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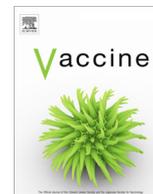
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## Short communication

# Cost-effectiveness analysis on elderly pneumococcal vaccination in the Netherlands: Challenging the Dutch Health Council's advice

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## ABSTRACT

Recently, the Dutch Health Council advised on elderly pneumococcal vaccination favouring the conventional polysaccharide vaccine over the novel conjugated vaccine. This advice was strongly inspired by a cost-effectiveness analysis considered to show favourable outcomes for the polysaccharide but not for the conjugated vaccine. We argue that using the same data and methods as presented by the Health Council, a different perspective on the results leads to a conclusion that not only the polysaccharide but also the conjugated pneumococcal vaccine is cost-effective. Our alternative perspective concerns the use of realistic vaccine prices, and applying an adequate time horizon for cost-effectiveness modelling. Notably, for one-off vaccination of 65-years old elderly, in all investigated analyses, also the conjugated vaccine seems cost-effective; i.e. well below the threshold of €20,000 per quality-adjusted life year, reflecting the most stringent threshold used for vaccines in the Netherlands.

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## 1. Introduction

A recent advice of the Dutch Health Council recommends uptake of a pneumococcal vaccination program for elderly using the conventional 23-valent pneumococcal polysaccharide vaccine (PPV23) [1]. The Dutch authorities have analysed pneumococcal vaccination several times, but so far the Netherlands had been among the 8 out of 28 EU-countries that until recently never recommended or implemented an elderly vaccination program using PPV23 [2]. The quest for the Health Council's advice was also inspired by recent local evidence that has become available on the alternative novel 13-valent pneumococcal conjugated vaccine (PCV13) from a large randomized clinical trial among approximately 80,000 Dutch individuals aged 65-years and over ("community-acquired pneumonia immunization trial in adults"; CAPITA), potentially warranting a PCV13-based elderly pneumococcal vaccination program [3].

As in many countries nowadays, health technology assessment (HTA) provides a core aspect in the Dutch national authorities' approach to advise and decide on the introduction of a new vaccination campaign. Within the context of healthcare decision-making, cost-effectiveness analysis – as one of the seven criteria

for introducing new vaccinations [4] – constitutes a crucial element, with the cost per quality-adjusted life year (QALY) generally as its main outcome. Informed by a separate analysis [5], the Health Council inferred that universal elderly vaccination with PPV23 is cost-effective, whereas PCV13 was estimated not cost-effective, applying a strict threshold cost-effectiveness at €20,000 per QALY, a limited time horizon and officially listed prices for individual use [1]. This result can be considered surprising as it contradicts previous Dutch cost-effectiveness analyses on PCV13 in elderly persons [6,7], also based on CAPITA.

Here, we argue that a different view on the same economic data would result in a different conclusion in which both vaccines could be considered cost-effective options if a lifetime time horizon for analysis is taken and/or realistic pricing is considered; well below the aforementioned lowest limit for cost-effectiveness at €20,000 per QALY for the Netherlands [8]. To derive our arguments, secondary analysis on selected data from the published cost-effectiveness study [5] was performed.

## 2. A broader health-economic perspective on the dutch health council advice

With the core role for the cost-effectiveness analysis in the Dutch recommendation for PPV23 to be implemented in a future universal elderly pneumococcal vaccination program [1], it seems

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appropriate to review this analysis in more detail [5]. In the economic model, evidence on the effectiveness of PCV13 against invasive pneumococcal disease and pneumonia was taken from the CAPITA-study (Table 1). For PPV23, effectiveness against IPD was obtained from a recent meta-analysis [9], whereas for effectiveness against pneumonia it was not possible to identify appropriate data. An assumption based on the contribution of the PPV23 serotypes in the overall serotype distribution in the Netherlands was made for PPV23's effectiveness on pneumonia. For PCV13 lasting protection up to 15 years was assumed as well as long-term herd immunity effects, whereas for PPV23 only short-term protection was assumed [5]. Finally, we note that list prices were used to reflect costs of vaccination.

Over the 10-year time horizon mostly applied in the Health Council analyses, QALY gains for PCV13 surpass those by PPV23 with 196 as an aggregate for the whole of the Netherlands, for vaccinating 10 cohorts of 65-years old and measuring benefits during those 10 years only. The corresponding cost-effectiveness estimated was €44,000 per QALY for PCV13 and labelled “not cost-effective” [5]. This relatively short time horizon of 10-years was used, instead of the generally preferred lifetime time horizon. Guidelines for pharmacoeconomic research recommends the lifetime time horizon (for example, the Dutch guidelines [10]) to allow for adequate capturing of the whole spectrum of costs and benefits [11]. Specifically, the 10-year time horizon may be considered too short to capture all impacts of, in particular, for PCV13 with longer lasting protective effects thus underestimating the economic value of PCV13. Notably, in the last cohorts vaccinated in the 10-year time period, adequate time to reap the benefits of vaccination at all is not allowed in the model. In sensitivity analyses, the model was evaluated over longer time frames, including lifetime. Based on applying lifetime costs and effects, cost-effectiveness for PCV13 was indeed estimated much lower at €15,400 per QALY for vaccinating 65-years olds [5], below the limit of €20,000 per QALY.

It is well known that list prices – as applied for general pharmaceuticals – do not reflect the costs of vaccines for the public health authorities within public programs. For example, costs reported for the Dutch public authorities for PCV10 and the HPV-vaccine included in the Dutch national vaccination program are ranging from €17 to €23 [12], reflecting grossly 15–40% of listed prices [13]. Obviously, the exact level of discounts provided is confidential and is likely to be dependent on the type of program, the specific disease targeted with vaccination, the availability of competitors, the design of the tenders and the negotiation power of the parties involved. However, that the net price will be substantially below the list price seems a reasonable assumption. An assumed price reduction of 50% would result in a cost-effectiveness ratio of €18,900 per QALY for PCV13 (calculations by the authors on the reported data [1,5] with a limited 10-year time horizon).

**Table 1**  
Core assumptions in the Dutch cost-effectiveness model for PCV13 versus PPV23 [5].

	PPV23	PCV13
Vaccine costs (list prices)	€21.20	€72.67
Vaccine effectiveness 1st 5 years		
IPD	56-0% [9]*	75% [3]
CAP	20-0% [assumed]	38% [3]
Vaccine effectiveness next 10 years		
IPD	0%	75-0% [assumed]**
Pneumonia	0%	38-0% [assumed]**

\*Linear decrease from year 1 to 5; \*\*Linear decrease from maximum in 1st 5 years to 0% in 10 years; IPD = invasive pneumococcal disease; CAP = vaccine-type hospitalised community-acquired pneumonia.

Combining a 50% price reduction and the longer time horizon in a secondary analysis on those data reported in the published paper [5] resulted in cost-effectiveness ratios listed in Table 2, with various scenarios estimated in the lifetime time horizon. We build on the scarcely reported lifetime cost-effectiveness results in the published data [5]; i.e., two cost-effectiveness ratios (CERs) for the age group of 65-years olds at €15,400 and €3,200 per QALY for PCV13 and PPV23, respectively (base-case estimates). Building on this reported base-case, estimated savings and QALYs were calculated per case averted over 10-years period and subsequently used for estimating total savings and QALYs gained over the lifetime period (see Annex for details on methodology). Sensitivity analysis was performed on the savings and QALYs per case, by varying + and –25% in the estimates, to derive uncertainty intervals. As, currently, no elderly pneumococcal vaccination is performed in the Netherlands, the comparison of PCV13 and PPV23 with absence of vaccination – as made in the original comparison of the Health Council – seems an appropriate one. Yet, health-economics theory might also warrant an incremental cost-effectiveness analysis relating the likely more expensive alternative (PCV13) to the less expensive one (PPV23). Table 2, additionally mentions these incremental cost-effectiveness ratios (ICERs). Notably, the base-case ICER for PCV13 over PPV23 was estimated at €31,400 (uncertainty interval: €26,100; €46,300) per QALY at baseline, and a corresponding break-even price of PCV13 at €20,000 per QALY of 61.2% (50.7–69.7%) of the list price. Finally, as evidence on effectiveness for community-acquired pneumonia (CAP) is scarce and contradictory [1], we also analysed absence of effectiveness of PPV23 on CAP, using the same secondary-data analysis methodology as outlined above (and in the Annex).

### 3. Discussion

It is likely that the integrative nature of the economic model is very attractive to authorities. However, we need to stay critical about such analysis. Above, we have shown that the same data used for the Dutch Health Council's advice on elderly pneumococcal vaccination can – or likely should – result in a different conclusion on the economic attractiveness of elderly vaccination with PCV13. In our alternative approach, almost all analyses investigated indicated a favourable cost-effectiveness of PCV13 if evaluated at €20,000 per QALY. This result contrasts the Health Council report [1] that labelled PCV13 as not-cost-effective.

We argue that the time horizon of 10 years – that was mostly considered in the Health Council report [1,4] – is too low to capture the full benefits of PCV13 vaccination and seems in contrast with international guidelines that favour a long, ideally, lifetime time horizon. Changing to a long-term time horizon acknowledges the full benefits of PCV13 and consequently, cost-effectiveness is lowered to acceptable levels. Particularly, both the adequate longer time horizon as well as expected reductions on the list price indicate a cost-effectiveness for PCV13 well below the strict €20,000-per-QALY threshold. The Health Council's focus on the short 10-year time horizon results, in contrast to international guidelines, was motivated by pointing to the uncertainty in future trends [1,5]. The issue of uncertainty raised by the authors is fair, in particular for pneumococcal epidemiology, however, should possibly better be dealt with by applying adequate discount rates on future health benefits and savings according to standard health-economic theory rather than deviating from the preferred lifetime time horizon. Discounting was indeed performed in the analysis according to the Dutch health-economic guidelines. Discounting as well as reducing the time-horizon seems like “double counting” in penalising for uncertainty, which needs to be avoided. Notably, a recent report by the National Institute for Health & Care Excellence (NICE)

**Table 2**  
Selected exploratory scenarios from secondary data analysis on reported cost-effectiveness information [5] estimating cost-effectiveness ratios (CERs) and incremental CERs (ICERs) in €/QALY, with corresponding uncertainty intervals. Scenarios are based on reported base-case CERs of €15,414 and €3195 for PCV13 and PPV23, respectively.

Scenarios	CER PCV13		CER PPV23		ICER	
1. Reduced price PCV13	€4,390	[3,217–5,202]	€3,195	NA*	€5,950	[3,244–8,213]
2. Reduced price both	€4,390	[3,217–5,202]	CS**	[CS-CS]	€13,364	[11,237–15,836]
3. No CAP PPV23	€15,414	NA*	€12,917	[10,265–14,920]	€16,771	[15,626–19,429]
4. No CAP PPV23 and reduced price PCV13	€4,390	[3,217–5,202]	€12,917	[10,265–14,920]	CS**	[CS-1,937]
5. No CAP PPV23 and reduced price both	€4,390	[3,217–5,202]	€3,782	[2,516–4,995]	€4,720	[2,222–6,535]

\* NA: not applicable as this was the input in our back calculation process for net costs and net QALY gains in the estimation procedure outlined above;

\*\* CS: cost saving; CAP = vaccine-type hospitalised community-acquired pneumonia; CER = cost-effectiveness ratio; ICER = incremental cost-effectiveness ratio; PCV13 = 13-valent pneumococcal conjugated vaccine; PPV23 = 23-valent pneumococcal polysaccharide vaccine.

as well as the Joint Committee of Vaccination & Immunization (JCVI) reinforced the use of a lifetime time horizon and adequate discounting, in particular for vaccines [14]. Whereas a lifetime approach may be considered optimal, already after a finite period the vast majority of savings and health gains would be harvested. In particular, with average life expectancy at 65 years at approximately 20 years, a time horizon of 20 years after the last cohort considered is vaccinated could be sufficient to capture the vast majority of benefits. This is however still far more than 10 years.

Some further analyses seem warranted. Notably, the Health Council's report did not follow the societal perspective as preferred in the Dutch guidelines [10]. This perspective would, for example, advocate inclusion of sickness leave and production losses due to pneumonia. These can be significant for those in their sixties and become increasingly important, considering the increasing pension age in the Netherlands. In this respect the cost-effectiveness estimates, in particular, those for PCV13 given the higher initial protection, should again be conceived as underestimates. Finally, we note that some potentially relevant calculations were not reported in the Dutch Health Council report and could also not be deduced from the reported data [1,5]. A combined strategy of initial vaccination with PCV13 and re-vaccination with PPV23 was not analysed but has been suggested in the literature as a potentially cost-effective approach [15,16]. For Germany, this sequential approach applied to all individuals at risk was estimated cost-effective at €14,000 per QALY from the societal perspective, varying from €3,300 to €29,600 per QALY in scenario analysis [16].

In conclusion, instead of the cost-effectiveness results presented by the Dutch Health Council that favour PPV23 over PCV13 – the latter labelled as “not cost-effective” – a more appropriate selection of analyses that adheres to international pharmacoeconomic guidelines on time horizon and acknowledges economies of scale shows that rather both vaccination strategies have potentials of being (highly) cost-effective. Best estimates of cost-effectiveness for PCV13 are consistently (well) below €20,000 per QALY, which reflects an often used threshold for vaccines. We conclude that an adequate and consistent weighting of the analyses of the Dutch Health Council makes PCV13 elderly vaccination more economically attractive than suggested, giving rise to two potentially cost-effective options of elderly pneumococcal vaccination in the Netherlands: both PPV23 as well as PCV13.

### Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: This work was supported by an unrestricted grant from Pfizer, the Netherlands. Pfizer was not involved in the design, conduction and reporting of the analyses and paper. Prof Maarten J. Postma reports grants and honoraria from various pharmaceutical companies, including all major industries developing, producing and marketing pneumococcal and other vaccines.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2019.08.051>.

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