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Combination Vaccine Against Invasive Meningococcal B and Pneumococcal Infections

Potential Epidemiological and Economic Impact in The Netherlands

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Abstract

Background: *Streptococcus pneumoniae* and *Neisseria meningitidis* group B are among the main causes of invasive bacterial meningitis infections in infants. Worldwide, these diseases lead to significant mortality, morbidity and costs. The societal impact is especially severe since the majority of cases occur in very young infants. A combination vaccine consisting of 9-valent conjugated pneumococcal and meningococcal B components is currently being developed. The aim of this study was to estimate the potential impact and cost effectiveness from the societal perspective of vaccinating infants in The Netherlands with this combination pneumococcal and meningococcal B vaccine versus no vaccination.

Methods: A Markov cycle model was developed using epidemiological and healthcare resource use data from 1996 to 2001. This model was used to project the annual costs, benefits and health gains associated with vaccinating all newborns. The base year for the costing was 2003 and all costs and health effects were discounted at 4%. The results of the analysis are expressed in costs per QALY and both probabilistic and univariate sensitivity analyses were used to identify the robustness of the results.

Results: Annually, an average of 755 cases of invasive pneumococcal and meningococcal B infection occurred in infants aged 0–10 years in The Nether-

lands. Introduction of the combination vaccine would prevent 201 cases of meningococcal B meningitis and 165 cases of invasive pneumococcal disease per year. Additionally, 3410 cases of pneumococcal pneumonia and 46 350 cases of otitis media would be prevented. Vaccination would save 35 lives per year and prevent 71 cases of severe sequelae. This translates into 860 life-years gained, or 1128 QALYs gained.

Alongside these health gains, vaccination would prevent €17 681 370 of direct medical and indirect costs attributable to meningococcal and pneumococcal infections in The Netherlands. Depending on vaccine price, cost effectiveness varied from €3160 (vaccine price per dose €20) to €32 170 (vaccine price €60 per dose) per QALY. Base-case cost effectiveness (vaccine price €40) was €17 700 per QALY. The model was most sensitive to changes in incidence, vaccine price and duration of protective efficacy.

Conclusion: Our results suggest that the introduction of a combination meningococcal B and pneumococcal vaccine into the Dutch infant vaccination programme is potentially cost effective compared with no vaccination.

Invasive bacterial infections such as meningitis, bacteraemia and septic shock are associated with high mortality rates and a high percentage of complications. The largest burden of meningitis worldwide is caused by meningococcal and pneumococcal infections. Survivors of invasive meningococcal or pneumococcal infections often experience lifelong neurological or physical sequelae.[1-5] Pneumococcal infections are also a major cause of non-invasive disease such as pneumonia and otitis media, creating a large burden of disease.[6-8] It is estimated that every child in Western Europe experiences at least one episode of otitis media.[7]

The majority of meningococcal infections in Europe, Australia and Asia are caused by serogroup B or C infections, with meningococcal B infections accounting for the largest share.[9,10] A meningococcal group B vaccine is still under development, and results from a phase II clinical trial of a 6-valent meningococcal vaccine show that it is tolerable and able to induce protective antibodies in infants.[11-13] To offer a higher level of protection, a 9-valent meningococcal group B vaccine consisting of serosubtypes P1.7.16, P5.2.2, P19.15.1, P5.2.10, P12.1.13, P7.2.4, P22.14, P7.1.1 and P18.1.3.6, is under development. This vaccine uses three outer membrane vesicles, each containing three different types of PorA protein. The 6-valent vaccine (HexaMen) has been shown to induce good protective immunity, and since the 9-valent vaccine is directly derived from HexaMen, protective immunity is expected to be similar. Vaccines against serogroup C infections are available, and vaccination campaigns using these vaccines have been implemented in various countries such as the UK, The Netherlands, Australia and Belgium.[14,15]

A tolerable and effective 7-valent conjugate pneumococcal vaccine is licensed worldwide for paediatric use.[16-18] A 9-valent pneumococcal conjugate vaccine (containing serotypes 1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F) is under development and has also been shown to be tolerable.[19]

Infant vaccination programmes have greatly reduced the burden of infectious diseases and are cost-effective preventive measures according to the World Bank.[20] However, the number of total immunisations given throughout childhood is relatively high (up to 16), which can cause stress in both the

parents and the child.[21] Lieu et al.[22] showed that parents are concerned about the large number of injections given to children (the pincushion syndrome), and the results of a willingness-to-pay study showed that parents were willing to pay a premium of up to $US50 (year 2000 values) to reduce the number of injections. Thus, infant vaccination programmes with stand-alone meningococcal B and pneumococcal vaccines may be more difficult to implement than a combination vaccine, especially since each vaccine requires multiple doses before full efficacy is achieved.

We used a model simulating vaccination of all newborns in The Netherlands to present the epidemiological and economic impact (from the societal perspective) of a combined 9-valent meningococcal B and pneumococcal vaccine. This combined vaccine is currently being developed by a partnership of the Netherlands Vaccine Institute and Wyeth Pharmaceuticals. It is expected to be on the market by 2010.

Methods

Model Design

The impact of the combination vaccine was estimated using a Markov cycle model with a 1-month cycle length. Vaccination with the combination vaccine at the age of 2, 3, 4 and 11 months was compared with no vaccination against meningococcal B and pneumococcal infections (the current situation). We constructed a Markov model that accounted for the most common representations of pneumococcal and meningococcal B infections.

In the model, pneumococcal infections could lead to the following diseases: uncomplicated pneumococcal meningitis or bacteraemia; complicated pneumococcal meningitis with septic shock; and pneumococcal pneumonia or pneumococcal otitis media. Similarly, a meningococcal B infection could lead to uncomplicated meningococcal meningitis or complicated meningitis with septic shock. The long-term consequences of both pneumococcal meningitis or bacteraemia and meningococcal meningitis or meningitis with septic shock were also taken into account. Since the model used average transition probabilities, it is possible that an infant would contract both meningococcal and pneumococcal meningitis in their life. However, since the incidence of disease is low, this is highly unlikely. It is more likely that infants become infected with otitis media and pneumonia, and the model also allows for this.

The Markov model modelled the costs, benefits and health gains of an annual cohort of infants born in The Netherlands (approximately 202 600).[23] Figure 1 shows a schematic representation of the Markov model.

Epidemiological Data

The annual incidence of pneumococcal and meningococcal B infections was assessed using epidemiological data from the Netherlands Reference Laboratory for Bacterial Meningitis (RBM) [Amsterdam, The Netherlands] from 1996 to 2001.[10] The RBM collects isolates from blood or cerebrospinal fluid (CSF) of patients with bacterial meningitis, bacteraemia or septic shock in The Netherlands and identifies the aetiology of the causative agent.

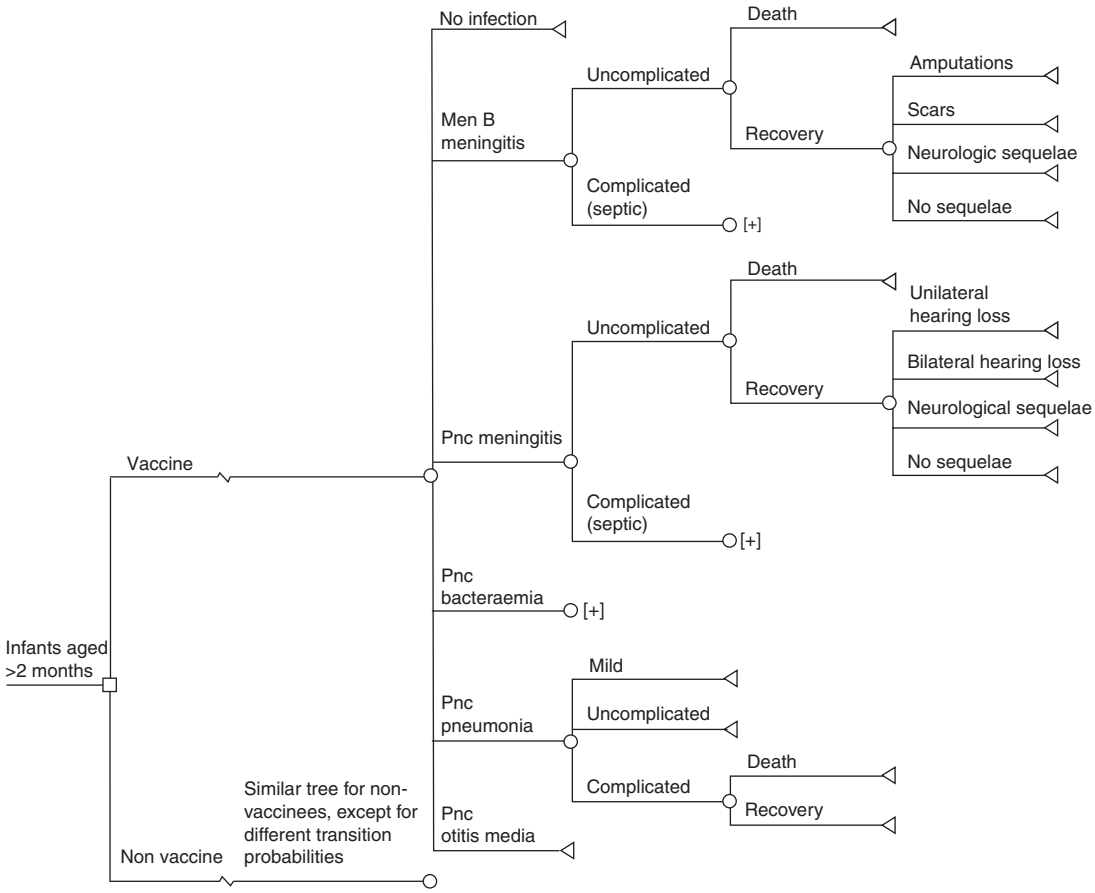

Fig. 1. Schematic representation of one cycle of the Markov model estimating the impact of a combination vaccine against meningococcal B (Men B) and pneumococcal (Pnc) infections in infants. [+] indicates that the same tree as for uncomplicated applies but with other probabilities.

Data from an expert panel[1] estimated that complicated pneumococcal meningitis with septic shock would occur in 40% of cases, and that 15% of all cases of meningococcal B meningitis occurred with septic shock. When *Streptococcus pneumoniae* was isolated only from blood (and not the CSF), the case was characterised as bacteraemia, and a similar resource-use pattern was assumed as uncomplicated pneumococcal meningitis. Pneumococcal and meningococcal B meningitis or septic shock often lead to severe lifelong sequelae.[1-4] Only sequelae leading to long-term care were considered in the model, and probabilities were derived from the international literature.

1 The expert panel consisted of members of the infectious diseases section of the Dutch Paediatric Society, which consists of representatives of most of the paediatric departments of university hospitals in The Netherlands. The expert panel was consulted on both the resource use of meningococcal and pneumococcal infections as well as assumptions on the severity of disease. Opinions of all specialists were noted and mean values were obtained for resource use (apart from number of inpatient days, which were derived from Prismant Healthcare).[24] For further details regarding the procedure, see Bos et al.[25]

The age-specific incidences of pneumococcal pneumonia and otitis media were estimated using data from the Integrated Primary Care Information Project (IPCI) database. The IPCI database contains computer-based patient records from 150 general practitioners (GPs) in 80 practices in The Netherlands.[26] Data were collected from 1 January 1997 to 31 October 2000. Since the IPCI database does not contain information regarding the aetiology of the causative agent of otitis media and pneumonia, estimates from the literature were used to derive the incidence of otitis media and pneumonia caused by *S. pneumoniae*.[27-29]

Table I summarises the epidemiological parameters used in the model.

Meningococcal Infections

Over the period 1996–2001, the annual number of invasive *Neisseria meningitidis* group B infections remained at an average of 416 cases per year in children aged 0–9 years.[10] This corresponded with an annual incidence of approximately 15–20 cases per 100 000 in infants aged 0–9 years, or 2–4 per 100 000 in the general population. Data from the Dutch registration of hospitals (Prismant Healthcare, a database that contains patient hospital admission data from the majority of hospitals in The Netherlands)[24] indicated that 15% of the invasive meningococcal B infections involved septic shock.[25] We divided sequelae after meningococcal infections into the following major categories: neurological sequelae, amputations and scars. Other possible complications occur less often and were ignored in the model. Neurological sequelae includ-

Table I. Model epidemiological and quality-of-life parameters[a]

Parameter	Value	References
Meningococcal infection		
Meningococcal B infection leading to septic shock or complicated meningitis	15%	25
Meningococcal infection leading to non-complicated meningitis	85%	25
Mortality rate meningitis	5%	1,25
Mortality rate septic shock	35%	1,2
Patients with neurological sequelae	8%	Expert panel, 1-3
Patients with amputations	1%	Expert panel, 1-3
Patients with scars	4%	Expert panel, 1-3
Pneumococcal infections		
Meningitis and bacteraemia	17%	4,5
Invasive pneumonia	6%	4,5
Sequelae after pneumococcal meningitis		
Unilateral hearing loss	11%	Expert panel, 4
Bilateral hearing loss	5%	Expert panel, 4
Spasticity	4%	Expert panel, 4
Mental retardation	4%	Expert panel, 4
Quality-of-life values (95% CI)		
Invasive pneumonia	0.9 (0.809, 0.991)	30
Neurologic sequelae[b]	0.82 (0.702, 0.938)	30
Bilateral hearing loss	0.77 (0.669, 0.871)	30
Unilateral hearing loss	0.89 (0.832, 0.948)	30

a The monthly risk in acquiring disease is derived from the incidence rates. The epidemiological parameters displayed in the table are mortality and complication rates. Since the timeframe of the clinical acute phase of the diseases is mostly short, these rates can be used as transition probabilities from meningococcal or pneumococcal infection to death or sequelae.

b Includes mental retardation, spasticity and seizures.

ed seizures, spasticity, hearing loss and mental retardation (table I).[1-4]

Pneumococcal Infections

Over the period 1996–2001, the annual number of pneumococcal meningitis infections remained stable at an average of 113 cases per year in children aged 0–9 years. The average age of illness was 5 months for meningitis or bacteraemia and 14 months for pneumonia.[10] Two categories of sequelae were considered: hearing impairments and neurological sequelae (table I). On average, 226 cases per year of pneumococcal bacteraemia occurred in children aged 0–9 years over the period.

Age-specific incidence rates per year were used to assess the impact of the vaccine on pneumonia and otitis media cases. Data from the IPCI database indicated an incidence of pneumonia (all causes)[26] of 1490 per 100 000 per year in children aged 0–9 years during the study period. Pneumonia was diagnosed as a common upper or lower respiratory tract infection, as indicated by the appropriate International Classification for Primary Care (ICPC) codes. Estimates from the literature indicated that approximately 25–30% of these cases were caused by pneumococcal infections.[27-29] An average annual incidence of 37 300 cases per 100 000 cases of otitis media (all causes) among children aged 0–9 years was found in the IPCI database.[26] Since the IPCI database only accounts for cases seen by a GP, it is likely that these figures are an underestimation of the total incidence of this disease. Data from the Dutch General Practitioners Society estimated that approximately 25–30% of all cases of otitis media are treated by a GP, indicating an incidence of pneumococcal otitis media of approximately 9400–11 200 per 100 000.[29]

Assessment of Vaccine Efficacy and Vaccine Parameters

In our analysis, we assumed the efficacy of the combination vaccine to be similar to the single vaccines and based our baseline efficacy on the results

Table II. Vaccine efficacy and coverage rates employed in the model

Parameter	Base value [%] (95% CI)	References
9-valent vaccine coverage of meningococcal B serosubtypes: base case	67 (66, 71)	10
Meningococcal B vaccine efficacy		
first dose	0	12,13
second dose	0	12,13
third dose	40 (31, 49)	12,13
fourth dose	91 (83, 96)	12,13
Duration of efficacy of vaccine after fourth dose	9 years	28
9-valent pneumococcal vaccine coverage against serotypes causing		
meningitis	65 (61, 70)	Based on RBM data 1996–2001[10]
bacteraemia	61 (57, 67)	Based on RBM data 1996–2001[10]
Vaccine efficacy for invasive disease pneumococcal infections		
first dose	0	32
second dose	94 (84, 94)	32
third dose	87 (71, 94)	32
fourth dose	97 (76, 100)	32
Pneumococcal vaccine effectiveness for non-invasive infections		
otitis media	6 (−4, 16)	18
pneumonia	11 (−14, 31)	33

RBM = The Netherlands Reference Laboratory for Bacterial Meningitis.

Table III. Direct and indirect costs (year 2003) of illness and average length of hospital stay employed in the model

Illness	Length of hospital stay (days)		Costs (€)	References for	Reference for costs
	standard care	intensive care		length of stay	and other resource use
Meningococcal meningitis	15		5 340	24,25	Expert panel, 36
Meningococcal septic shock	13	5	11 880	24,25	Expert panel, 36
Pneumococcal meningitis or bacteraemia	10	2	5 730	24,34	Expert panel, 36
Complicated pneumococcal bacteraemia involving septic shock	14	7	19 320	24,34	Expert panel, 36
Pneumococcal pneumonia					
mild	0		84		Expert panel, 36
non-complicated	0		184		Expert panel, 36
complicated	8		2 680	24,34	36
Otitis media			12	34	36
Neurological sequelae			317 800	25,34	25
Treatment of scars	8		530	25	Expert panel, 36
Treatment of amputations	8		3 360	25	Expert panel, 36
Indirect costs per case of meningitis or septic shock			265	25,34	23
Indirect costs per case of otitis media or pneumonia			75	34	23

of clinical studies.[11-13,18,31-33] These studies indicated the occurrence of protective efficacy after the second dose for the pneumococcal vaccine and after the third dose for the meningococcal B vaccine.[11-13] The efficacy per serotype of the 9-valent meningococcal B vaccine was assumed to be similar to the 6-valent vaccine, except for the added coverage due to the inclusion of more serotypes. It was assumed that the combination vaccine would induce protective efficacy against pneumococcal and meningococcal infections for up to 9 years after the last dose. This assumption was based on an immunogenity study of the pneumococcal conjugate vaccine and observations of the *Haemophilus influenzae* type B conjugate vaccine.[28]

Vaccine effectiveness against meningitis and septic shock was defined as efficacy (derived from clinical trial data) multiplied by vaccine serotype coverage.[34] For vaccine effectiveness against serotypes causing otitis media or pneumonia, non-serotype specific effectiveness data were used from studies for other countries, including the US.[18,33] Because of a lack of reliable data, no correction was applied to account for possible differences in serotype epidemiology between The Netherlands and the US.

Adverse effects with the combination vaccine were assumed to be minor and similar to the single vaccines.[9] The impact of cross-reactivity of meningococcal B serotypes in the base case was assessed using data from Vermont et al.[35] In the sensitivity analysis, the impact of different rates of cross reactivity was analysed. Table II lists the vaccine parameters used in the model.

Healthcare Resource Use

Healthcare resource use due to acute invasive pneumococcal and meningococcal B infections and sequelae (such as amputations or lifelong mental handicaps) was estimated using data from Prismant Healthcare (1996–2001)[24] and the expert panel. Further details can be found in Bos et al.[25,34]

The number of hospital inpatient days for illnesses caused by meningococcal B or pneumococcal infections is shown in table III. More details on the exact healthcare resource use (amount of care delivered) and costing parameters of pneumococcal in-

fections and the exact healthcare resource use of infants with meningococcal B infections has been described in Bos et al.[25,34]

Costs

Healthcare unit costs (see table III) were assessed using unit cost estimates from the Dutch reference prices for pharmacoeconomic studies by Oostenbrink et al.[37] If unit costs were not available, tariffs from the National Health Tariffs Authority and Health Care Insurance Board were used.[36-39] Because the vaccine price is unknown as yet, cost effectiveness was calculated for a range of values. For the baseline analysis, a vaccine price of €40 per dose was assumed, reflecting an average vaccine price per dose of recently introduced vaccines in developed countries (personal observations).

Indirect costs attributed to future work loss of infants who die of pneumococcal or meningococcal infections were not included in the analysis, since the friction cost method (as used according to the Dutch guidelines for pharmacoeconomic research) does not account for this. Indirect costs attributed to work loss of parents because of time caring for their sick children were included in the analysis. In The Netherlands, working adults are allowed to take some days off (the specific number depending on the individual working contract) for severe illness of a relative. We used an average of 3 days off for taking care of children with meningitis or bacteraemia. For caring for an infant with otitis media or pneumonia, we used an average of 5.9 hours off per episode of illness.[40] For the valuation of work loss, we used the average production value for 1 hour of work per parent (€12.6).[23] The timeframe of the analysis was 78 years and corresponds with the average life expectancy at birth in The Netherlands.[23]

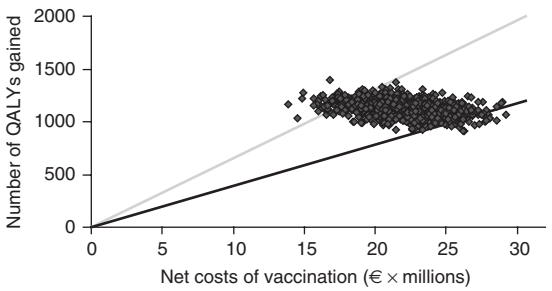

Fig. 2. Results of Monte Carlo simulation of costs (year 2003 values) and effects of vaccination. Lines indicate both lower and upper limits of 95% uncertainty intervals.

The base year for costs (€) was 2003; older prices were adjusted to 2003 using healthcare-specific inflation indexes.[23]

Cost-Utility Analysis

The outcome parameter was cost per QALY. For the valuation of quality of life we used specific weighting factors for diseases in The Netherlands as derived by Stouthard et al.[30,41] using a panel approach in which Dutch healthcare professionals evaluated a large number of health states. Further details can be found in the publications by Stouthard et al.[30,41] Because the acute phase of meningococcal disease and septic shock was not valued in the study by Stouthard et al.,[30] we only took loss of quality of life due to neurological sequelae, physical sequelae, hearing loss and invasive pneumonia into account, as defined by the EuroQol (EQ)-5D+ codes 212111 and 112112.

The analysis was performed according to the Dutch guidelines for pharmacoeconomic research.[42] As such, health and monetary effects were discounted at 4% per annum.

Sensitivity Analyses

Univariate sensitivity analyses were performed on several key parameters of the model such as sequelae and protective efficacy. The assumption of efficacy used in our study might not properly reflect the efficacy of the combination vaccine or population effectiveness, and was, therefore, varied in sensitivity analyses. The coverage of the meningococcal B vaccine depends on the amount of cross-

protection against serosubtypes not included in the vaccine. To calculate the impact of this effect, three scenarios were developed: (i) no cross-reactivity (vaccine coverage 50%); (ii) cross-reactivity based on Vermont et al.[35] (vaccine coverage 67%, base-case scenario); and (iii) maximum cross-reactivity (vaccine coverage of 84%).[35] The impact of antigenic shift was also calculated by assuming a 10% decrease in vaccine coverage per 5-year period for both vaccines.

Probabilistic sensitivity analysis was performed on all vaccine parameters (e.g. efficacy and coverage of the vaccines and values for quality of life) using standardised beta-distributions for parameters that have to be bound between 0 and 1. Proportions are often assumed to be Normally distributed.[43] However, some distributions used have to be bound between 0 and 1, since values outside the interval might be biologically impossible. Therefore, a standardised beta-distribution might be employed, since the standardised beta-interval is bound between 0 and 1 and resembles a Normal distribution.[44] Details on choices of distributions can be found in Briggs.[44] Probabilistic sensitivity analysis was not performed on other parameters in the model as they were estimated by our expert panel, and characteristics of their respective distributions were unknown. One thousand simulations were performed to derive the 95% uncertainty interval using TreeAge DATA™ 3.5.

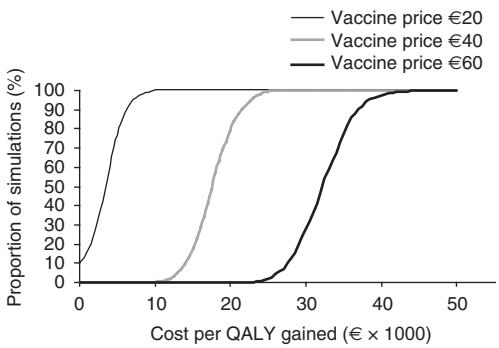

Fig. 3. Cost-effectiveness acceptability curves for different vaccine prices (year 2003 values) per dose.

Results

Health Effects

The use of the combination vaccine would result in the annual prevention of 201 cases of meningococcal B meningitis and 54 cases of pneumococcal meningitis. Vaccination would also prevent 111 cases of pneumococcal bacteraemia. Additionally, the combination vaccine would prevent approximately 46 350 cases of pneumococcal otitis media and 3410 cases of pneumococcal pneumonia. This would save 35 lives per year and 71 cases of lifelong sequelae, rendering 1128 discounted QALYs or 860 discounted life-years gained (LYG) per year. Of these saved QALYs, 49% would be saved by the pneumococcal component and 51% by the meningococcal B component. In our analysis, not discounting health benefits, vaccination would result in 2894 QALYs or 2206 LYG per year.

Costs and Cost Effectiveness

Our model estimated the yearly direct and indirect costs of pneumococcal infections in infants in The Netherlands at approximately €84 500 000. Of these costs, €28 300 000 were caused by invasive pneumococcal infections, whereas €56 200 000 were caused by pneumococcal pneumonia and otitis media. The yearly costs of meningococcal B infections were estimated at approximately €10 900 000.

In our model, vaccination of all newborns in The Netherlands at a vaccine price of €40 plus €6.20 administration fee per dose would cost €37 440 400 per year. Of these costs, a total of €17 681 400 would be offset by savings in direct and indirect costs of disease.

The vaccination programme would result in the prevention of approximately €3 956 600 of the

acute medical costs and €10 271 700 of the future costs of sequelae of pneumococcal and meningococcal infections. The prevention of work loss would result in total savings of €3 453 100.

Cost effectiveness depends on vaccine price. A vaccine price of €40 per dose resulted in a cost-effectiveness ratio (CER) of €17 700 per QALY (95% CI 12 050, 23 280). A vaccine price of €20 resulted in a CER of €3160 (95% CI from cost saving, 8609), whereas a price of €60 per dose resulted in a CER of €32 200 (95% CI 25 010, 39 530). All CERs presented are incremental ratios compared with a no-vaccination scenario.

The results of the Monte Carlo simulation are displayed in figure 2. Figure 3 displays the cost-effectiveness acceptability curve, indicating the probability that the vaccine will be cost effective for a given price per dose. For a vaccine price of €20 per dose, all simulations resulted in a CER of <€10 000 per QALY. When the vaccine price was €40 per dose, approximately 80% of simulations resulted in a CER of <€20 000 per QALY, while for a vaccine price of €60 per dose, the majority of simulations resulted in a CER of >€30 000 per QALY.

Sensitivity Analysis

The impact of different aspects of the efficacy of the combination vaccine was investigated in sensitivity analyses. The results of the univariate sensitivity analyses are shown in figure 4. Assuming a shorter duration of protective efficacy of 5 years instead of 9 years after the last dose of vaccine results in an increase in cost effectiveness of 50%. A 20% higher vaccine coverage leads to a CER of €12 600 (29% decrease in CER) versus €26 100 per QALY (44% increase in CER) for a 20% lower vaccine coverage. A 50% reduction in the prevalence of sequelae in survivors of meningococcal and pneumococcal infections results in an increase in the CER of 23%. The assumption of high cross reactivity against meningococcal type B strains not in the vaccine leads to a decrease in cost effectiveness of 10%, whereas the assumption of no cross reactivity results in an increase in the CER of 24%. Finally, the model is sensitive to changes in the incidence of infections and discounting health.

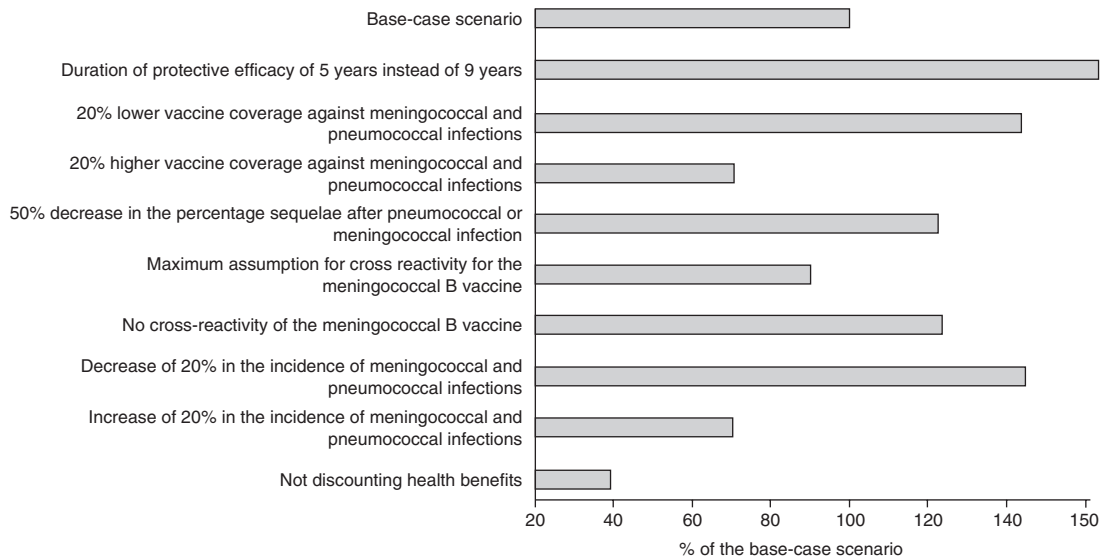

Fig. 4. The results of the univariate sensitivity analyses at a vaccine price of €40.

Discussion

With the implementation of a 9-valent pneumococcal and meningococcal B combination vaccine together with the current vaccination against *H. influenzae* type b, infants in The Netherlands will be protected against the most common causes of bacterial meningitis. Worldwide, there has been an increase in the incidence of meningococcal infections in recent years, stressing the need for vaccination.[9] The majority of meningococcal infections are caused by serogroups B and C, and a number of countries have already implemented separate meningococcal C vaccination programmes for infants.

However, small epidemics involving meningococcal A, W135 or Y infections occur from time to time. Therefore, incorporation of these other components may also be advantageous depending on the country-specific incidence. Sensitivity analysis showed that the model was most sensitive to vaccine effectiveness, incidence of infections and vaccine price. Total vaccine effectiveness can be influenced by at least three separate mechanisms. First, serotype replacement: the replacement of serotypes covered by the vaccine with other serotypes could have a negative effect on the cost effectiveness. Serotype replacement of pneumococcal bacteria has been observed in clinical studies, although the relevance for vaccine effectiveness is unclear as yet.[17,45] Second, the amount of cross-protection offered by the meningococcal B vaccine against other serotypes is unclear, but could have an impact on the effectiveness of the vaccine.[46] Finally, the efficacy of the single components in the combination vaccine might be different from the efficacy of the separate vaccines because of interference of components.

In the analysis, we only accounted for indirect costs caused by work loss of parents. This value for indirect costs is small because we assume that parents only need to take time off work for visiting the infant at the hospital. However, indirect costs could be of considerable importance if parents are forced to provide full-time care for their child over his or her expected lifetime, or if the child's future loss of productivity because of disability is valued. Accounting for these costs would significantly improve the cost effectiveness of the intervention.

To assess the use of healthcare facilities and disease variables associated with pneumococcal infections we used opinions of national experts and data from the international literature, respectively. This has consequences for the level of uncertainty and transferability of our study results. Since the members of our expert panel were representatives of academic hospitals, which usually treat the more severe cases of disease, our estimates of resource use could be high and may only be applicable for countries with comparable health systems to The Netherlands.

In our analysis, we used utility weightings for the end stages of pneumococcal sequelae. As a consequence, our analysis might be an underestimation of the total impact on quality of life since the utility loss of short-term events such as septic shock or meningitis was not valued. Data on quality of life of these very young infants was not available and would be difficult to derive.

Another limitation of our study was the use of a static model to assess the epidemiological effects of vaccination. As a consequence, no indirect effects of vaccination on herd immunity and age-specific incidence rates were assumed. Whitney et al.[46] recently reported that paediatric use of the pneumococcal vaccine led to herd immunity against non-invasive and invasive pneumococcal illness, both in children and adults.[46] The occurrence of herd immunity could lead to better protective efficacy, but could also induce a shift in age-specific incidence of pneumococcal meningitis. This has potentially positive implications for the incidence of disease, since many cases of pneumococcal meningitis are found in children who are too young to be protected by

vaccination. Whitney et al.[46] also found a decrease in the incidence of invasive pneumococcal infections in adults as a result of reduced carriage of pneumococcal serotypes in vaccinated children. A reduction of invasive pneumococcal disease in adults because of herd immunity has a potentially large positive effect on cost effectiveness. This is an important topic and more research is necessary to identify the full transmission dynamics of pneumococcal bacteria.

Conclusion

The model presented was developed as a tool for assessing the epidemiological impact of a combination meningococcal B and pneumococcal vaccine in countries with health systems and epidemiology comparable to The Netherlands. Our results indicate that the introduction of such a combination vaccine in the Dutch infant vaccination programme is potentially cost effective (vs no vaccination) from a societal perspective.

Acknowledgements

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Jasper Bos was primary investigator and conducted the major share of study design, data analysis and reporting.

Hans Rümke and Loek van Alphen co-authored on the paper, provided the vaccine-specific expertise and assisted in data collection.

Robert Welte co-authored and assisted in the design of the analysis.

Lodewijk Spanjaard co-authored and assisted in data collection and verification.

Maarten Postma and Loek van Alphen supervised all stages of the project.

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