GS, Stålhammar NO. On future non-medical costs in economic evaluations. Health Econ. 2008;17(5).
24. Lee RH. Future costs in cost effectiveness analysis. J Health Econ. 2008 Jul;27(4):809–18.
25. Meltzer D. Response to "Future costs and the future of cost-effectiveness analysis." Vol. 27, Journal of Health Economics. 2008.
26. Feenstra TL, van Baal PHM, Gandjour A, Brouwer WBF. Future costs in economic evaluation. A comment on Lee. J Health Econ. 2008;27(6):1645–9.
27. Nyman JA. Measurement of QALYS and the welfare implications of survivor consumption and leisure forgone. Health Econ. 2011;20(1):56–67.
28. Liljas B. Welfare, QALYs, and costs - A comment. Health Econ. 2011;20(1):68–72.
29. Morton A, Adler AI, Bell D, Briggs A, Brouwer W, Claxton K, et al. Unrelated Future Costs and Unrelated Future Benefits: Reflections on NICE Guide to the Methods of Technology Appraisal. Vol. 25, Health Economics (United Kingdom). 2016.
30. van Baal P, Morton A, Meltzer D, Brouwer W. Future unrelated medical costs need to be considered in cost effectiveness analysis. Vol. 20, European Journal of Health Economics. 2019.
31. Weinstein M, Zeckhauser R. Critical ratios and efficient allocation. J Public Econ. 1973;2(2).
32. Meltzer D, Johannesson M. Inconsistencies in the "societal perspective" on costs of the panel on cost-effectiveness in health and medicine. Vol. 19, Medical Decision Making. 1999.
33. Morris S, Devlin N, Parkin D. Economic analysis in health care. Chichester: Wiley; 2007.
34. Grima DT, Bernard LM, Dunn ES, McFarlane PA, Mendelssohn DC. Cost-effectiveness analysis of therapies for chronic kidney disease patients on dialysis: A case for excluding dialysis costs. Vol. 30, PharmacoEconomics. 2012.
35. van Baal P, Meltzer D, Brouwer W. Pharmacoeconomic Guidelines Should Prescribe Inclusion of Indirect Medical Costs! A Response to Grima et al. Pharmacoeconomics. 2013.
36. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the panel on cost-effectiveness in health and medicine. J Am Med Assoc. 1996;276(15):1253–8.
37. van Baal P, Morton A, Brouwer W, Meltzer D, Davis S. Should cost effectiveness analyses for NICE always consider future unrelated medical costs? BMJ. 2017 Nov;359.
38. Weinstein MC, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C. Principles of good practice for decision analytic modeling in health-care evaluation: Report of the ISPOR task force on good research practices - Modeling studies. Value in Health. 2003;6(1).
39. Cobiac LJ, Tam K, Veerman L, Blakely T. Taxes and Subsidies for Improving Diet and Population Health in Australia: A Cost-Effectiveness Modelling Study. PLoS Med. 2017;14(2):1–18.
40. Van Baal PHM, Van Den Berg M, Hoogenveen RT, Vijgen SMC, Engelfriet PM. Cost-effectiveness of a low-calorie diet and orlistat for obese persons: Modeling long-term health gains through prevention of obesity-related chronic diseases. Value in Health. 2008;11(7):1033–40.
41. Barendregt JJ, Bonneux L, van der Maas PJ. The Health Care Costs of Smoking. New England Journal of Medicine. 1997;337(15):1052–7.
42. Gandjour A, Lauterbach KW. Does prevention save costs? Considering deferral of the expensive last year of life. J Health Econ. 2005;24(4):715–24.
43. Van Baal PHM, Wong A, Slobbe LCJ, Polder JJ, Brouwer WBF, De Wit GA. Standardizing the inclusion of indirect medical costs in economic evaluations. Pharmacoeconomics. 2011;29(3):175–87.

44. Zweifel P, Felder S, Meiers M. Ageing of population and health care expenditure: A red herring? Health Econ. 1999;8(6):485–96.
45. Van Baal PHM, Feenstra TL, Polder JJ, Hoogenveen RT, Brouwer WBF. Economic evaluation and the postponement of health care costs. Vol. 20, Health Economics. 2011.
46. Assaria M. Health care costs in the English NHS: reference tables for average annual NHS spend by age, sex and deprivation group. CHE research paper 147. 2017.
47. van Baal PHM, Hoogendoorn M, Fischer A. Preventing dementia by promoting physical activity and the long-term impact on health and social care expenditures. Prev Med (Baltim). 2016;85.
48. Briggs ADM, Scarborough P, Wolstenholme J. Estimating comparable English healthcare costs for multiple diseases and unrelated future costs for use in health and public health economic modelling. PLoS One. 2018;13(5).
49. Meltzer D. Future costs in medical cost-effectiveness analysis. In: The Elgar Companion to Health Economics, Second Edition. 2012. p. 481–9.
50. Kruse M, Sørensen J, Gyrd-Hansen D. Future costs in cost-effectiveness analysis: An empirical assessment. European Journal of Health Economics. 2012;13(1):63–70.
51. Johannesson M, Meltzer D, O'Conor RM. Incorporating future costs in medical cost-effectiveness analysis: Implications for the cost-effectiveness of the treatment of hypertension. Medical Decision Making. 1997;17(4):382–9.
52. Manns B, Meltzer D, Taub K, Donaldson C. Illustrating the impact of including future costs in economic evaluations: an application to end-stage renal disease care. Health Econ. 2003 Nov;12(11):949–58.
53. Meltzer D, Egleston B, Stoffel D, Dasbach E. Effect of future costs on cost-effectiveness of medical interventions among young adults: The example of intensive therapy for type 1 diabetes mellitus. Med Care. 2000;38(6):679–85.
54. Ramos IC, Versteegh MM, de Boer RA, Koenders JMA, Linssen GCM, Meeder JG, et al. Cost Effectiveness of the Angiotensin Receptor Neprilysin Inhibitor Sacubitril/Valsartan for Patients with Chronic Heart Failure and Reduced Ejection Fraction in the Netherlands: A Country Adaptation Analysis Under the Former and Current Dutch Pharmacoeco. Value in Health [Internet]. 2017;20(10):1260–9. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L616887302%0Ahttp://dx.doi.org/10.1016/j.jval.2017.05.013
55. Bleichrodt H, Quiggin J. Life-cycle preferences over consumption and health: When is cost-effectiveness analysis equivalent to cost-benefit analysis? J Health Econ. 1999;18(6):681–708.
56. Cutler D, Deaton A, Lleras-Muney A. The determinants of mortality. Journal of Economic Perspectives. 2006;20(3).
57. Tilling C, Krol M, Tsuchiya A, Brazier J, Brouwer W. In or out? Income losses in health state valuations: A review. Value in Health. 2010;13(2).
58. Adarkwah CC, Sadoghi A, Gandjour A. Should Cost-Effectiveness Analysis Include The Cost Of Consumption Activities? An Empirical Investigation. Value in Health. 2014;17(7):A370.
59. Nyman JA. Cost Recommendations in the Second Edition of Cost-Effectiveness in Health and Medicine: A Review. MDM Policy Pract. 2018;3(1):238146831876516.
60. Drost RMWA, Van Der Putten IM, Ruwaard D, Evers SMAA, Paulus ATG. Conceptualizations of the societal perspective within economic evaluations: A systematic review. Vol. 33, International Journal of Technology Assessment in Health Care. 2017.
61. Ekman M. Consumption and production by age in Sweden: basic facts and health economic implications. Studies in health economics: modelling and data analysis of costs and survival. [Stockholm]: Stockholm School of Economics; 2002.

62. Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-effectiveness in health and medicine: report of the Panel on Cost-effectiveness in Health and Medicine. New York: Oxford Univ Pr. 1996.
63. Borg S, Nahi H, Hansson M, Lee D, Elvidge J, Persson U. Cost effectiveness of pomalidomide in patients with relapsed and refractory multiple myeloma in Sweden. Acta Oncol (Madr). 2016;55(5).
64. Gros B, Soto Álvarez J, Ángel Casado M. Incorporation of future costs in health economic analysis publications: Current situation and recommendations for the future. Vol. 15, Expert Review of Pharmacoeconomics and Outcomes Research. 2015.
65. Dutch National Healthcare Institute. Guideline for economic evaluations in healthcare [Internet]. 2016. Available from: https://english.zorginstituutnederland.nl/publications/reports/2016/06/16/guideline-for-economic-evaluations-in-healthcare
66. The Dental and Pharmaceutical Benefits Agency. General guidelines for economic evaluations. 2003.
67. Svensson M, Hultkrantz L. A Comparison of Cost-Benefit and Cost-Effectiveness Analysis in Practice: Divergent Policy Practices in Sweden. Nordic Journal of Health Economics. 2017;5(2).
68. Heintz E, Arnberg K, Levin LÅ, Liliemark J, Davidson T. The impact of health economic evaluations in Sweden. Z Evid Fortbild Qual Gesundhwes. 2014;108(7).
69. Pirhonen L, Davidson T. Experiences of including costs of added life years in health economic evaluations in Sweden. Farmeconomia Health economics and therapeutic pathways. 2014;15(2):45–53.
70. The Dental and Pharmaceutical Benefits Agency. Ändring i Läkemedelsförmånsnämndens allmänna råd (LFNAR 2003:2) om ekonomiska utvärderingar. 2015.
71. The Dental and Pharmaceutical Benefits Agency. Ändring i Tandvårds - och läkemedelsförmånsverkets allmänna råd (TLVAR 2003:2) om ekonomiska utvärderingar. 2017.
72. Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: Second panel on cost-effectiveness in health and medicine. JAMA - Journal of the American Medical Association. 2016;316(10):1093–103.
73. Meltzer DO, Smith PC. Theoretical issues relevant to the economic evaluation of health technologies. In: Pauly MV, Mcguire TG, Barros PP, editors. Handbook of health economics. Amsterdam: Elsevier; 2011. p. 433–69.
74. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013 [Internet]. National Institute for Health and Care Excellence. 2013. Available from: http://www.nice.org.uk/media/D45/1E/GuideToMethodsTechnologyAppraisal2013.pdf
75. Russel LB. Is prevention better than cure? Washington: DC: Brookings Institution; 1986.
76. Nord E, Lamøy C. Including Future Consumption and Production in Economic Evaluation of Interventions that Save Life-Years: Commentary. Vol. 2, PharmacoEconomics - Open. 2018.
77. Reckers-Droog VT, van Exel NJA, Brouwer WBF. Looking back and moving forward: On the application of proportional shortfall in healthcare priority setting in the Netherlands. Health Policy (New York). 2018;122(6):621–9.
78. van Baal P, Perry-Duxbury M, Bakx P, Versteegh M, van Doorslaer E, Brouwer W. A cost-effectiveness threshold based on the marginal returns of cardiovascular hospital spending. Health Economics (United Kingdom). 2019;28(1).
79. Brouwer WBF, Van Exel NJA, Baltussen RMPM, Rutten FFH. A dollar is a dollar is a dollar - Or is it? Value in Health. 2006;9(5).
80. de Vries LM, van Baal PHM, Brouwer WBF. Future Costs in Cost-Effectiveness Analyses: Past, Present, Future. Pharmacoeconomics. 2019;37(2):119–30.
81. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). Volksgezondheidenzorg.info [Internet]. Available from: Volksgezondheidenzorg.info

82. World Health Organisation, European Commission; Organisation for Economic Co-operation and Development. A System of Health Accounts [Internet]. 2011. Available from: http://www.oecd-ilibrary.org/social-issues-migration-health/a-system-of-health-accounts_9789264116016-en
83. Wong, A, et al. Exploring the influence of proximity to death on disease-specific hospital expenditures: a carpaccio of red herrings. Health Econ. 2011;20(4):379–400.
84. Central Bureau for Statistics (CBS). Statline.
85. Polder JJ, Barendregt JJ, van Oers H. Health care costs in the last year of life-The Dutch experience. Soc Sci Med. 2006;63(7):1720–31.
86. De Meijer C, Koopmanschap M, d'Uva TB, van Doorslaer E. Determinants of long-term care spending: Age, time to death or disability? J Health Econ. 2011;30(2).
87. Alessie R, Ree J. Explaining the hump in life cycle consumption profiles. Economist. 2009;157(1):107–20.
88. Kellerborg K, Brouwer W, Versteegh M, Wouterse B, Baal P. Distributional consequences of including survivor costs in economic evaluations distributional consequences of survivor costs in economic evaluations. Health Econ. 2021.
89. Nelson JA. Household Economies of Scale in Consumption: Theory and Evidence. Econometrica. 1988;56(6):1301.
90. Hagenaars A, de Vos K, Zaidi M. Poverty statistics in the late 1980s: research based on micro-data. 1994;200. Available from: http://books.google.com.mx/books?id=51qLQgAACAAJ
91. Gheorghe M, Brouwer WBF, van Baal PHM. Did the health of the Dutch population improve between 2001 and 2008? Investigating age- and gender-specific trends in quality of life. European Journal of Health Economics. 2015;16(8):801–11.
92. Van Gils CWM, De Groot S, Redekop WK, Koopman M, Punt CJA, Uyl-De Groot CA. Real-world cost-effectiveness of oxaliplatin in stage III colon cancer: A synthesis of clinical trial and daily practice evidence. Pharmacoeconomics. 2013;31(8):703–18.
93. Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. The Lancet. 2019;393(10183):1819–30.
94. Chen PC, Muo CH, Lee YT, Yu YH, Sung FC. Lung cancer and incidence of stroke: A population-based cohort study. Stroke. 2011;42(11):3034–9.
95. Fernández-Villaverde J, Krueger D. Consumption over the life cycle: Facts from Consumer Expenditure Survey data. Vol. 89, Review of Economics and Statistics. 2007.
96. Versteegh MM, Ramos IC, Buyukkaramikli NC, Ansaripour A, Reckers-Droog VT, Brouwer WBF. Severity-Adjusted Probability of Being Cost Effective. Pharmacoeconomics. 2019;37(9):1155–63.
97. Bakx P, O'Donnell O, van Doorslaer E. Spending on Health Care in the Netherlands: Not Going So Dutch. Fisc Stud. 2016;37(3–4):593–625.
98. Zaidi A, Burchardt T. Comparing incomes when needs differ: Equivalization for the extra costs of disability in the U.K. Vol. 51, Review of Income and Wealth. 2005.
99. Gourinchas PO, Parker JA. Consumption over the life cycle. Econometrica. 2002;70(1).
100. Hakkaart-van Roijen L, Van der Linden N, Bouwmans CAM, Kanters T, Tan SS. Costing manual: Methodology of costing research and reference prices for economic evaluations in healthcare. 2015.
101. Andre FE, Booy R, Bock HL, Clemens J, Datta SK, John TJ, et al. Vaccination greatly reduces disease, disability, death and inequity worldwide. Vol. 86, Bulletin of the World Health Organization. 2008.
102. Mauskopf J, Standaert B, Connolly MP, Culyer AJ, Garrison LP, Hutubessy R, et al. Economic Analysis of Vaccination Programs: An ISPOR Good Practices for Outcomes Research Task Force Report. Value in Health. 2018;21(10):1133–49.

103. Perry-Duxbury M, Asaria M, Lomas J, van Baal P. Cured Today, Ill Tomorrow: A Method for Including Future Unrelated Medical Costs in Economic Evaluation in England and Wales. Value in Health. 2020.
104. Kellerborg, K, Perry-Duxbury, M, de Vries, L, van Baal, P. Practical Guidance for Including Future Costs in Economic Evaluations in The Netherlands: Introducing and Applying PAID 3.0. Value in Health. 2020;23(11):1453–61.
105. Hammer B, Prskawetz A, Freund I. Production activities and economic dependency by age and gender in Europe: A cross-country comparison. J Econ Ageing. 2015;5:86–97.
106. Ratushnyak S, Hoogendoorn M, van Baal PHM. Cost-Effectiveness of Cancer Screening: Health and Costs in Life Years Gained. Am J Prev Med. 2019;57(6):792–9.
107. Mangen MJJ, Rozenbaum MH, Huijts SM, Van Werkhoven CH, Postma DF, Atwood M, et al. Cost-effectiveness of adult pneumococcal conjugate vaccination in the Netherlands. European Respiratory Journal. 2015;46(5):1407–16.
108. van Hoek AJ, Andrews N, Waight PA, Stowe J, Gates P, George R, et al. The effect of underlying clinical conditions on the risk of developing invasive pneumococcal disease in England. Journal of Infection. 2012;65(1):17–24.
109. Central Bureau for Statistics (CBS). Statline - Consumer prices. 2020.
110. Zwaap J, Knies S, Meijden C van der, Staal P, Heiden L van der. Cost-effectiveness in practice [Internet]. 2015. Available from: https://english.zorginstituutnederland.nl/publications/reports/2015/06/16/cost-effectiveness-in-practice.
111. Dutch Health Council, Dutch National Healthcare Institute. In Dutch: "Gezamenlijke notitie Zorginstituut en Gezondheidsraad bij adviezen over vaccinatie van ouderen tegen pneumokokken." 2018.
112. Casparie AF, Van Hout BA, Simoons ML. In Dutch: "Richtlijnen en kosten." Ned Tijdschr Geneeskd. 1998;142(38):2075–7.
113. Stolk EA, van Donselaar G, Brouwer WBF, Busschbach JJ V. Reconciliation of Economic Concerns and Health Policy. Pharmacoeconomics. 2004;22(17):1097–107.
114. Dutch National Healthcare Institute. In Dutch: "Ziektelast in de praktijk: De theorie en praktijk van het berekenen van ziektelast bij pakketbeoordelingen." 2018.
115. Vondeling GT, Cao Q, Postma MJ, Rozenbaum MH. The Impact of Patent Expiry on Drug Prices: A Systematic Literature Review. Appl Health Econ Health Policy. 2018;16(5):653–60.
116. European Patent Office. European Patent Register [Internet]. Available from: https://www.epo.org/
117. Finkelstein A, Luttmer EFP, Notowidigdo MJ. What good is wealth without health? The effect of health on the marginal utility of consumption. J Eur Econ Assoc. 2013;11(SUPPL. 1):221–58.
118. Jönsson B. Ten arguments for a societal perspective in the economic evaluation of medical innovations. The European Journal of Health Economics volume. 2009;357–9.
119. Meltzer D. Accounting for future costs in medical cost-effectiveness analysis. J Health Econ. 1997;16(1):33–64.
120. Bobinac A, van Exel NJA, Rutten FFH, Brouwer WBF. Willingness to pay for a quality-adjusted life-year: The individual perspective. Value in Health. 2010;13(8):1046–55.
121. Bobinac A, Van Exel NJA, Rutten FFH, Brouwer WBF. Valuing qaly gains by applying a societal perspective. Health Economics (United Kingdom). 2013;22(10):1272–81.
122. Kouakou CRC, Poder TG. Willingness to pay for a quality-adjusted life year: a systematic review with meta-regression. European Journal of Health Economics. 2022;23(2).
123. Finkelstein A, Luttmer EFP, Notowidigdo M. Approaches to Estimating the Health State Dependence of the Utility Function. SSRN Electronic Journal. 2011.
124. Gyrd-Hansen D. A Stated Preference Approach to Assess whether Health Status Impacts on Marginal Utility of Consumption. Health Economics (United Kingdom). 2017;26(10):1224–33.

125. Krol M, Brouwer W, Sendi P. Productivity Costs in Health-State Valuations: Does Explicit Instruction Matter? Pharmacoeconomics. 2006;24(4):401–14.
126. Shiroiwa T, Igarashi A, Fukuda T, Ikeda S. WTP for a QALY and health states: More money for severer health states? Cost Effectiveness and Resource Allocation. 2013;11(1).
127. Layard R, Nickell S, Mayraz G. The marginal utility of income. J Public Econ. 2008;92(8–9).
128. Sendi P, Brouwer WBF. Is silence golden? A test of the incorporation of the effects of ill-health on income and leisure in health state valuations. Health Econ. 2005;14(6):643–7.
129. Smith KF, Goldberg M, Rosenthal S, Carlson L, Chen J, Chen C, et al. Global rise in human infectious disease outbreaks. J R Soc Interface. 2014;11(101).
130. Vos T, Abajobir AA, Abbafati C, Abbas KM, Abate KH, Abd-Allah F, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. The Lancet. 2017;390(10100):1211–59.
131. Alleweldt F, Kara S, Osinski A, van Baal P, Kellerborg K, Aarestrup FM, et al. Developing a framework to assess the cost effectiveness of COMPARE - a global platform for the exchange of sequence-based pathogen data. Rev Sci Tech. 2017;36(1):311–22.
132. Alleweldt F, Kara Ş, Best K, Aarestrup FM, Beer M, Bestebroer TM, et al. Economic evaluation of whole genome sequencing for pathogen identification and surveillance - results of case studies in Europe and the Americas 2016 to 2019. Euro Surveill. 2021;26(9).
133. Aarestrup FM, Koopmans MG. Sharing Data for Global Infectious Disease Surveillance and Outbreak Detection. Trends Microbiol. 2016;24(4):241–5.
134. van Baal P, Morton A, Severens JL. Health care input constraints and cost effectiveness analysis decision rules. Soc Sci Med. 2018 Mar;200:59–64.
135. Morton A, Thomas R, Smith PC. Decision rules for allocation of finances to health systems strengthening. J Health Econ. 2016;49:97–108.
136. Hossain A, Politi C, Mandalia N, Cohen AL. Expenditures on vaccine-preventable disease surveillance: Analysis and evaluation of comprehensive multi-year plans (cMYPs) for immunization. Vaccine. 2018;36(45):6850–7.
137. Himmler S, van Exel J, Perry-Duxbury M, Brouwer W. Willingness to pay for an early warning system for infectious diseases. Vol. 21, European Journal of Health Economics. 2020.
138. Kaul I, Grunberg I, Stern MA. Global Public Goods. Oxford University Press; 1999.
139. Smith R, Beaglehole R, Woodward D, Drager N. Global Public Goods for Health: Health, Economic and Public Health Perspectives [Internet]. 2003. 314 p. Available from: http://books.google.fr/books?id=oR3vCQR_b6gC
140. Sparkes SP, Kutzin J, Earle AJ. Financing Common Goods for Health: A Country Agenda. Health Syst Reform. 2019;5(4):322–33.
141. Morton A, Arulselvan A, Thomas R. Allocation rules for global donors. J Health Econ. 2018;58:67–75.
142. Philipson T. Economic Epidemiology and Infectious Diseases. 1999. (Working Paper Series).
143. Claxton K. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. J Health Econ. 1999;18(3):341–64.
144. Dixit AK, Pindyck RS. Investment under uncertainty. Investment under Uncertainty. 2012. 1–468 p.
145. Birch S, Gafni A. Cost effectiveness/utility analyses. Do current decision rules lead us to where we want to be? J Health Econ. 1992;11(3).
146. Johannesson M, Weinstein MC. On the decision rules of cost-effectiveness analysis. J Health Econ. 1993;12(4).
147. Himmler S, Jonker M, van Krugten F, Hackert M, van Exel J, Brouwer W. Estimating an anchored utility tariff for the well-being of older people measure (WOOP) for the Netherlands. Soc Sci Med. 2022;301.

148. Mokri H, Kvamme I, de Vries L, Versteegh M, van Baal P. Future medical and non-medical costs and their impact on the cost-effectiveness of life-prolonging interventions: a comparison of five European countries. The European Journal of Health Economics. 2023.
149. Brouwer WBF, Culyer AJ, van Exel NJA, Rutten FFH. Welfarism vs. extra-welfarism. J Health Econ. 2008;27(2).
150. Scharff RL, Besser J, Sharp DJ, Jones TF, Peter GS, Hedberg CW. An Economic Evaluation of PulseNet: A Network for Foodborne Disease Surveillance. Am J Prev Med. 2016;50(5):S66–73.
151. Oreshkova N, Molenaar RJ, Vreman S, Harders F, Oude Munnink BB, Hakze-van der Honing RW, et al. SARS-CoV-2 infection in farmed minks, the Netherlands, April and May 2020. Eurosurveillance. 2020;25(23).
152. Baltussen W, van der Veen H. In Dutch: "Sanering nertsenhouderij in Nederland: een actualisatie." Wageningen; 2008.