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Short communication

Huge impact of assumptions on indirect effects on the cost-effectiveness of routine infant vaccination with 7-valent conjugate vaccine (Prevnar®)

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ABSTRACT

Several recently published European cost-effectiveness studies on the 7-valent pneumococcal conjugate vaccine (PCV-7: Prenvar®) have included net-indirect vaccine benefits for non-vaccine protected groups into their studies, which might be too optimistic an approach given recent data. Net-indirect effects result from herd protection minus serotype replacement effects. In this study we analyze the impact of net-indirect effects in non-vaccine protected groups of 5 years of age and older with updated assumptions regarding epidemiologic data and health care unit costs. Without net-indirect benefits for non-vaccine protected groups included the cost-effectiveness ratio is estimated at €72,360 per QALY. In order to obtain cost-effectiveness ratios below the threshold of €50,000 per QALY – which is in the middle of the range that is often referred to in the Netherlands – the net-indirect protective effect should at least be 16% of which has been observed in the USA after the introduction of PCV-7.

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1. Introduction

Several recently published European cost-effectiveness studies on the 7-valent pneumococcal conjugate vaccine (PCV-7; Prenvar®) have included net-indirect vaccine benefits for non-vaccine protected groups in their analyses (indirect effects) [1–4]. Net-indirect effects result from herd protection minus serotype replacement effects. Net-indirect benefits were often extrapolated based on a specific observational study from the USA, after the introduction of PCV-7 [5]. In particular, herd protection effects vastly outweighed any serotype replacements taking place. Inclusion of these indirect effects in elderly resulted in favourable cost-effectiveness ratios (CERs) [3,4], or even in cost savings [1,2]. However, three years after the introduction of routine vaccination there is no overall reduction in IPD incidence observed in adults in any European country including Spain, France, and the UK [6–8]. This might be due to an increase in non-vaccine serotypes – offsetting the potential herd protection benefits – or due to that fact that only a few birth cohorts have been vaccinated yet, which might not be enough to reduce the transmis-

sion of disease in the community sufficiently. In this brief report, we show the impact of the inclusion of indirect effects in the cost-effectiveness model and estimate the level of net-positive indirect effects needed (as a percentage of that observed in the USA) in order to label routine infant vaccination as cost-effective.

2. Methods

Our static cohort model builds on our previously reported studies [3,9]. It was updated to include recent epidemiologic and resource use data [10]. For invasive pneumococcal disease (IPD: meningitis and bacteraemia), age-specific data regarding baseline disease risk, duration of hospitalization, case-fatality rates and the occurrence of sequelae were taken from a recently published Dutch study [10]. In our model it was assumed that sequelae could lead neurological problems requiring life-time institutionalized care or lifetime special educations and to hearing problems, with corresponding high costs involved [9].

National hospital and GP-registrations were used to estimate the age-specific incidences for acute otitis media (AOM) and community-acquired pneumonia (CAP). Both CAPs to be treated in GP-practices and CAPs requiring hospitalization were estimated separately as was done previously as well [9].

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Fig. 1. The cost-effectiveness ratio per QALY of as a function of varying the level of net-indirect effects included for invasive pneumococcal disease for non-vaccine protected individuals aged 5 years and onwards.

Vaccine efficacy for IPD was estimated at 97.4% for 7 serotypes included into the vaccine IPD, 11.1% for hospitalized CAP, 6% for CAP treated by the GP and 7% against AOM, based on the Kaiser trial [11–13]. PCV-7 was assumed to be effective after two doses of vaccination for the birth cohort analyzed (180,000 infants; corresponding to the size of the Dutch birth cohort). As the aim of this paper was to show the indirect effects in unvaccinated individuals due to routine vaccination of children we excluded serotype placement and herd protection effects for the followed cohort. The time horizon of our cohort analysis was 5 years, which justifies the use of a stable vaccine efficacy for IPD. For non-invasive disease it was conservatively assumed that children would be protected up to the second year of life [14].

Indirect effects for those outside the vaccine-protected cohort were implemented in a sub-module using straightforward proportional calculus on registered numbers of IPDs [10]. Three studies present data on the net-indirect effects (herd protection benefits

minus serotype replacement) on IPD among non-vaccinated groups in the USA [5,15,16]. The most recent study was performed by Hsu et al., focussing solely on meningitis for all age groups [15]. In another study, detailed information was available on IPD for citizens aged 50 years and over [16]. Finally, a study performed by Whitney et al. describes the net-indirect effects on an aggregated level for all IPD together, but does present data from the age 20 and onwards [5]. The net-indirect effects assumed in our study for those outside the followed cohort (i.e., individuals aged 5 years and older) were based on Hsu et al. regarding meningitis, for all other IPD the findings of Whitney et al. were used for those aged 5–50 years (assuming that the effects in children aged 5–19 years are similar to those observed in individuals aged 20–40 years) and those by Lexau et al. [16] for the age groups of 50 years and over. Table 1 summarizes the assumptions on the net-indirect effects. In this table negative percentages indicate a relative decrease in the disease incidence and positive percentages indicate an increase (as compared to the pre-vaccination incidence; 2004–2006). To be conservative, when net-indirect effects are included we only assumed loss of utility and costs due to hospitalized IPD, so utility losses and costs related to sequelae were excluded. Also, we did not include net-indirect effects for non-invasive pneumococcal disease due to lack of data on this issue.

The main outcome measures were life years, quality-adjusted life years (QALYs) and costs. QALYs for IPD and non-invasive infections were taken from [22], sequelae related utilities were based on two specific studies [17,18]. The analysis was performed from a societal perspective including both direct medical and indirect non-medical costs of production losses (measured using the friction cost method), all updated to 2008 [9,19]. The costs of vaccination were assumed at €50 per dose including administration costs, which reflects the current price of PCV-7 in the Dutch vaccination program. Given 3+1 dose schedule applied in the Netherlands, pneumococcal vaccination would cost €200 per infant. According to the Dutch guidelines, effects and cost were discounted at 1.5% and 4%, respectively [19].

Table 1

Assumptions on the direct effects of PCV-7 for the vaccinated cohort (those aged less than 5 years) and the indirect effect on those outside vaccine-protected cohort (those aged 5 years and older). Negative percentages indicate direct (those aged less than 5 years) or herd protection effects (those aged 5 years and older), positive percentages indicate serotype replacement (those aged 5 years and older).

Age category	0–4	5–17	18–39	40–64	65+
Meningitis					
PCV-7 serotypes	–97%	–8%	–69%	–62%	–67%
PCV-7 related types ^a	N/A	0%	–52%	39%	–66%
Other types	N/A	1%	76%	68%	–37%
Net-overall effect meningitis ^b	–97%	–2%	–1%	6%	–53%
Age category	0–4	5–19	20–39	40–49	50+
Invasive Pneumonia					
PCV-7	–97%	–40%	–40%	–14%	–48%
PCV-7 related serotypes ^c /23PPV ^d	N/A	–22%	–22%	–4%	11%
Other types	N/A	–20%	–20%	–1%	26%
Net-overall effect pneumonia ^b	97%	–29%	–27%	–4%	–15%
Age category	0–4	5–19	20–39	40–49	50+
Bacteraemia					
PCV-7	–97%	–40%	–40%	–14%	–77%
PCV-7 related serotypes ^c /23PPV ^d	N/A	–22%	–22%	–4%	–36%
Other types	N/A	–20%	–20%	–1%	–29%
Net-overall effect bacteraemia ^b	–97%	–29%	–27%	–4%	–54%

^a Related serotypes for meningitis based on Hsu et al. 6A, 9A, 9L, 9N, 18A, 18B, 18F, 19B, 19C, 23A, 23B [15].

^b Overall change after correction for Dutch serotype specific incidence data [10].

^c Related serotypes for invasive pneumonia and bacteraemia for individuals aged less than 50 years based on Whitney et al. 6A, 9A, 9L, 9N, 18A, 18B, 18F, 19A, 19B, 19C, 23A, and 23B [5].

^d The 16 serotypes not included the PCV-7 but yet in the 23-valent pneumococcal polysaccharide vaccine (1, 2, 3, 5, 7F, 8, 9N, 10A, 11A, 12F, 15B, 17F, 19A, 20, 22F, and 33F) for those aged 50 years and older and all other types based on Lexau et al. [16].

N/A: Not Applicable.

3. Results

Without net-indirect effects being incorporated in the model, PCV-7 is estimated to prevent 5778 cases of non-invasive disease and 128 cases of invasive disease in the followed birth cohort over a period of 5 years, corresponding to a total gain of 292 life years or 422 QALYs. The totals cost of vaccination is estimated at €34.2 million. Subtracting the cost savings on medical and non-medical costs from these vaccination costs, resulted in a net total cost of €30.6 million. Dividing the net cost by the number of QALYs or life years saved resulted in CERs of approximately €72,360 per QALY or €104,790 per life-year gained.

Yet, if similar indirect effects as observed in the USA are included into the model, additionally 1113 LY or 1117 QALYs will be gained. The amount of QALYs and LY gained is almost equal as the vast majority of QALY gained is due to averted deaths and utility losses related to sequelae were excluded. The additional averted costs of €4.8 million lower the total net costs down to €25.8 million. Dividing the net cost by the health benefits resulted in vastly more favourable CERs of €16,750 and €18,360 for the cost per QALY and life-year gained, respectively.

Fig. 1 illustrates our findings for the CER per QALY gained through varying the level of net-indirect effects on IPD for individuals aged 5 years and onwards who are not directly protected by the vaccine. Again, it can be seen that the impact of these net-indirect effects on the CERs are tremendous.

4. Discussion

We estimated that without the inclusion of net-indirect effects vaccination with a 4-dose schedule would approximately costs €72,360 per QALY gained or €104,790 life-year gained. Full inclusion of indirect effects would lower these cost-effectiveness ratios to €16,750 and €18,360 per QALY and life year, respectively.

In the Netherlands, CERs above €80,000 certainly reflect unfavourable cost-effectiveness. Indeed 80,000 have been explicitly mentioned in this respect [20]. One other cut-off point that has been mentioned for the Dutch situation is €20,000 per life-year gained [21]. Certainly, below €20,000 cost-effectiveness can be labelled favourable. One might infer from these two cut-off points that assuming an implicit threshold of €50,000 per QALY in the Netherlands are not unreasonable.

In order obtain a CER for PCV-7 below the implicit Dutch threshold of €50,000 per QALY, the net-overall indirect effects should at least be 16% of those observed in the USA and above specified in Table 1 [5,15,16]. At this moment no overall decrease in the incidence in IPD incidence among those of 5 years older in any European country has been observed and it is obviously uncertain if this will happen in the future [6–8]. So at this moment it is uncertain if the Dutch PCV-7 programme will be cost-effective in the future or not.

We conclude that the exact assumption applied to indirect effects hugely determine cost-effectiveness estimates for PCV-7 vaccination. Future work should concentrate on explicitly modelling these indirect effects preferably using dynamic models which might be difficult due to the large number of relevant serotypes.

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