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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

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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.

1. Background

Vaccination has greatly reduced the burden of infectious diseases around the world [1]. 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) [2]. 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 [2]. The cost-effectiveness of an intervention can then be evaluated by comparing the ICER to a predefined cost-effectiveness threshold [3]. 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 [2].

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 rele-

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vant in the context of CEA [4]. 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 [5]. 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 [6,7]. It was shown, using theoretical models, that including all future medical costs would be required for optimal decisions from a healthcare perspective [8]. 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) [7]. 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) [15] and was recently recommended in the US by the Second Panel on Cost Effectiveness in Health and Medicine [16]. 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 [16].

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') [10], and NMC and productivity are typically higher in middle ages [11,12]. Healthcare costs are also generally higher for people with underlying health conditions for which medical treatment is needed [13], 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 [14]. Also, for the UK, it was shown that including future UMC led to an increase in the ICER of between 7% and 13% [15]. A last example is from the Netherlands, where a tool was developed and updated to include both future NMC and UMC [16]. 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 [17] 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 [18]. 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.

2. 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 Eq. (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 [19] 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 Section 2.1, 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 paper 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 [20]. 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 $\geqslant$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 [17].

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.

2.1. 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 [16]. 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 [21]. 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 Sections 6.1 and 6.2 in the appendix we explain in more detail how we derive per patient estimates.

2.2. 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 [22]. 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) [23]. 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 [24]. 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 [22]. 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 [22,25]. 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 [22].

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 [26,27]. 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 [27]. 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.

3. Results

3.1. 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.

3.2. Impact of future costs on ICERs for preventing fatal cases

Fig. 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 Fig. A.1 in Section 6.3 in the appendix 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.

3.3. 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.

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

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.

Cost category	Risk group	Age				
		18	50	65	75	85
UMC decedents	Low	8,736	23,399	29,422	32,906	42,170
	Medium	28,938	31,917	41,020	44,048	59,547
	High	85,770	128,203	174,370	106,932	72,876
UMC survivors	Low	2,180	2,941	4,054	6,475	15,050
	Medium	8,576	6,071	7,438	10,810	23,779
	High	31,711	18,232	13,264	12,877	20,536
UMC average	Low	2,181	2,997	4,343	7,233	17,581
	Medium	8,592	6,262	8,126	12,423	28,250
	High	32,010	20,543	17,424	16,629	25,276
NMC	All	19,337	22,279	22,019	20,274	18,801

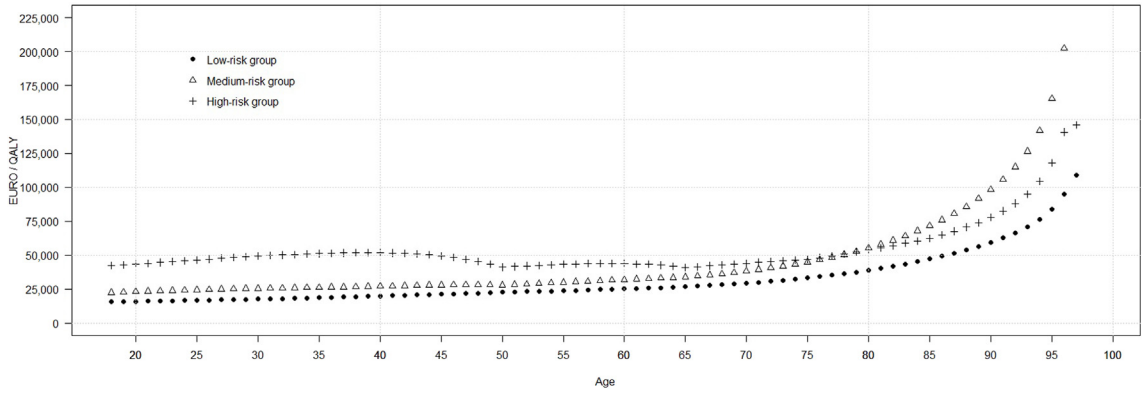

Fig. 1. Impact future unrelated medical costs and non-medical consumption on ICER for saving a life by age and risk group.

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).*

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.

4. 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., [14,28,29]). 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 [16]. 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 [7]. 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 [30] (note that the patent of the studied vaccine has not yet expired [31]).

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 [32]. 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., [28,29]). 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 paper, we want to note the ongoing discussion on what costs should be considered in CEA. The issue currently under debate is whether the benefits of future non-medical costs are fully captured in the QALY, and, if this is not the case, what this implies for including future non-medical costs [7]. 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 [33]. It is also unclear to what extent thresholds to which ICERs are compared include these benefits [7]. Further research into these issues is therefore recommended.

To conclude, in this paper we estimated the impact of including future UMC and NMC in the CEA of vaccination with PCV13 against pneumococcus disease. It was shown that the inclusion of these costs has a substantial effect on the ICER, especially when people at higher risk with underlying health conditions are saved. Given this impact, interventions that were first projected to be cost-saving, were shown to be cost-ineffective after inclusion, when judged against relevant thresholds. Although this indicates the need to consider ethical considerations regarding how to deal with such situations, especially when they could exacerbate health inequalities, ignoring these real medical and societal costs does not solve the underlying issue and is not in line with optimizing outcomes with limited resources.

CRediT authorship contribution statement

L.M. de Vries: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization, Project administration. **K.M. Kellerborg:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing - review & editing, Visualization. **W.B.F. Brouwer:** Writing - review & editing, Supervision, Funding acquisition. **P.H.M. van Baal:** Conceptualiza-

tion, Methodology, Validation, Writing - review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: K.M. Kellerborg, W.B.F. Brouwer, and P.H.M. van Baal report grants from the European Commission, during the conduct of the study. L.M. de Vries declares no competing interests.

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Appendix

6.1. 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). Eq. (A.1) shows this relation by presenting total healthcare expenditures for disease i at age a (hce_i (a)) as average costs for disease i at age a, conditional on having disease i ($ac_i(a|i)$), 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.

$$\begin{aligned} total\ \ hce_i(a) &= ac_i(a|i) * patients_i(a) \\ &= ac_i(a) * population(a) \end{aligned} \tag{A.1}$$

By writing patients/population as the prevalence (p), this can be rewritten into Eq. (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.

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

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. Note here, that the prevalence is assumed to be equal for the different diseases within a risk group. 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 Eq. (A.3). for per capita costs and in Eq. (A.4) for per patient costs.

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

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

Eqs. (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 Eq. (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.

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

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

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

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

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

6.2 Matching ICD codes

(See Table A1)

6.3 Results

(See Fig. A1 and Table A2)

Table A1
Matched diseases and ICD-10 codes from different sources.

Risk group	Condition original study	UK study	ICD-10	PAID
Medium	Alcoholism	Not included		Drug and Alcohol Dependence
	Cerebrospinal fluid leaks	Individuals with cerebrospinal fluid leaks	G96.0	Other diseases of the nervous system and sense organs
	Chronic cardiovascular disease	Chronic heart disease	I05, I06, I07, I08, I09, I11, I12, I13, I20, I21, I22, I25, I27, I28, I3, I40, 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, Q33, Q34, Q35, Q36, Q37	Asthma and chronic obstructive pulmonary disease (COPD); other respiratory diseases; other congenital anomalies, excluding Down's syndrome
	DM with insulin DM	Diabetes	E10, E11, E12, E13, E14, E24, G59.0, G63.2, G73.0, G99.0, N08.3, O24, P70.0, P70.1, P70.2	Diabetes mellitus including diabetic complications; other endocrine, nutritional and metabolic diseases; other diseases of the nervous system and sense organs; pregnancy; other conditions originating in the perinatal period
	DM without insulin	Diabetes	E10, E11, E12, E13, E14, E24, G59.0, G63.2, G73.0, G99.0, N08.3, O24, P70.0, P70.1, P70.2	Diabetes mellitus including diabetic complications; other endocrine, nutritional and metabolic diseases; other diseases of the nervous system and sense organs; pregnancy; other conditions originating in the perinatal period
High	AIDS	not included	B20, B21, B22, B23, B24	HIV/AIDS
	Functional or anatomic asplenia	Asplenia or dysfunction of the spleen	D73, D56.1, D57.8, D57.0, D57.1, K90.0	Diseases of the blood and blood-forming organs; other diseases of the digestive system
	Chronic liver disease	Chronic liver disease	K70, K71, K72, K73, K74, K75, K76, K77, P78.8, Q44	Chronic liver disease and cirrhosis; other liver diseases; other conditions originating in the perinatal period
	Chronic renal failure	Chronic kidney disease	N00, N01, N02, N03, N04, N05, N07, N08, N11, N12, N14, N15, N16, N18, N19, N25, Q60, Q61	Nephritis and nephropathy; acute renal and urinary infections; other renal and urinary diseases; other congenital anomalies, excluding Down's syndrome
	Malignancy	Malignancies affecting the immune system:	C81, C82, C83, C84, C85, C88, C90, C91, C92, C93, C94, C95, C96	Other lymphoid cancer and leukemia; non-Hodgkin's disease
	Bronchial obstruction due to primary lung cancer		C34	Lung cancer
	Hodgkin		C81.90	Other lymphoid cancer and leukemia
	Human immuno-deficiency virus infection		B20, B21, B22, B23, B24	HIV/AIDS
	Leukemia	Malignancies affecting the immune system:	C81, C82, C83, C84, C85, C88, C90, C91, C92, C93, C94, C95, C96	Other lymphoid cancer and leukemia; non-Hodgkin's disease
	Lymphoma	Malignancies affecting the immune system:	C81, C82, C83, C84, C85, C88, C90, C91, C92, C93, C94, C95, C96	Other lymphoid cancer and leukemia; non-Hodgkin's disease
	Multiple myeloma		C90	Other lymphoid cancer and leukemia
	Receipt of immunosuppressive therapy	Conditions affecting the immune system:	D56.1, D57.8, D57.0, D57, D61, D70, D71, D72, D73, D76, D80, D81, D82, D83, 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

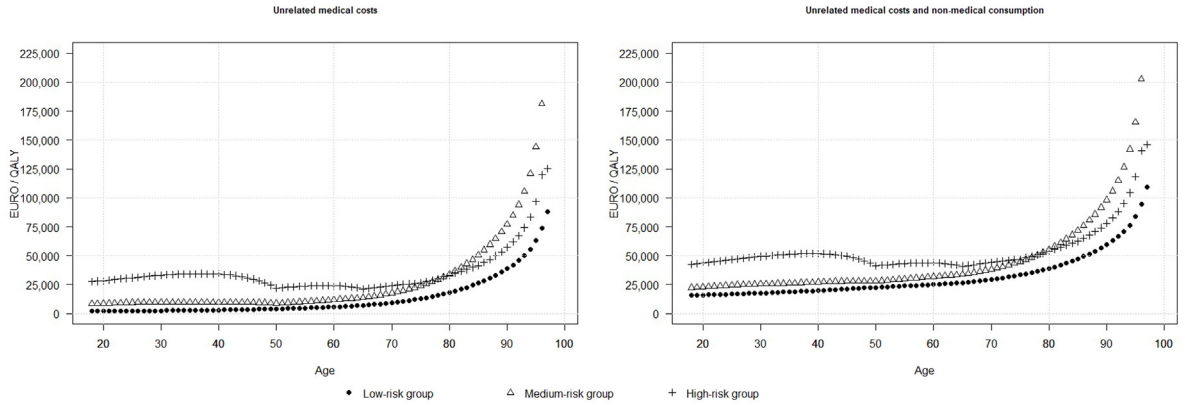

Fig. A1. Impact future costs on incremental cost-effectiveness ratio for saving a life by age and risk group.

Table A2
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 €).

Age	*Risk*	Impact			Thresholds (proportional shortfall)[a]
		UMC	*NMC*	*UMC + NMC*	
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).*

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