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General Introduction

HISTORY OF VACCINATION

Vaccination is considered to be one of the most effective methods of preventing infectious diseases. Vaccines can prevent or ameliorate the effects of infection by pathogens and can be defined as the administration of antigenic substance to stimulate the immune system to develop adaptive immunity to a disease. The earliest documented examples of vaccination are from India and China in the 17th century, where vaccination with powdered scabs from people infected with smallpox was used to protect against the disease[1]. In1721 Lady Montagu brought the knowledge of variolation to England after witnessing the practice of inoculation against smallpox – variolation – in Turkey. Although the immunity acquired after variolation was considered reliable, the death rate was reported to still be around a tenth of that from natural infection (20–30%). An important step forward was made by Benjamin Jesty who deliberately inoculated his children with cowpox after noting that people infected with cowpox, a relatively mild disease, were subsequently protected against smallpox[1]. Later, in 1798, the British scientist Edward Jenner published the results of his experiments of inoculation with cowpox which showed that using cowpox for variolation was less dangerous but just as effective as using human smallpox[2]. These experiments inspired the word vaccination which is derived from vacca, the Latin word for cow. Given the relatively short history of vaccines, vaccine developments over the last century have been unprecedented.

National Immunization Program in the Netherlands

The first experiment with cowpox vaccination started in the Netherlands in 1799 and in 1823 vaccination policies required that children received the vaccine before entering school[3,4]. In the next century the vaccine uptake varied but was generally low. In the 1940s, effective whole–cell vaccines against *Bordetella pertussis* were developed, which became available in the Netherlands in 1949[5,6]. From 1953 a combination vaccine against diphtheria, tetanus and pertussis (DTP) was freely available for the Dutch population within mass vaccination programmes[5]. The coordination and surveillance was in the hands of a wide variety of organizations and differed significantly from one area of the country to another[7]. After a poliomyelitis epidemic in 1956 the government initiated a centrally organized mass vaccination campaign against polio in 1957 which is considered to be the start of the National Immunization Programme (NIP). The NIP expanded gradually since 1957 and covers currently 12 infectious diseases (see Table 1). The most recent additions to the Dutch NIP are the bivalent HPV vaccine targeting 12–year–old girls and a hepatitis B vaccine administered concomitantly with the DTaP, *Haemophilus influenzae* type b and polio vaccine components[8]. Next to these 12 infectious diseases, several new candidate vaccines are available targeting infectious agents such as a rotavirus and varicella (zoster) virus[9,10]. Besides targeting new infectious agents, the currently used vaccines in the infant programme could also be extended to other risk groups. For example, the current pertussis vaccination programme could be extended to adolescents while high–risk groups and the elderly could be vaccinated against pneumococcal disease. Also the replacement of current vaccines included in the NIP by vaccines which can prevent a larger

burden of disease, such as the 13–valent pneumococcal conjugated vaccine (PCV13) in the case of pneumococcal vaccination or the quadrivalent HPV vaccine for the protection against cervical cancer and genital warts, can be considered.

Table 1. The current Dutch National Immunization Programme[12]

Age	Injection 1	Injection 2
0 Months	HepB[a]	
2 Months	DTaP, IPV, Hib, HepB	Pneu
3 Months	DTaP, IPV, Hib, HepB	Pneu
4 Months	DTaP, IPV, Hib, HepB	Pneu
11 Months	DTaP, IPV, Hib, HepB	Pneu
14 Months	MMR	Men C
4 years	DTaP, IPV, Hib	
9 years	DT–IPV	MMR
12 years	HPV (3x)	

a= Only for children of whom the mother tested positive for HBsAg, Hib= *Haemophilus influenzae* type b, HepB= Hepatitis B, Pneu= Pneumococcal vaccination, MMR= Mumps, Measles and Rubella (German Measles), Men C= Meningitis C, HPV= Human Papilloma Virus (girls only), DTaP= Diphtheria, tetanus, and acellular pertussis, IPV= Polio–myelitis vaccine (inactivated)

Infectious disease modelling

Given the multitude of (new) vaccines available for possible introduction into NIPs, health economic modelling of new vaccines is becoming increasingly important in informing decisions on allocating scarce resources. For example, in the Netherlands the decision to introduce the 7–valent pneumococcal conjugated vaccine (PCV7) into the Dutch NIP for infants, has in part been driven by cost–effectiveness considerations[11].

To estimate the epidemiological and the economic impact of vaccination programs two types of models can be used, i.e. 'static' and 'dynamic' models[13-15]. The traditional static models for evaluation of infectious disease interventions are not always appropriate. This type of model ignores the fundamentally transmissible nature of infectious diseases, which can lead to distorted estimates of program effectiveness and cost–effectiveness. Yet, static models can provide useful initial or preliminary estimates. In particular, the risk of acquiring a transmissible infection is often related to the number of infectious individuals in the population. So, if an immunization program can reduce the number of infectious individuals in the population also non–vaccinated individuals can be indirectly protected against disease. This indirect protection of unvaccinated individuals is called 'herd–immunity'[16]. Next to positive indirect herd effects, vaccination can also have negative indirect effects, such as an increase in the average age of infection. Only dynamic models are able to predict these indirect effects. Hence, it is usually preferable to use a dynamic model to determine the effects and cost–effectiveness of vaccines.

Focus of this thesis

The focus of this thesis is on vaccines which can either replace the currently used vaccines in the NIP or which can be used for the extension of the currently targeted individuals in the NIP by using both static and dynamic models. In particular, static models will be used to estimate the impact of the pneumococcal vaccines that recently became available. A dynamic model will be used to estimate the impact of extending the current Dutch childhood pertussis vaccination programme to adolescents and/or adults.

Pneumococcal disease

Streptococcus pneumoniae is a gram–positive capsulated bacterium and is a common colonizer of the human nasopharynx. Next to being commensal, pneumococci are also opportunistic pathogens. Infections caused by *S. pneumoniae* are a major cause of morbidity and mortality worldwide, with the highest incidence rates seen among the infants, immunocompromised and elderly. Pneumococcal infections include frequently occurring mucosal non–invasive infections such as acute otitis media (AOM) and non–bacteraemic pneumonia, but also less common diseases that may be invalidating or fatal such as pneumococcal sepsis and meningitis. More than 90 immunologically distinct serotypes of the pneumococcus have been described that vary in their capsular polysaccharide composition. These serotypes are further categorized into 46 different serogroups based on immunological cross–reactivity[17]. Of all known serotypes, approximately 15 are assumed to be responsible for the majority of all invasive pneumococcal disease (IPD)[18].

Polysaccharide vaccines

A 23–valent pneumococcal polysaccharide vaccine (PPV23) has been available since the early 1980s which progressed from a 4–valent precursor vaccine over a 50 year time period[19]. Although many countries recommend this vaccine for vaccination of elderly, the efficacy and the duration of protection of this vaccine is uncertain and most probably limited, and there is a reduced antibody response to revaccination[20-22]. PPV23 stimulates mature B–lymphocytes, but not T–lymphocytes resulting in an immune response which is neither long–lasting nor characterized by an anamnestic (i.e., booster) response upon re–vaccination[23,24]. PPV23 does not elicit a protective immune response among infants and very young children, since children respond poorly to T–independent antigens. However, protein–conjugated polysaccharides do stimulate a T–helper–cell response, resulting in a substantial primary response among infants and a strong booster response at re–exposure[24].

Conjugated pneumococcal vaccines

In 2000, the 7–valent pneumococcal conjugated vaccine (PCV7) that covers seven serotypes (4, 6B, 9V, 14, 18C, 19F and 23F), was licensed for vaccination among infants and children in the USA. It has been shown in clinical trials and post licensure studies that PCV7 is highly effective in preventing invasive disease in young children[25-33]. Several other PCVs containing additional serotypes have been clinically investigated. Of these vaccines, a 10–valent vaccine (PCV10), containing the serotypes

included in PCV7 and serotypes 1, 5, and 7A is currently licensed for the use in infants and young children[34]. In addition to PCV10, the 13–valent vaccine (PCV13) also includes serotypes 3, 6A and key replacement serotype 19A. Similar to PCV10, PCV13 can also be used in infants and children, but in addition, it is also licensed for the use in adults aged 50 years and older[35].

Pneumococcal vaccination in the Dutch NIP

In the Netherlands, an infant pneumococcal vaccination programme with PCV7 was introduced in June 2006 using the recommended 3+1 dose schedule without a catch–up campaign. In other countries, such as the UK, PCV7 was introduced using a schedule of 2, 4, and 13 months, combined with a catch–up vaccination for children aged up to 2 years[36]. Next to favourable direct effects, herd protection and serotype replacement effects were additionally seen. Partially, due to replacement disease, PCV7 is being substituted in most countries by PCV13[28,36]. In the Netherlands, however, as from 2011 PCV7 has been replaced by PCV10 using a 3+1 dose schedule.

Pertussis

B. pertussis is a small, gram–negative bacterium with exclusive affinity for the mucosal layers of the human respiratory tract. It can cause pertussis, or whooping cough, which is a highly contagious infection of the respiratory tract. Most cases of clinically recognizable pertussis occur in children aged 1–5 years, while most severe disease and death occur in infants aged less than 2 months who are unimmunized[37]. Clinical manifestations of whooping cough may show substantial variation depending on age, clinical condition, and previous vaccination or infection. In general, a patient will develop catarrhal symptoms including cough after an incubation period of 9–10 days. In the subsequent paroxysmal phase, lasting several weeks, severe and spasmodic cough episodes with a characteristic whoop occur, often with cyanosis and vomiting[37]. In young infants, who may not have the strength to have a whoop, pertussis may cause apnoea and cyanosis. Finally, the last convalescent phase, is characterized by a continuous decline of the cough. However, paroxysms with subsequent respiratory infections may recur for many months after the initial onset of pertussis.

Pertussis vaccines

Two types of pertussis vaccines are available, i.e. whole–cell vaccines and acellular vaccines. Whole–cell pertussis vaccines are suspensions of inactivated *B. pertussis* organisms, while acellular vaccines are based on highly purified, selected components of this agent. [37]. The efficacies of the whole–cell vaccines and acellular pertussis vaccines vary depending on the case definition of pertussis used, but are generally considered as being equally effective[37]. A difference between the vaccines concerns the frequency of minor adverse reactions. The whole–cell vaccines are frequently associated (1 in 2–10 injections) with adverse reactions such as local redness and swelling, while the adverse event profile of acellular is milder[38].

Pertussis vaccination in the Dutch NIP

In the Netherlands, a vaccination against DTP was introduced in 1953 for a large part of the population. The NIP offering DTP and inactivated polio vaccination in a programmatic approach to all children born from 1945 onwards started in 1957[39]. Until 2001, the pertussis vaccination schedule in the Netherlands consisted of four doses (currently at ages 2, 3, 4 months and a booster at age 11 months) of the whole–cell pertussis vaccine within the combination of diphtheria, tetanus and polio vaccine. From 2001 onwards, an additional acellular booster vaccination was given to 4–year–old children. Starting in 2005, the pertussis component in the combination vaccine was changed from the whole cell to an acellular one.

Aim and outline of this thesis

The general aim of this thesis is to provide analyses of both the epidemiological and economic impact of new pneumococcal and pertussis vaccination strategies. The thesis is structured into two parts. In PART I the epidemiology and economics of pneumococcal vaccination are presented while PART II focuses on the impact of the introduction of extended pertussis vaccination strategies.

PART I

In many European countries, the implementation of pneumococcal vaccination programs against *S. pneumoniae* has partially been driven by the indirect beneficial impact as observed among various non–targeted age groups in Northern America. **Chapter 2** focuses on the transferability of these indirect effects using the post–marketing experiences with PCV7. In particular, this chapter provides a descriptive overview of the available epidemiological post–marketing data and experiences with PCV7 in different countries and populations. The impact of extrapolating net–indirect effects in non–vaccine protected groups from the USA to the Netherlands is analysed in **chapter 3**. **Chapter 4** provides an estimate of the cost–effectiveness of pneumococcal vaccination by using PCV7, PCV10, or PCV13. In contrast to **chapter 3,** for this analysis we did include serotype placement for vaccinated children. In **chapter 5,** the cost–effectiveness of extending the pneumococcal vaccination programme to elderly was calculated. Next to elderly, also individuals with certain clinical conditions such as immunocompromised patients are at increased risk of IPD[40]. Therefore, the impact of vaccinating these high–risk groups was calculated in **chapter 6**. In contrast to the other chapters in this thesis, this study was not performed for the Dutch setting but focused on the UK. One of the outcomes of **chapters 5 and 6** is that the cost–effectiveness is largely influenced by the etiological fraction of *S. pneumoniae* causing community acquired pneumonia (CAP). Therefore, **chapter 7** presents a meta–analysis to specifically estimate this fraction.

PART II

The second part of this thesis discusses the epidemiological and economic impact of extended pertussis vaccination booster strategies using dynamic models. In **chapter 8** a dynamic model is

presented which was used to estimate the epidemiological impact of various booster vaccination strategies. In **chapter 9**, it is described how the model as presented in **chapter 8** was extended and modified in order to calculate the cost–effectiveness of various vaccination strategies. Several analyses were performed to determine the most cost–effective vaccination strategy. In **chapter 10**, all the published dynamic models which have been used to analyse the impact of a pertussis vaccination are reviewed.

Finally, the results of this thesis are summarized and discussed in **chapter 11**. Here, the findings of the thesis are translated into final conclusions and recommendations.

Part I

Costs and effectiveness of extended vaccination strategies against pneumococcal disease

Observed differences in invasive pneumococcal disease epidemiology after routine infant vaccination

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ABSTRACT

Healthcare decisions on vaccination programs mainly rely on the direct burden of illness and related costs of the disease. Next to the expected direct beneficial effect of pediatric immunization programs against *Streptococcus pneumoniae*, worldwide implementation of these programs has also been driven by the indirect beneficial impact as observed among various nontargeted age groups in Northern America. In this article, we provide a descriptive overview of the post–marketing surveillance and show that there are large differences in the observed disease epidemiology after implementation of pediatric pneumococcal immunization programs across countries. Possible factors responsible for these differences may include vaccine–serotype coverage, implemented vaccination schedules, antibiotic resistance rates and pneumococcal disease incidence prior to vaccination. A potential limitation can be found in the installation or enhancement of existing surveillance systems as well as other potential confounding bias, which may have influenced observed disease rates in the included observational studies. We conclude that the health and economic impact should be addressed in light of the country specific pneumoccocal disease epidemiology to support decisions on immunization programs.

INTRODUCTION

Currently, many countries have introduced, decided to introduce or are on the brink of deciding to introduce a childhood vaccination program against *Streptococcus pneumoniae*[41,42]. Conversely, several countries, in particular low–income countries, have not yet implemented a vaccination program or only recommend vaccination strategies directed at certain high–risk groups[42]. In such countries, budget constraints especially have been the principal driver in decision making. In European countries, favorable (cost–) effectiveness outcomes have played a decisive role[43]. In most European countries these cost–effectiveness outcomes were driven by the inclusion of indirect protection benefits in nontargeted populations[43]. Indirect protection benefits were based on the observed herd–protection effects in adults after nationwide implementation of the seven–valent pneumococcal–conjugated vaccine (PCV7) in the USA in 2000[43]. In the USA, only limited replacement disease was identified (i.e., pneumococcal disease caused by serotypes not covered by the vaccine[44-46].

It is important to discuss the use and applicability of country specific epidemiological data for healthcare decision making on immunization programs. In particular, as an example, it was recently shown that epidemiological data on pneumococcal infections – both before and after implementation of a pediatric pneumococcal vaccination program – did not consistently support previous (cost–) effectiveness outcomes[43,47]. Therefore, we hypothesized that post–marketing experience with immunization programs and effectiveness of vaccines may be substantially different between countries and/or even specific populations.

In the current article, we aimed to address the following aspects: first, to provide a descriptive overview of the available epidemiological post–marketing data and experience with PCV7 in different countries and populations; second, to explore potential influencing factors that could explain observed differences; and third, to discuss issues related to the use of the national data in (cost–) effectiveness modeling. By achieving these aims, our review might help in understanding the factors responsible for epidemiological differences between countries, which could be important both from the perspective of the WHO and from national/regional policy makers who are responsible for the recommendation or introduction of national immunization programs[48].

METHODS

We searched PubMed for relevant post–marketing studies published after 2000 (the introduction year of PCV7 in the USA). Additional information was retrieved from references ('snowballing') from relevant articles. Search terms included 'pneumococ*', 'pneumococcal infections', and 'epidemiology'. The search was performed during November 2009 and February 2010. All studies published in English that determined the effects of pediatric immunization with pneumococcal vaccines on the epidemiology of invasive pneumococcal disease (IPD) were reviewed. For that reason we included original research papers that investigated the epidemiology of IPD before and after implementation or recommendation of a conjugated pneumococcal infant vaccination program. Papers describing

the epidemiology before the introduction of routine infant vaccination, focusing on the impact of the polysaccharide vaccine among elderly, or on pneumococcal carriage or noninvasive disease rather than on IPD were excluded.

RESULTS

Pneumococcal disease

Infections caused by *S. pneumoniae* are a major cause of morbidity and mortality worldwide, with the highest incidence rates seen among the elderly and infants. Pneumococcal infections include frequently occurring mucosal noninvasive infections such as acute otitis media (AOM) and nonbacteremic pneumonia, but also less common diseases that may be invalidating or fatal such as bacteremic pneumonia and meningitis. More than 90 immunologically distinct serotypes of pneumococcus have been described that vary in their capsular polysaccharide composition. These serotypes are further categorized into 46 different serogroups based on immunological cross–reactivity[17]. Of all known serotypes, approximately 15 are assumed to be responsible for the majority of all IPD[18].

PCV7

In 2000, the seven–valent pneumococcal conjugated vaccine that covers seven serotypes (4, 6B, 9V, 14, 18C, 19F and 23F), was licensed for vaccination among infants and children in the USA. In Europe and the USA, PCV7 is registered and indicated for the prevention of sepsis, meningitis, bacteraemia, pneumonia and AOM in infants and children from 2 months to 5 years of age[49]. It was shown in clinical trials that PCV7 is highly effective in preventing invasive disease in young children[25,26]. Although a 3+1 dosing schedule is recommended, alternatively, a 2+1 dosing schedule may also be provided (see later) [26,28,50].

Other more valent vaccines: PCV10 & PCV13

Several other PCVs containing additional serotypes have been clinically investigated. Of these vaccines, a 10–valent vaccine (PCV10) is registered for use in Europe and a 13–valent vaccine (PCV13) is licensed in both Europe and the USA[34,35,51]. Also, other countries such as Canada, Australia and Argentina recently approved (one) of these more valent vaccines. For the 10–valent vaccine, which in addition contains serotypes 1, 5 and 7F, a 3+1 dose vaccination schedule is recommended by the European Medicines Agency (EMA)[34,52]. In addition to PCV10, PCV13 also includes serotypes 3, 6A and 19A and both a 3+1 and 2+1 dose schedule have been approved by the EMA[51]. No study for one of these more valent vaccines has yet proven protective efficacy against IPD. The efficacy claim is based on the assessment of the immune responses as recommended by the WHO[53]. Clinical trials showed that both vaccines elicit an immune response to all included serotypes[35]. However, compared with PCV7, these more valent vaccines seem to be (slightly) less immunogenic for some serotypes; the clinical relevance of this is as yet unknown[34,35].

Pneumococcal vaccination implementation & vaccination schedules among different countries

In Europe, 24 countries recommended or have implemented a routine infant pneumococcal vaccination program of which 17 (partly) reimburse vaccination for all infants rather than only for high–risk groups (see also Figure 1). A growing number of countries recommend a 2+1 dose vaccination schedule rather than a 3+1 dose schedule[42]. Clinical protection against IPD after less than four doses was already observed in the PCV7 licensure study[25]. Furthermore, evidence for reduced–dose schedules in preventing invasive disease in vaccinated individuals was also observed in a large case–control study during a period of vaccine shortage in the USA. This study showed an effectiveness against vaccine serotype (VT)–IPD of 98% (95% CI: 75–100%) for a 2+1 dose schedule and even a comparable effectiveness of 95% (95% CI: 88–99%) for a 2–dose schedule[28]. Furthermore, recent immunogenicity studies also support introduction of a reduced–dose schedule[50,54]. Consequently, more than 60% of the European countries which introduced a pneumococcal vaccination use a 2+1 dose schedule[42]. Besides these European countries only few countries (notably USA, Australia, Canada, New Zealand, Hong Kong, Costa Rica, Mexico, South Africa, Uruguay, Brazil, Israel and South Korea) implemented routine vaccination for (high–risk) children[41,55].

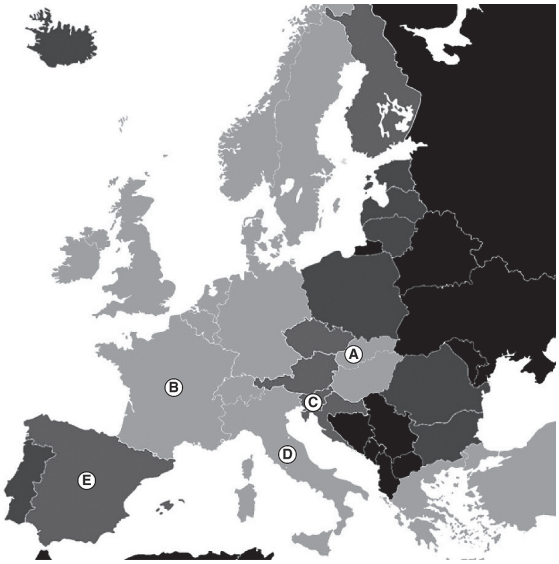

Figure 1. Countries colored light grey represent countries in which universal pneumococcal vaccination is free of charge, medium gray represents countries in which universal pneumococcal vaccination is only free of charge for children at increased risk of infection, and dark grey represents those countries where vaccination is not available free of charge[42,56]. No data were available for countries colored black. (A) In Slovakia, 96% of the costs of pneumococcal vaccination are reimbursed[42]. (B) Depending on the insurance status, vaccination is completely reimbursed or only for 65% in France[42]. (C) Although not reported on the website of EUVAC.NET[56], a recent paper reported that in Slovenia vaccination is completely reimbursed for children at increased risk for invasive pneumococcal disease[42]. (D) In Italy, in 15 out of the 20 regions, vaccination is offered free of charge to children, while in five regions it is free of charge for high–risk children[42]. (E) In Spain, the vaccine is reimbursed for all children under 5 years of age who are at increased risk for infection. In addition, in the Madrid region the vaccine is also included free of charge for all children as from November 2006.

Indirect effects & differences across countries

Immunization programs can result in two types of effects: first, *direct effects* – protecting those successfully immunized from carriage or infection; and second, *indirect effects* – providing protection in unsuccessfully immunized and unvaccinated individuals by reducing the transmission of the organism in the population. As (young) children are the main pneumococci reservoir with high colonization rates, eradication of the colonizing VT by vaccination of these children reduces transmission to adults and subsequently the community (herd–protection effects). Several studies have shown reductions in carriage after vaccination with conjugated pneumococcal vaccines[57-60]. However, eradication of these VTs in asymptomatic carriers has created an ecological niche for nonvaccine serotypes (NVTs), which has led to rapid increase of colonization by NVTs[57-60]. This *indirect effect* is known as serotype replacement. Serotype replacement in the nasopharynx may be problematic if these NVTs cause disease.

Table 1. Country–specific vaccination characteristics[42,56]

Country and reference	Recommended schedule	Catch–up	Implemented/ recommended and extent	Coverage of serotypes that cause IPD before vaccination	References
USA	3+1	Yes[a]	2000 universal	82% (<5yr) 74% (Alaska Native children)	25,63,66-68
Australia	3+0/3+1+1[b]	Yes[c]	2001 risk based 2005 universal	NS	69,70
Canada	2+1 (Quebec) 3+1 (Alberta)	Yes[d] Yes[d]	2004 universal in Quebec 2002 universal in Alberta	>80% (Children)	71,72
France	2+1/3+1[e]	Yes[a]	2003 risk based 2006 universal	68% (<2yr)	73
Spain	3+1	NA	2001 risk based 2006 universal (Madrid region)	68% (Children)	74,75
Portugal	3+1	NA	2001 risk based	56% (<1yr) 70% (1–5 yr)	76
Germany	3+1	Yes[a]	2001 risk based 2006 universal	70% (<5y) 60% (<16 yr)	77
Norway	2+1	Yes[f]	2006 universal	73% (<5yr)	78
Netherlands	3+1	No	2006 universal	69% (<5yr)	79
UK	2+1	Yes[g]	2002 risk based 2006 universal	73% (<2yr)	80,81
Denmark	2+1	Yes[h]	2007 universal[i]	60–65% (<5yr)	82
Austria	3+1	No	2003 universal	82% (1–2yr) 65% (2–5yr)	83

a All children up to 23 months and up to 59 months for high–risk children.
b Healthy children get a 3+0 dose schedule, children at risk do get fourth dose of PCV at 12 months of age, and a booster dose of 23–valent polysaccharide vaccine at 4 years of age.
c Children born between 1 January 2003 and 31 December 2004.
d All children up to 5 years of age in Quebec and all high–risk children up to 5 years in Alberta.
e Conflicting results are reported for France, the use of a 2+1 dose schedules is reported by EUVAC and by Carcalho *et al.*[42,107], while a 3+1 dose schedule is reported by Le Poutre *et al.*[73].
f All children born in 2006.
g All children up to 2 years of age (in 2002 PCV7 use was alreasy recommended to cover at risk children up to 5 years of age).
h All children between 12 and 17 months born after 30 April 2006.
i Before 2007 PCV7 was also recommended for high–risk children.
IPD= invasive pneumococcal disease; NS= not stated; NA= not applicable.

In this article, the direct and indirect impact of vaccination on disease incidence and/or prevalence for vaccinated as well as for unvaccinated cohorts will be discussed based on observed epidemiology data for various countries and/or populations (see Table 1 & Supplementary Table). Data from the USA, Canada and Australia will be reviewed first after which data from European countries will be discussed. The rationale for this separation was based on measured prevaccination epidemiological differences[18,25,46,61,62], the earlier introduction of a national pneumococcal immunization program in the USA compared with other countries[24], the expectation that the indirect effects in the European countries would be comparable to those observed in the USA and the presence of some specific ethnic populations with an increased risk of pneumococcal disease in the USA and Australia[63-65].

Direct & indirect effects in the USA, Canada & Australia

In the USA, routine infant pneumococcal vaccination was implemented in the second half of the year 2000 for all children 2–23 months of age, with additional recommendations for immunization of all children up to 59 months of age who were at increased risk for pneumococcal disease[24]. Although there was a vaccine shortage from August 2001 until September 2004, in 2001 the VT–IPD incidence was reduced by 78% (95% CI: 74–82%) in children less than 2 years of age compared with 1998 and 1999 data [46]. Furthemore, in 2007, the IPD incidence due to VT in children less than 5 years of age had declined by 100% (95% CI: 99–100%)[84]. While, VT–IPD incidence continued to decline until 2007, overall IPD incidence rates leveled out after the first years owing to the increase in the incidence of NVT–IPD[67,84]. Overall, the reduction in incidence in 2007 was estimated at 76% (95% CI: 73–79%)[84].
In unvaccinated cohorts of 20 years of age and older, a significant lower incidence rate of IPD was observed in the first year after introduction. The largest decrease in VT–IPD incidence (40%; 95% CI: 29–49%) was observed in the group 20–39 years of age comprising in large part parents of vaccinated infants[46]. Also, NVT–IPD (in this study defined as serotypes not included in PCV7 nor related to the seven serotypes included in PCV7) decreased significantly (20%; 95% CI: 1–35%) in this similar age group. However, more recent studies showed significant increases in IPD due to NVTs in the unvaccinated age groups limiting the indirect herd effect of the vaccine[44,45,84,85], serotype 19A increased rapidly (see also below), making it the most common serotype among all age groups in the USA[84,86,87]. Despite these increases in NVT–IPD, there are still significant reductions in overall IPD incidence (45%; 95% CI: 42–47%)[84].

Several studies also provided more detailed epidemiological data on pneumococcal syndrome level[44,45,84,85]. Bacteremia without focus decreased significantly ($p<0.001$) among the adult age groups without significantly increasing incidence due to NVTs[45,84]. Also, a clear herd effect was shown for VTs causing meningitis and bacteremic pneumonia in adults with risk reductions of 80–90% ($p<0.001$)[84]. However, the herd effect of meningitis and partially also the herd effects for bacteremic pneumonia were counterbalanced by a substantial increase in NVT disease in 2007[44,45,84].

Indirect effects were also observed for groups with increased IPD risk. A US study showed that the incidence of VT–IPD in patients with HIV infections was reduced by 62% (95% CI: 53–70%) in 3 years after the introduction of vaccination. However, an increase of 45% ($p<0.001$) was also observed

for NVT–IPD[88]. In addition some specified ethnic populations (e.g., native American Indians, Alaskan native population and the Australian Aboriginals) experience a much higher rate of IPD[63-65]. Before implementation of vaccination (1995–2000), Alaskan native children experienced an excess burden of disease compared with non–Alaskan native children with three–times higher annual incidence rates (403 vs 135 cases per 100,000 population annually from 1995 to 2000 for children aged <2 years, respectively)[63]. During the PCV7 period a more than doubling (140%; 95% CI: 47to -200%) in the IPD incidence was seen in Alaskan native children due to NVTs, which largely limited the direct effect of vaccination on VT (-96%; 95% CI: -100 to -86%)[63]. In Alaska Native adults, the increase in NVT disease leveled out or even increased the net–overall IPD incidence[63]. Also, the VT–IPD incidence decreased dramatically – similar to the Alaskan native population – in the Navajo Nation and the White Mountain Apache populations. However, in contrast to the Alaskan native population, the increase in NVT was only found significant in the adult White Mountain Apache population[65] while in the Navajo population no significant change was observed at any age[64].

After the introduction of vaccination in Canada**,** significant reductions in overall IPD were found in young children (6 months–4 years of age) and (most) adults groups[72]. Except for the age group containing 16–64 year old individuals no overall significant changes in IPD incidence due to NVTs was found. Similar results were found by Bettinger *et al.* who focused on children of less than 16 years of age[89]. Similar to the USA, in Australia the incidence of IPD was also higher (three– to four–times) among indigenous children aged less than 2 years compared with nonindigenous children of the same age before the introduction of PCV7[69,90]. After the introduction of vaccination, significant overall decreases in IPD rates for all age groups (in both indigenous and nonindigenous groups) were observed, while NVT–associated disease incidence remained unchanged[69]. Rates in VT–IPD in indigenous children decreased less (78% between 2002 and 2006) than in nonindigenous children (91% between 2004 and 2005). It should be noted that vaccination of indigenous children was implemented 4 years earlier (2001) than routine infant vaccination (2005).

Direct & indirect effects in European countries

While at least 24 different European countries have recommended infant pneumococcal vaccination, country specific epidemiological data is limited or not yet available. The existing evidence for indirect effects on invasive and noninvasive disease for several countries is discussed below.

In France, vaccination was recommended in 2003 for all children at risk for infection and in 2006 a routine vaccination program was implemented which resulted in an uptake of 44% in the same year. Most recent surveillance data showed a decline of 71% in VT–IPD incidence between 2001/2002 and 2006 among children <2 years of age. However, an 85% increase in IPD cases due to NVTs resulted in a net decline of only 21% (95% CI:10–31%)[73]. While no significant changes in the incidence of meningitis were observed for other age groups the incidence of cases of pneumococcal bacteremia increased significantly in these age groups ($p=0.013$)[73]. Additionally, another study showed an overall decline in the number of meningitis cases of 28% ($p<0.05$) among children[91]. Although based on a small population, a much larger decrease in the incidence of meningitis was observed by Dubos *et al.* (82%, 95% CI: 52–95%)[92].

In Spain, a risk based vaccination program was introduced in 2001 with gradually increasing region–specific coverage to approximately 50%[74]. Multiple regional reports from Spain showed geographical differences in the trends of IPD in children after PCV7 implementation. After implementation, no change in IPD incidence in children less than 5 years of age was observed in several different regions of Spain[93-96]. An increase (58%; 95% CI: 2–145%) in overall IPD was observed among children aged less than 2 years of age for the Barcelona region in the late PCV7 period[97] while in the Basque region, a decrease was observed in the IPD rate (see Supplementary Table 2)[98-100]. Most of the Spanish studies do specifically report an increase in the incidence or proportion of IPD caused by NVT[29,93,94,97,98,101].

In Barcelona, the overall incidence of IPD increased for both adults aged 18–64 years (49%; 95% CI: 22–82%) and for adults aged 65 years and older (23%; 95% CI: -0.3–51%)[74]. These increases coincided with clonal expansion of NVTs among adults in Barcelona. Overall IPD due to VTs decreased significantly in adults above 65 years of age (37%; 95% CI: 7–57%) but not among adults 18–64 years of age (-12%; 95% CI: -40–28%)[74]. The incidence of VT meningitis decreased nonsignificantly in adults by 45% (95% CI: -40–249%), whereas the overall meningitis incidence increased significantly (137%; 95%CI: 40–303%) owing to a significant increase of meningitis caused by NVT (214%; 95% CI: 59–523%).

In Portugal, PCV7 became available in 2001. Although not included in an immunization program, the vaccine uptake for children (more than three doses) increased to 51% in the 2005 birth cohort[102]. One study showed that after introduction of the vaccine the incidence of IPD did not change in children aged less than 1 year of age[76]. Another study found a significant reduction for VT–IPD among both children aged less than 5 years and adults (see Table 2)[102].

In Germany, PCV7 vaccination was recommended for children at increased risk of infection in 2001 (e.g., children with chronic heart and lung diseases). This resulted in a 8% uptake between 2000 and 2003. In 2006, vaccination of all children was recommended, and combined with a catch–up program[77]. A significant reduction in IPD incidence was observed for children 2 years of age from 20.0 (95% CI: 19.1–20.9%) cases per 100,000 population in 1997-2003 to 11.0 (95% CI: 9.3–12.9%) cases per 100,000 population in 2007–2008. By contrast, for children aged 24 years, a nonsignificant upward trend in IPD incidence was observed from 5.6 (95% CI: 5.3–6.1%) cases per 100,000 population in 1997–2003 to 7.2 (95% CI: 6.1–8.4%) cases per 100,000 population in 2007–2008. Furthermore, the incidence of NVT disease remained stable.

In Norway, an universal immunization program was introduced in 2006 and 2 years after the introduction, statistically significant reductions in VT–IPD were observed for all age groups, except for those aged 20–49 years. The largest decline was observed among children less than 5 years of age. Here, the incidence rate decreased from 26.89 cases/100,000 population to 1.36 cases/100,000 population (Incidence Rate Ratio, IRR 0.05; 95% CI: 0.02–0.14)[103]. Similar increases in NVT–IPD were only significant for adults aged ≥65 years with a 22% higher incidence (IRR: 1.22 95% CI: 1.05–1.42). In the Netherlands, PCV7 vaccination was implemented in 2006. A recent study describing the impact of vaccination during the first two years after introduction of the immunization program,

showed that in children eligible for PCV7 vaccination of less than 2 years of age, the VT–IPD incidence decreased by 90% (95% CI 68%–97%)[104]. Furthermore, the incidence of NVT–IPD simultaneously increased by 70% (p=0.12), resulting in an overall decrease in IPD of 44% (95% CI: 7–66%). No such evident changes in overall IPD incidence were found for other age–groups. However, in addition to a smaller increase in NVT–IPD in children eligible for vaccination, recent unpublished data also suggest occurrence of herd–immunity in unvaccinated cohorts[105]. However it should be noted that the share of meningitis may be over–represented in this study.

In the UK, PCV7 was recommended for use in risk groups of children less than 5 years of age in 2002. In 2006, vaccination was introduced into the routine childhood immunization program using a 2+1 dose schedule for infants combined with a catch–up campaign for children up to 2 years of age. National surveillance results from the Health Protection Agency (HPA) in the UK show a major absolute reduction in the number of IPD reports due to VTs among children less than 2 years of age from approximately 330 cases in 2005 to 40 cases in 2008. This reduction, however, was immediately followed by IPD increase due to NVTs in the same period (from 120 cases to 270 cases). Similar effects are present and identified in the cohort of children aged 2–4 years. Indirect protection effects in persons aged over 5 years were also observed. However, increases in IPD due to NVTs seem to completely counterbalance the decrease in IPD cases due to VTs (see Supplementary Table 1 for specific details)[53].

In Denmark, vaccination was introduced in 2007 with the application of a 2+1 dose schedule combined with a two dose catch–up schedule. One year after the introduction of the Danish immunization program, the overall IPD incidence decreased from 55 to 24 cases per 100,000 (IRR: 0.43; 95% CI: 0.29–0.62) in children aged <2 years, whereas the incidence of VT–related disease decreased by 80% (IRR 0.20; 95% CI: 0.09–0.38)[82]. Furthermore, this study also observed a decrease in the overall disease incidence of approximately 10% (IRR: 0.90; 95% CI: 0.84–0.97) in the population older than 2 years of age. In addition, a tendency to an increasing incidence of IPD among children 2–4 years of age was observed.

In Austria, PCV7 vaccination has been recommended since 2003, but as it was only reimbursed for children at increased risk the coverage remained low at approximately 25% in 2007. Probably owing to the low coverage, the IPD incidence rate was not significantly lower after implementation of the vaccine. Nevertheless, the incidence of meningitis decreased significantly from 3.1 to 1.6 per 100,000 (p<0.05) children less than 5 years of age. Furthermore, no significant increases in NVTs disease were observed[83].

Comparison between countries & populations

Similar to the large reduction in VT–IPD in the USA, large reductions in European countries with high vaccine uptake (e.g., the Netherlands, Norway, Germany and the UK) have been observed in vaccinated cohorts. Initially, increases in NVT–IPD in the USA were low and nonsignificant for children less than 2 years of age[46]. In 2004, a significant increase (20%; 95% CI: 10–40%) in overall NVT–IPD was observed for children aged less than 5 years of age[66], while more recent data show much higher

increases for the same age[84]. Nevertheless, the absolute magnitude of this increase in the USA is still relatively small compared with the corresponding decrease in VT disease. Increases in NVTs have been observed in some European countries in the first 2–3 years after vaccination. For example, in the UK, a country with a high vaccination coverage, the number of incident cases due to NVT–IPD more than doubled in individuals less than 5 years of age in the third year after the introduction of PCV7[81,82]. Despite lower vaccination coverage, increases in NVTs were also observed in France, Spain and Portugal[73,74,76,102]. Conversely, in Norway, Denmark, Germany and Austria (a country with a low vaccination coverage) the incidence rate of NVT–IPD in vaccinated cohorts remained quite stable[77,82,83,103]. Thus, the reported effect on the incidence of NVT–IPD is largely different between countries, even in countries with comparable levels of vaccine uptake. These differences may be explained by other factors that will be discussed later.

Similarly to the vaccinated cohorts, initial herd–protection benefits were observed for unvaccinated cohorts in the USA without increases due to NVTs[46]. However, more recent studies do show increases in NVT–IPD. In particular, large increases were found among some high–risk populations[44,45,63,66,84,88,106], however, for other high–risk populations such increases were limited[64,65]. The differences observed between high–risk populations may be related to factors such as the use of antibiotics (discussed later). Data regarding the indirect effects for European countries are scarce. Only few studies report data on unvaccinated cohorts and data on the elderly are rarely available. In the Netherlands and Germany, significant changes in overall disease incidence among unvaccinated cohorts were not observed[77,105]. Data from the UK show a clear herd–effect for individuals greater than 5 years of age, which is however, completely counterbalanced by an increase in NVT–IPD[53]. Large increases in overall IPD in unvaccinated cohorts are reported for Spain[74,97], while for France small overall increases were seen for meningitis[73]. Finally, significant overall IPD decreases are reported for Norway and Denmark[82,103]. In Norway this was accompanied with a significant increase in NVT–IPD among elderly individuals 65 years of age or older[103].

Possible explanation for the observed differences in pneumococcal epidemiology across countries

The differences in (in–)direct effects are probably due to a combination of different factors. First, the serotype coverage largely differs between countries. For example, in the USA serotype coverage before routine vaccination was high at approximately 82% for young children[68]. In European countries, the coverage before vaccination was much lower and varied between 56% and 82% for studies included in this article (see Table 1). Also, in adults the serotype coverage was higher in the USA (55%) compared with European countries (approximately 35%)[18]. Another major difference between most European countries and the USA is that in Europe mild IPD cases in children are treated outside the hospital without blood culturing, whereas blood culturing is routine practice for all children with high fever in the USA[62,66]. In children less than 2 years of age, the incidence of IPD was estimated in the USA at 170–190 cases per 100,000[46,61,62] while for this same age group in European countries the incidence was much lower with a mean incidence of 27 cases per 100,000

(ranging from 11.3 to 93 per 100,000[62]. Interestingly, the incidence of meningitis is essentially similar with 7.5–10 cases per 100,000 in the USA[44,46,61] and 7–11 cases per 100,000 in Europe[61]. In contrast to bacteremia without focus, significant increases in the USA were observed for bacteremic pneumonia and meningitis in both vaccinated children and unvaccinated adults[45,84]. As the majority of the IPD cases in European infants are represented by meningitis, bacteremic pneumonia and bacteremia with focus, the reduction in IPD incidence in children in European countries after vaccination is more likely to be similar to the reduction in incidence of these specific diseases rather than to the overall IPD disease burden in the USA (of which a large share is due to bacteremia without focus). However, increasing blood culturing practices in European countries can also artificially increase the apparent incidence of the disease (discussed later).

Other potential differences that may have led to observed effects are the vaccine uptake, differences in immunization schedules, antibiotic use (discussed later)[107,108], epidemiological conditions[63,109], differences in pneumococcal nasopharyngeal carriage rates and age of first acquisition of pneumococcal colonization (which is related to the proportion and age of children attending day care centers[110] vaccination schedules used (3+1 or 2+1) and initial inclusion of a catch–up program. With (initially) low vaccine uptake, both the direct and indirect impact of vaccination can be expected to be limited at first. By contrast, indirect effects would be expected to appear earlier if a catch–up program was implemented. Epidemiological conditions such as crowding, low indoor air quality and the frequency of comorbid conditions (such as chronic lung disease or HIV) increases the risk of IPD and also appears to increase the level of replacement IPD (also discussed later)[44,45,63,64,66,84,88,106]. Furthermore, reduced dose schedules might be less efficient in eliciting adequate antibody levels to prevent carriage compared to a full 3+1 dose schedule[50,54,59,111].

Limitations of comparisons & other factors influencing IPD epidemiology

There are many caveats for comparing the impact of pneumococcal vaccination between countries. Besides the potential vaccine impact, increased surveillance, changing practice in antibiotic prescribing and secular trends may also have confounded observed changes in pneumococcal disease epidemiology.

First, installation or intensified surveillance systems might have led to an increase in the number of reported isolates each year. Indeed, some studies did observe a temporal trend in more frequent blood culturing, especially in cases of bacteremia without focus[97,102]. For example, Muñoz–Almagro *et al.* report in their study a 531% (95% CI: 151–1487) increase in the rate of IPD due to NVTs among children less than 2 years of age in Barcelona, Spain[97], despite a relatively low vaccine coverage (36% in 2005 and 47% in 2007). Although the authors did not show a significant increase in blood culturing practice (which might be due to the lack of sufficient power to show this difference), the incidence of pneumococcal occult bacteremia among children less than 2 years of age increased from 14.5 to 21.4 episodes per 100,000 population. This increase contributed by a substantial proportion to the overall increase in IPD[112]. Increasing surveillance may also have influenced the results as presented on the website of the Health Protection Agency in the UK[81].

Second, antibiotic pressure might have influenced the distribution of specific serotypes causing replacement disease. Increasing disease incidence by drug–resistant clones of serotype 19A in the postvaccination period was observed in almost all countries included in this article. Nevertheless, in the prevaccination period increases due to serotype 19A have also been observed for both invasive and noninvasive pneumococcal disease[76,107,108,113]. This could lead to the theory that emergence of serotype 19A would mainly be attributable to antibiotic pressure[112]. However, a recent Norwegian study shows no change in the incidence of IPD (whole population) caused by penicillin–nonsusceptible pneumococci–serotype 19A, despite a significant increase in overall incidence of serotype 19A[103]. Although the numbers in this study are small, this trend supports the hypothesis that an increase in the incidence of serotype 19A can also be attributable to vaccination rather than due to antibiotic pressure alone. The difference between this study and studies showing an increase in the prevaccination area could be related to the low antibiotic consumption and subsequently the low prevalence of antimicrobial resistance of *S. pneumoniae* in Norway. Another recent study suggests that in children who suffered from an invasive pneumococcal infection, the number of PCV7 doses received before they developed the invasive infection is positively correlated with the isolation of a serotype 19A[86]. Also arguing towards the effect of vaccination, Moore *et al.* showed that the IPD incidence due to penicillin–resistant serotype 19A and penicillin–nonresistant serotype 19A both increased after the introduction of PCV7 in the USA[87]. Finally, a recent randomized controlled study showed a positive association between a 2+1 dose PCV7 schedule and nasopharyngeal acquisition of serotype 19A during the first 2 years of life[114].

Thirdly, secular trends in the distribution of pneumococcal serotypes are known to occur over time[115]. For example, in the USA between 1928 and 1998 the proportion of pneumococcal infections caused by the serogroups included into the 7 valent conjugate vaccine increased in children from 53% to 87% and in adults from 15% to 59%[115]. Furthermore, early observational studies after the routine introduction of PCV7 in the USA also found a decrease in the incidence of NVT diseases that are not likely to be related to the seven serotypes included into the conjugated vaccine during the post vaccination period[45,46].

Finally, the distribution of pneumococcal serotypes can change as different strains pass through a community. For example, clones of serotype 1 have frequently spread rapidly within local, community and national levels. In particular, in the case of a relatively small population size or in cases where the study area is limited, single geographical area fluctuations can have a large impact on the outcome[112].

Most common serotypes & serotype–specific characteristics

Despite substantial differences between countries, the most important NVTs causing disease after the introduction of routine infant PCV7 vaccination seem to be 19A, 7F, 3, 22F, 10A, 33F, and 1. In the USA, serotype 19A is the most common serotype in the postvaccination area. Also, in European countries, 19A is an important postvaccination serotype[116-118]. The possible impact of antibiotic pressure and vaccination regarding the increase in serotype 19A was discussed previously. However,

other factors could also have influenced its emergence[66,87]. First, after serotype 6A, 19A was the second most common NVT causing IPD in children in the USA before PCV7 introduction[61]. Second, serotype 19A might be more invasive compared with other NVTs[80,119,120]. Finally, VT pneumococci may acquire a 19A capsule in order to escape the effects of the vaccine, by means of capsular switching[74,121].

A clinically relevant concern of serotype replacement relates to the fact that shifts in serotype distribution of IPD may be accompanied by a change in disease severity and burden–of–illness[79]. Several studies suggest that there may be an inverse correlation between the invasive disease potential associated with a specific serotype and the frequency of detection of the specific serotype in carriage. The latter potentially implies that the most invasive serotypes and serogroups were the least commonly carried, while the most frequently carried are least likely to cause invasive disease[80,119,122]. For example, Brueggemann *et al.* showed in a meta–analysis that the serotypes 1, 5, and 7 versus 14 were 60–fold more invasive versus those with the lowest odds ratio (serotypes 3, 6A, and 15 versus 14)[122]. Furthermore, recent studies suggest that clones with a higher invasive disease potential, behave as primary pathogens, being more likely to cause disease in healthy (younger) individuals[79,123,124]. In contrast to this, serotypes with a lower relative risk of causing invasive disease primarily affect patients with an underlying disease and, therefore, behave more like opportunistic pathogens[79,123,124]. Interestingly, serotypes with the highest disease potential tend to have smaller capsule size and seem to cause milder disease (lower case–fatality) compared with serotypes with a lower invasive disease potential, which even holds true after correction for underlying patient and disease characteristics[79,123,124,124-126]. These findings were, however, not supported by a recent (smaller) German study that showed the highest case–fatality for serotype 7F in children[127]. Furthermore, two other studies concluded that invasive serotypes as a group were not significantly associated with a higher mortality rate[84,128]. This does not, however, not exclude the possibility of an association between individual serotypes and disease severity.

Impact on the cost–effectiveness & applicability to different countries

Assumptions regarding both serotype replacement and herd–immunity effects have a very large impact on effectiveness and cost–effectiveness outcomes that are used to support healthcare decisions on immunization programs. In European countries one of the main drivers for decisions on the introduction of a childhood vaccination program against *S. pneumoniae* are effectiveness and cost–effectiveness outcomes. Most cost–effectiveness outcomes for pneumococcal vaccination programs were driven by the inclusion of indirect protection benefits in unvaccinated cohorts. These indirect protection benefits were generally assumed to be similar to those observed in the USA[43,47]. In this article, we show that there are large differences between and even within countries and/or populations. These differences might represent 'real' differences but might also be caused by aforementioned confounding factors. The large indirect benefits as observed in the USA have not (yet) been observed in European countries. This probably relates to several factors, of which the most important might be the lower serotype coverage. The difference in the overall IPD incidence in

children is largely due to the apparent difference in bacteremia without focus. As previously argued by Jefferson *et al.*, the incidence of bacteremia without focus might be more influenced by the number of blood cultures than the number of infections[62]. The issue is whether these undetected cases, which are now likely to be prevented by vaccination in countries that introduced the vaccine, have profound beneficial effects. Although in terms of morbidity, mortality and costs, bacteraemia without focus is reportedly less severe compared with meningitis or bacteremic pneumonia, the incidence is much higher in children less than 5 years of age. Owing to the higher incidence, the potential prevention of these cases might have a considerable impact on epidemiological and cost–effectiveness outcomes. Nevertheless, before this can be included there is a need for more data regarding the incidence and costs related to bacteremia without focus. Similarly, in general the severity and costs related to nonbacteremic community–acquired pneumonia (CAP) and AOM are less compared with IPD, however, the incidence of these noninvasive diseases is much higher. Therefore, nonbacteremic CAP and AOM are important drivers of cost–effectiveness of the PCVs. In particular, for routine infant vaccination programs, the estimated efficacy against AOM is an important cost–effectiveness driver[43], whereas the incidence and vaccine efficacy against nonbacteremic CAP has been shown to be one of the main cost–effectiveness drivers for a potential pneumococcal vaccine in the elderly[129].

New, increased valency vaccines are now available, which might limit the impact of the increase in serotype replacement due to increased serotype coverage of these new vaccines, at least during the first years after implementation. Before making a decision regarding the implementation of these new vaccines, most countries will again require new cost–effectiveness estimates. Taking into account the large differences observed between and even within countries, (cost–) effectiveness studies should be performed using country–specific epidemiological data. However, one also needs to be aware of the limitations that such country specific data might have, in particular observed trends in IPD might be biased by increased surveillance. If these country specific data are lacking, assumptions should be based on data from countries with similar epidemiology (e.g., serotype distribution) and other comparable characteristics (e.g., expected vaccine coverage and immunization program in terms of schedule and catch–up). All (cost–) effectiveness results should be interpreted in light of the country–specific disease epidemiology and with consideration of the effects of vaccination strategies that are per definition not directly generalizable between countries and can as such not be used for health policy decisions.

DISCUSSION

Expert commentary

Since its registration a decade ago, conjugated pneumococcal vaccines have been implemented in national pediatric immunization programs in more than 40 countries in both full (4–dose) and reduced 3–dose schedules. Despite its huge proven beneficial impact on VT–IPD reduction among infants, currently, a more extended and wider implementation is hindered by the observed changes

in pneumococcal epidemiology that are not yet fully understood. From a health–economical point of view, we have shown that major drivers of the economical benefits determining the cost–effectiveness of a pneumococcal vaccination program are the etiological fraction of the pneumococcal serotypes causing IPD covered by the vaccine versus those not covered by the vaccine, and the vaccine's impact on these fractions in the vaccinated individual and on the transmission to other nonvaccinated populations. Post–marketing studies as presented in this article have clearly shown large differences in bacteremic pneumococcal epidemiology between the USA and Europe, but also between European countries and even regions within countries. Although the possible explanations might range from annual fluctuations to the antibiotic pressure and vaccination schedules implemented, it is clear that such incomparability renders one–size–for–all cost–effectiveness studies invalid. In our view, policy makers should therefore value the installation of valid surveillance systems to monitor the pneumococcal epidemiology and use their national data to best tailor the input for a cost–effectiveness model to their needs.

Five–year view

As only a limited amount of countries have introduced a national infant or childhood immunization program against pneumococcal disease, in the upcoming years many of the remaining countries are expected to introduce such programs. Countries that have not yet introduced any immunization program against *S. pneumoniae* can now choose from multiple vaccines, while countries that already introduced PCV7 previously should make a decision on whether or not to switch to vaccines of increased valency. Aside from the impact on the disease epidemiology, switching to one of the more valent vaccines might also have an impact on the infant pneumococcal vaccination schedule. In the future, countries may not only need to make a decision on infant pneumococcal vaccination strategies but might also consider vaccination of the elderly with a pneumococcal conjugated vaccine; currently, the 13–valent pneumococcal vaccine is being evaluated for use in these elderly individuals. Although extension of the serotype coverage of the 10– and 13–valent vaccines might reduce the potential for disease caused by NVTs in both children and the elderly, it can still be expected that serotypes not included in the vaccine will emerge in time. Considering the immunogenicity issues, adding more serotypes to the conjugated vaccines seems impractical. Therefore, it might be necessary, depending on the level of serotype replacement, to revise the composition of the protein conjugated vaccines in the future. A next–generation pneumococcal vaccine, targeting conserved pneumococcal protein antigens that are found in all pneumococcal organisms rather than single serotypes, may overcome the problems of serotype replacement by targeting all pneumococcal organisms[130]. In the meantime it is important to continue IPD surveillance in order to identify the emergence of new relevant strains to direct the formulation of future conjugated vaccines.

Supplementary data

Supplementary data associated with this article can be found at:
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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 (PCV7: Prevnar®) 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 PCV7.

INTRODUCTION

Several recently published European cost–effectiveness studies on the 7–valent pneumococcal conjugate vaccine (PCV7; Prevnar®) have included net–indirect vaccine benefits for non–vaccine protected groups in their analyses (indirect effects)[131-134]. 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 PCV7[46]. 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)[133,134], or even in cost savings[131,132]. 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[73,81,97]. 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 transmission 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.

METHODS

Our static cohort model builds on our previously reported studies[133,135]. It was updated to include recent epidemiologic and resource use data[79]. 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[79]. In our model it was assumed that sequelae could lead to neurological problems requiring life–time institutionalized care or lifetime special educations and to hearing problems, with corresponding high costs involved.

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[135].

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[25,136,137]. PCV7 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[138].

Indirect effects for those outside the vaccine–protected cohort were implemented in a sub–module using straightforward proportional calculus on registered numbers of IPDs[79]. Three studies present data on the net–indirect effects (herd protection benefits minus serotype replacement) on IPD among non–vaccinated groups in the USA[44-46]. The most recent study was performed by Hsu *et al.*, focussing solely on meningitis for all age groups[44]. In another study, detailed information was available on IPD for citizens aged 50 years and over[45]. 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[46]. 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.*[45] for the age groups of 50 years and over.

Table 1. Assumptions on the direct effects of PCV7 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					
PCV7 serotypes	-97%	-8%	-69%	-62%	-67%
PCV7 related types[a]	NA	0%	-52%	39%	-66%
Other types	NA	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					
PCV7	-97%	-40%	-40%	-14%	-48%
PCV7 related serotypes[c]/23PPV[d]	NA	-22%	-22%	-4%	11%
Other types	NA	-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					
PCV7	-97%	-40%	-40%	-14%	-77%
PCV7 related serotypes[c]/23PPV[d]	NA	-22%	-22%	-4%	-36%
Other types	NA	-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[44].
b. Overall change after correction for Dutch serotype specific incidence data[79].
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[46].
d. The 16 serotypes not included the PCV7 but yet in the 23–valent pneumococcal polyssacharide 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.*[45].
NA: Not Applicable

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 Melegaro *et al.*[139], sequelae related utilities were based on two specific studies[140,141]. 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[135,142]. The costs of vaccination were assumed at €50 per dose including administration costs, which reflects the current price of PCV7 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[142].

RESULTS

Without net–indirect effects being incorporated in the model, PCV7 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 total 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.

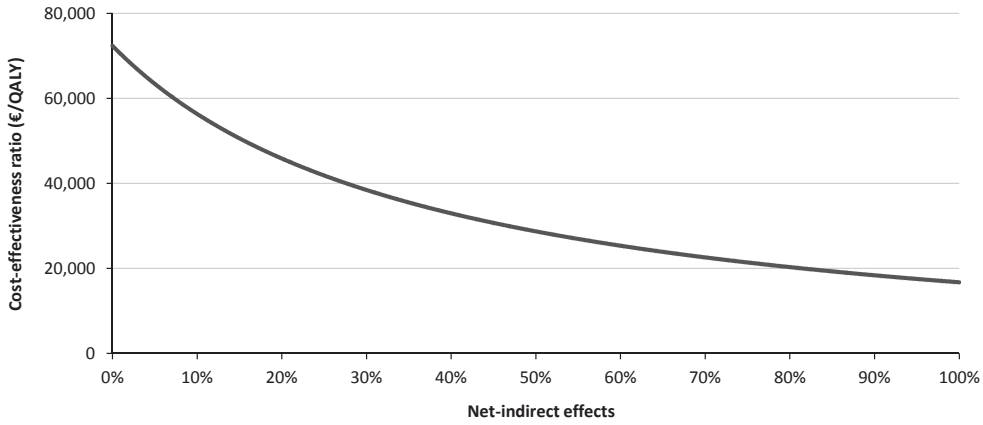

Figure 1. The cost–effectiveness ratio per QALY of as a function of varying the level of net–indirect effects included for invasive pneumococcal disease for non–vaccine protected individuals aged 5 years and onwards.

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[143]. One other cut–off point that has been mentioned for the Dutch situation is €20,000 per life–year gained[144]. Certainly, CERs of less than €20,000 per life–year gained are considered favorable in the Netherlands. 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 PCV7 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 (as specified in Table 1)[44-46]. 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[73,81,97]. So at this moment it is uncertain if the Dutch PCV7 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 PCV7 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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Cost effectiveness of pneumococcal vaccination among Dutch infants: economic analysis of the seven valent pneumococcal conjugated vaccine and forecast for the 10 valent and 13 valent vaccines

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ABSTRACT

Objectives: To update cost effectiveness estimates for the four dose (3+1) schedule of the seven valent pneumococcal conjugated vaccine (PCV7) in the Netherlands and to explore the impact on cost effectiveness of reduced dose schedules and implementation of 10 valent and 13 valent pneumococcal vaccines (PCV10 and PCV13).

Design: Economic evaluation comparing PCV7, PCV10, and PCV13 with no vaccination using a decision tree analytic model built from data in previous studies.

Setting: The Netherlands.

Population: A cohort of 180,000 newborns followed until 5 years of age.

Main outcome measures: Costs; gains in life years and quality adjusted life years (QALYs); and incremental cost effectiveness ratios.

Results: Under base case assumptions—that is, assuming a five year protective period of the vaccine and no assumed net indirect effects (herd protection minus serotype replacement) among children aged over 5 years—vaccination with PVC–7 in a four dose (3+1) schedule was estimated to prevent 71 and 5778 cases of invasive and non–invasive pneumococcal disease, respectively, in children aged up to 5 years. This corresponds with a total net gain of 173 life years or 277 QALYs. The incremental cost effectiveness ratio of PCV7 was estimated at €113,891 (£98,300; $145,000) per QALY, well over the ratio of €50,000 per QALY required for PCV7 to be regarded as potentially cost effective. A three dose (2+1) schedule of PCV7 reduced the incremental cost effectiveness ratio to €82,975 per QALY. For various assumptions and including 10% of the maximum net indirect effects among individuals aged 5 years and over, PCV10 and PCV13 had incremental cost effectiveness ratios ranging from €31,250 to €52,947 per QALY.

Conclusions: The current Dutch infant vaccination programme of four doses of PCV7 is not cost effective because of increases in invasive disease caused by non–vaccine serotypes, which reduces the overall direct effects of vaccination and offsets potential positive herd protection benefits in unvaccinated individuals. The 10 valent and 13 valent pneumococcal vaccines could have better net health benefits than PCV7 through less replacement disease and increased herd protection. Both these effects could substantially reduce the incremental cost effectiveness ratio to possibly acceptable levels, if total programme costs can be lowered by reduced schedules, reductions in vaccine prices, or both.

INTRODUCTION

Given the multitude of new vaccines available for introduction into national immunisation programmes, health economic modelling of various immunisation plans is becoming increasingly important in informing decisions on health policy. The decision to introduce the seven valent pneumococcal conjugated vaccine (PCV7) into the Dutch national immunisation programme for infants, for example, has in part been driven by cost effectiveness considerations[11]. The Dutch Health Council estimated the incremental cost effectiveness ratio of vaccination with PCV7 compared with no vaccination at €70,000 (£60,300; $89,200) and less than €20,000 per quality adjusted life year (QALY) in 2001 and 2005, respectively[11]. Crucial factors responsible for the change from a potentially unfavourable cost effectiveness ratio in 2001, exceeding €50,000 per QALY, to a favourable ratio in 2005 were the inclusion of data on observed herd protection effects in adults after nationwide implementation of PCV7 in the USA in 2000 and limited disease development caused by pneumococcal serotypes not present in PCV7 replacing pneumococcal serotypes eliminated by the vaccine (replacement disease)[44-46].

Next to direct effects on invasive disease in vaccinees, expected savings from herd protection were also part of health economic studies in other European countries that introduced PCV7 into their national immunisation programmes[131-134,139,145]. Both the four dose (3+1) vaccine schedule and the reduced three dose (2+1) schedule, as implemented in Norway and the UK[78,81], are highly effective against invasive pneumococcal disease caused by vaccine serotypes. However, the net overall benefit of national immunisation programmes in many European countries has been reduced by increases in invasive disease caused by non–vaccine serotypes[73,81,97,104]. Importantly, in the first 18–30 months after the introduction of PCV7 in the Netherlands, France, and the UK, no overall reduction in invasive disease in non–vaccinees was observed[73,81,104].

Given that both increases in invasive disease caused by non–vaccine serotypes and absence of herd protection may considerably affect the cost effectiveness of the current Dutch vaccination programme, we set out to update cost effectiveness estimates for the current four dose schedule of PCV7 by using recent data on epidemiology and resource use. Also, we investigate the cost effectiveness of reduced dose schedules and vaccine price reductions combined with the implementation of 10 valent and 13 valent pneumococcal vaccines (PCV10 and PCV13).

METHODS

Model

We designed a decision tree analytic model structure that builds on our previously reported model[133,135]. Various data sources were used to populate our model; these included clinical trials and observational studies for effectiveness of pneumococcal vaccines, laboratory data for incidence and serotype distributions of pneumococcal disease, and registrations for resource use and costs. Figure 1 shows the disease model for the health effects of pneumococcal vaccination, including the possibility of subsequent pneumococcal disease such as non–invasive pneumonia, otitis media,

and invasive pneumococcal disease. Assumptions regarding both costs and quality of life are summarised in Table 1 and are more thoroughly discussed in Appendix 1. In the analyses, a cohort of 180,000 newborns, representing the Dutch birth cohort, was run through the decision tree twice: once as a mainly vaccinated cohort (PCV7/PCV10/PCV13); and once as an unvaccinated cohort. The analytic time frame of the study was five years because vaccine effectiveness could not be assumed beyond five years. However, long term effects of invasive pneumococcal disease were extrapolated over the full lifetime of the individuals in the cohort (that is, until death or 100 years).

Table 1. Parameters used in the economic model.

	Mean or range	Distribution	References
Vaccine Efficacy			
IPD (all vaccine serotypes)	97.4%	Lognormal (SD 0.044)	25
CAP (hospitalized)	11.1%	Lognormal (SD 0.082)	136
CAP (general practitioner)	6.0%	Lognormal (SD 0.032)	136
Acute otitis media	7.0%	Lognormal (SD 0.011)	137
Case–fatality ratio (birth cohort)			
Meningitis	9%	Beta (3,32)	79
Pneumonia	0%	N/A	79
Bacteraemia with focus	0%	N/A	79
Bacteraemia without focus	9%	Beta (2,21)	79
Respiratory infections	0%	N/A	Assumed
Case–fatality ratio (5 years and older)			
Meningitis	9%–92%	Beta (age dependent)	79
Pneumonia	0%–29%	Beta (age dependent)	79
Bacteraemia with focus	0%–33%	Beta (age dependent)	79
Bacteraemia without focus	9%–67%	Beta (age dependent)	79
Respiratory infections	0%	N/A	Assumed
Direct costs (€)			
Bacteraemia[a]	1,091–27,318	Triangular (age dependent)	79,142
CAP	26–2,614	Triangular (severity dependent)	135,142,148
AOM	17–381	Triangular (severity dependent)	135,142,148
Special education (annual costs)	9,798–16,962	Triangular (age dependent)	135
Institutional care (annual costs)	39,583	Triangular (29,687; 39,583; 49,478)	142
Cochlear implantation	56,633	Triangular (42,475; 56,633; 70,792)	149

Table 1. Parameters used in the economic model. *(Continued)*

	Mean or range	Distribution	References
Indirect costs in (€)			
IPD[b]	0–974	Triangular (severity dependent)	79,142
Non–invasive pneumonia (hospitalized)[c]	0–2529	Triangular (severity dependent)	79,142
Non–invasive pneumonia (general practitioner)[b]	115–315	Triangular (severity dependent)	135,142
AOM[b]	58–23	Triangular (severity dependent)	135,142
Total QALY detriment			
Disability[d]	0.53	Beta (estimated)	140
bilateral hearing loss (first year)[d]	0.45	Beta (estimated)	139,141
Bilateral hearing loss cochlear device[d]	0.18	Beta (estimated)	139,141
All other hearing loss[d]	0.09	Beta (estimated)	140
Hospitalized bacteraemia[f]	0.0079	Beta (estimated)	139,150
Hospitalized meningitis[f]	0.0232	Beta (estimated)	139,150
Hospitalized CAP[f]	0.006	Triangular (0.001 ,0.006,0.01)	139
CAP treated at the general practitioner[c]	0.004	Triangular (0, 0.004,0.01)	139
AOM[f]	0.005	Triangular (0, 0.005,0.01)	139
Other parameters			
Increase in non–vaccine serotype IPD[g]	100%	Triangular (50%, 100%, 150%)	81,151[f]
Net–indirect effect for PCV10 and PCV13[h]	10%	Triangular (0%, 10%, 30%)	Assumed[g]
Discount rate health effects	1.5%	N/A	152
Discount rate costs	4%	N/A	152

a. Based on the average duration hospitalization (both IC and general hospitalisation days) and corresponding unit costs[142]. See also Appendix Table B for age specific hospitalisation costs
b. Indirect costs due to work loss of parents taking care of their children.
c. Indirect costs due to work loss of patient unable to work due to hospitalization.
d. Per year.
e. Same QALY decrement was assumed for invasive pneumonia, bacteraemia with another focus and bacteraemia without a focus.
f. Per case.
g. See also Appendix 2 Indirect effects in the analysed birth cohort.
h. See also Appendix 3. Indirect effects for those aged 5 years and older.

PCV7/10/13= 7/10/13–valent pneumococcal conjugated vaccine; IPD= invasive pneumococcal disease; AOM= acute otitis media.

Baseline disease risks

Surveillance data on the incidence and serotype distribution of invasive pneumococcal disease before national implementation of PCV7 were available for the period 2004–2006, including data on age, primary focus of infection, resource use, hospital admission, and outcome[79,146]. The case–fatality rate for meningitis and bacteraemia without focus in children was estimated to be 9% (Table 1)[135], which is in line with the international literature[131,139,147]. Invasive pneumonia and bacteraemia with focus were assumed not to result in death in children[135].

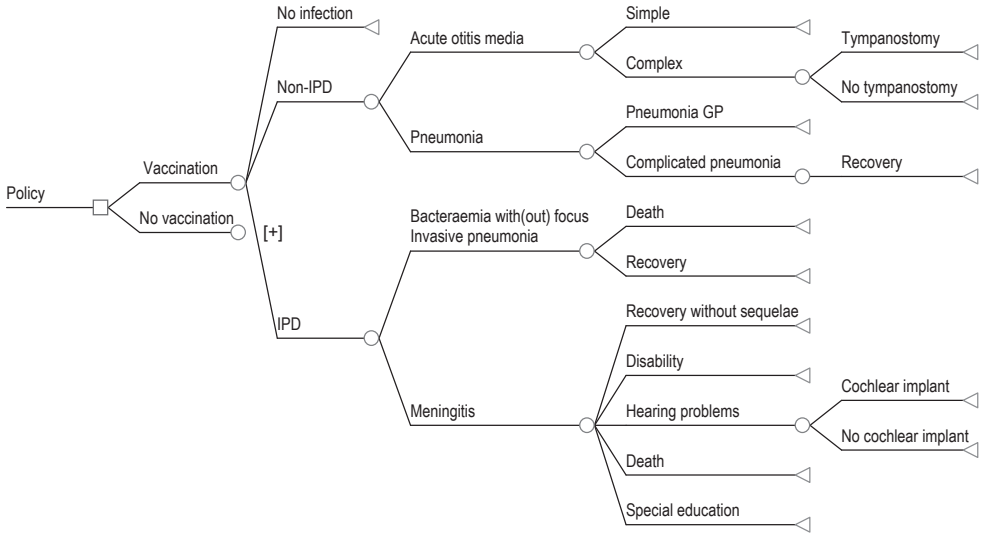

Figure 1. Decision tree used in conjunction with the cohort of 180,000 newborns. The "No vaccination" arm is a clone of the "Vaccination of all healthy infants" arm (as represented by the + sign; risk differ between both arms). IPD= invasive pneumococcal disease.

In our model, severe mental and physical handicap resulting from meningitis was assumed to occur in 13% of cases of pneumococcal meningitis in children, of which 50% would require special education and 25% intensive "round the clock" institutional care[133]. Jansen *et al.* found that hearing problems occurred in 32% of cases of meningitis, of which 50% were serious enough to require a cochlear hearing device[135]. Baseline risks for non–invasive pneumonia requiring hospital admission and for non–invasive pneumonia and acute otitis media treated in general practitioner practices were estimated from national hospital and general practitioner records, respectively (see Appendix Table A).

Vaccine efficacies

Vaccine efficacy against invasive pneumococcal disease was assumed at 97.4% after two doses for all seven serotypes of pneumococcal disease covered by PCV7 (Table 1)[25]. This value seems to be a conservative estimate if one takes into account the fact that only one vaccine failure has been reported in the Netherlands in the first two years after introduction of routine infant vaccination in June 2006. Routine vaccination for infants in a 2+1 dose schedule was introduced in Norway in 2006, and similarly no vaccine failures had occurred up to June 2008[78,136]. Protection against invasive disease was thus estimated to last for five years in the base case analysis[136,153]. Furthermore, in randomised controlled settings, the vaccine was shown to be effective against non–invasive pneumonia and otitis media in children[136,137,154]. For non–invasive pneumonia, efficacy of pneumococcal vaccination seems to increase with diagnostic certainty[136].

In our model, we applied the efficacy estimate of 11.1% for "clinical pneumonia and perihilar findings" to children admitted to hospital with the diagnosis of pneumonia in the Netherlands[136]. This definition of pneumonia seems to best fit the types of pneumonias treated in Dutch hospitals. An efficacy of 6.0% was assumed for patients who visited a general practitioner and were diagnosed with pneumonia[136]. In two randomised studies, PCV7 was found to prevent 6.4% to 7.0% of all cases of acute otitis media[136,136,155]. The interpretation of these studies for the Dutch setting is hampered by several factors, including the fact that the causal micro–organism is not recorded in cases of otitis media in the Netherlands. In our model, we used an overall efficacy estimate of 7.0% for otitis media on the basis of the most recent data from the Kaiser Permanente trial[137]. Given evidence for the duration of protection against non–invasive pneumonia and recent US surveillance data, we assumed that vaccinated children were protected against non–invasive pneumonia and otitis media up to their second year of life, starting after the second dose of the vaccine[79,138,154].

A vaccine efficacy of 97.4% against all serotypes included was assumed for PCV10 and PCV13, similar to the assumed efficacy of PCV7. In the absence of clinical data on the efficacy of PCV10 and PCV13 against non–invasive pneumonia and acute otitis media, the efficacy of these two vaccines was assumed to increase proportionally with the increase in serotype coverage for invasive pneumococcal disease.

Indirect effects

As well as estimations of the direct effects, we also estimated indirect effects of vaccination in our model. We included in our base case analysis herd protection against invasive pneumococcal disease for children in the birth cohort not yet fully protected by the vaccine and for non–vaccinated children, assuming this protection would be as effective as vaccination (Table 2)[81,104]. We also increased the incidence of invasive pneumococcal disease caused by non–vaccine serotypes to 100% for the analysed birth cohort (that is, we doubled the incidence of invasive pneumococcal disease caused by non–vaccine serotypes) on the basis of surveillance data from early after national introduction of PCV7 in the Netherlands and the UK[81,104]. See Appendix 2 for a more in depth description of the assumptions for our estimation of indirect effects in the birth cohort.

No serotype information for acute otitis media and non–invasive pneumonia is available in the Netherlands, and serotype replacement for these diseases may be assumed to be already included in the vaccine efficacy estimates in the first efficacy studies[136,137,154]. Therefore, we did not include an additional increase of non–vaccine serotype disease but also left out potential herd effects for otitis media and non–invasive pneumonia (see Appendix 2).

We assumed in our base case analysis for PCV7 that no net indirect effect would exist for individuals outside the modelled cohort. This assumption was made because no reduction in the incidence of invasive pneumococcal disease has been observed after the introduction of routine vaccination with PCV7 for individuals 5 years of age or older and because the observed herd protection effect in the UK in the third year after introducing routine vaccination was completely countered by a rise in invasive pneumococcal disease caused by non–vaccine serotypes[81]. In this

respect, net indirect effects are defined as cases of invasive disease averted by herd protection minus invasive cases of replacement disease.

Table 2. Serotype coverage and efficacy for direct effects and assumptions on indirect effects for the analysed birth cohort and the remaining population (those aged 5 years or older) for PCV7, PCV10, and PCV13

	PCV7	PCV10	PCV13
Serotypes covered	4, 6B, 9V, 14, 18C, 19F, 23F	+ 1, 5, 7F	+ 3, 6A, 19A
Increase in IPD caused by non–vaccine serotypes in the analysed birth cohort (serotype replacement)	100%	100%	100%
Efficacy and level of herd protection against vaccine serotypes of IPD in the analysed birth cohort[a]	97.4%	97.4%	97.4%
Net–indirect effect in the remaining population[b]	0%	10%	10%

a. Herd protection was assumed for the entire birth cohort including those not yet (fully) protected by the vaccine (either too young to be vaccinated or those who received only a single dose of the vaccine) and non–vaccinated children (5% of a birth cohort for the Dutch situation) assuming a protection effect of 97,4% against vaccine serotype similar to the vaccine efficacy.
b. Net–indirect benefits are defined as the benefits due to protection against invasive pneumococcal disease caused by vaccine serotypes minus the increase of invasive pneumococcal disease due to non–vaccine serotype.
PCV7/10/13= 7/10/13–valent pneumococcal conjugated vaccine.

Net indirect effects may occur in the future, especially if serotype coverage is extended by a change from seven serotype vaccines to vaccines with broader serotype coverage[79,104]. Therefore, in the base case analysis for PCV10 and PCV13, a net indirect effect for invasive disease at 10% of the potential maximum was applied for those aged 5 years or older (see Appendix 3). In particular, the potential maximum was defined as prevention of all cases of invasive disease caused by serotypes in the vaccine and absence of any replacement disease. Net protective indirect benefits against otitis media and non–invasive pneumonia were not included in any of the analyses[138]. Given that there is much uncertainty about the development of indirect effects, these assumptions were varied over a wide range in the sensitivity analyses.

Outcome measures and cost effectiveness analysis

The simulation model tracks all the specific disease cases and the deaths, costs, changes in QALYs and life years, and indirect effects (herd protection and serotype replacement). We were able to determine the net costs and net life years and QALYs gained by summing all the costs, life years, and QALYs and calculating the differences for the evaluations with and without vaccination. The incremental cost effectiveness ratio was calculated by dividing the net costs by either life years or QALYs. Health effects and cost were discounted at 1.5% and 4% for time preference, respectively, according to the Dutch guidelines for cost effectiveness research[152].

Incremental cost effectiveness ratios for routine vaccination were calculated by comparing different vaccination schedules against no vaccination. Following recently published evidence on the efficacy of PCV7 in reduced dose schedules[28,50], we investigated the effect of a three dose schedule (that is, 2+1) to test the effect of lower total vaccination costs (see Appendix 4).

We also forecasted the incremental cost effectiveness of potential shifts from PCV7 to pneumococcal vaccines that include additional serotypes (that is, PCV10 and PCV13).

For PCV7, the estimated current cost of €50 per dose within the Dutch national immunisation programme was used[133,135]. For PCV13, the officially listed price of €68.56 was applied, with administration costs of €5.95 being added (total cost per dose €74.51)[135]. For PCV10, no officially listed price is available in the Netherlands. Given that we know the pricing of PCV10 in other countries is pessimistic compared with PCV13, we assumed the total cost per dose of PCV10 at the midpoint between PCV7 and PCV13 (that is, €62.25)[156].

Scenario and sensitivity analyses

We performed univariate, threshold, scenario, and probabilistic sensitivity analyses. In the univariate sensitivity analyses, all relevant parameters were varied by 25% to explore the impact of each parameter relative to each other. One specific threshold analysis was performed in which the effect of the parameter on the incremental cost effectiveness ratio was investigated by varying the net indirect effects on individuals aged 5 years or older over a range of 0% to 30%. For the probabilistic sensitivity analyses, parameters were generated using Monte Carlo sampling, with outcome values generated by running the model 5000 times. Log normal, beta, and triangular distributions were used except for multinomial probabilities, where Dirichlet distributions were assumed (see Table 1 for specific distributions).

RESULTS

Cost effectiveness of PCV7

In the base case analysis, the estimated burden of pneumococcal infection for a birth cohort followed for five years was 170,788 cases of acute otitis media and 19,385 cases of non–invasive pneumonia, of which 2645 cases would result in hospital admission (Table 3). Applying the base case assumptions, 5372 cases of acute otitis media and 406 cases of non–invasive pneumonia would be prevented by vaccination with PCV7, corresponding to gains of 27 and 2 QALYs, respectively. Additionally, 188 cases of invasive pneumococcal disease a year were estimated in children under 5 years of age: 65 cases of meningitis; 45 cases of invasive pneumococcal disease; 38 cases of bacteraemia with focus; and 40 cases of bacteraemia without focus. In total, 71 cases of invasive disease would be prevented by vaccination with PCV7, corresponding to a total gain of 173 life years or 248 QALYs. In addition to the health gains, vaccination with PCV7 would also prevent approximately €2.2 million of direct costs and €0.4 million of indirect costs. Assuming a four dose schedule, the annual cost of vaccination is estimated at €34.2 million. Dividing the incremental costs by the incremental health benefits results in an incremental cost effectiveness ratio of €113,891 per QALY gained for PCV7. An incremental cost effectiveness ratio of less than €50,000 per QALY would be required for PCV7 to be regarded as potentially cost effective. Shifting from a 3+1 dose schedule to a 2+1 regimen could improve cost effectiveness of PCV7 to €82,975 per QALY (Table 4).

Table 3. Base–case analysis results for the analysed Dutch birth cohort.

	Acute otitis media	Non–invasive pneuminia	IPD disease	IPD related to net indirect effects[a]	Total
Cases (undiscounted)					
No vaccination	170,788	19,385	188	2410	NA
PCV7	165,416	18,979	117	210	NA
PCV10	164,664	18,922	80	2260	NA
PCV13	163,912	18,865	38	2229	NA
Cases averted					
PCV7	5372	406	71	0	NA
PCV10	6124	463	108	150	NA
PCV13	6876	520	150	181	NA
QALYs gained					
PCV7	27	2	248	0	277
PCV10	30	2	361	314	707
PCV13	34	2	470	384	891
Life years gained					
PCV7	0	0	173	0	173
PCV10	0	0	255	312	566
PCV13	0	0	336	381	717
Direct savings (€ 1000s), excluding vaccination costs					
PCV7	126	375	1,725	0	2226
PCV10	144	427	2,454	1398	4422
PCV13	161	479	3,181	1696	5518
Indirect savings (€ 1000s)					
PCV7	320	74	46	0	440
PCV10	365	84	67	161	677
PCV13	410	94	93	202	799

a. Only net indirect effects against invasive pneumococcal disease were included in the model for individuals aged 5 years or older. For PCV7, no net indirect effects were included for individuals aged 5 years or older in the base case analysis.

NA= Not applicable; QALY= quality adjusted life years; PCV7/10/13= 7/10/13–valent pneumococcal conjugated vaccine; IPD= invasice pneumococcal disease.

Cost effectiveness of PCV10 and PCV13

Compared with no vaccination, vaccination with PCV10 would prevent 6124 cases of otitis media, 463 cases of non–invasive pneumonia, and 258 cases of invasive pneumococcal disease, of which 150 would be averted by net indirect effects in individuals aged 5 years and older. Overall these health benefits would result in a gain of 707 QALYs. Vaccination with PCV13 would prevent 6876 cases of otitis media, 520 cases of non–invasive pneumonia, and 331 cases of invasive pneumococcal disease, resulting in a total gain of 891 QALYs.

Table 4. Incremental cost–effectiveness ratios in the base case, different scenarios and in specific sensitivity analyses.

	PCV7 €/QALY	PCV10 €/QALY	PCV13 €/QALY
3+1–dose schedule			
Without net–positive indirect effects for those aged 5 years and older[a]	**113,891**[b]	99,151	91,705
With 10% net–positive indirect effects for those aged 5 years and older[a]	59,937	**52,947**[b]	**50,042**[b]
With 20% net–positive indirect effects for those aged 5 years and older[a]	39,698	35,146	33,479
2+1–dose schedule			
Without net–positive indirect effects for those aged 5 years and older[a]	82,975	72,083	66,572
With 10% net–positive indirect effects for adults and elderly[a]	43,070	37,891	35,743
With 20% net–positive indirect effects for those aged 5 years and older[a]	28,101	24,718	23,488
Reduction in the cost of the vaccine (€50 per dose)[c]	**NA**[b]	41,106	31,250
Excluding herd effects in the analysed birth cohort for IPD[c]	129,069	57,770	55,055
Including herd effects in the analysed birth cohort for non–IPD[c]	111,153	52,211	49,407
Higher utility losses[c,d]	67,581	40,136	38,664
Exclusion of productivity losses (analysis from the health–care perspective)[c]	115,481	53,904	50,938
Efficacy against acute otitis media according to POET study[c,e]	78,527	43,048	41,457

a. Inclusion of net–positive indirect effects (herd protection against vaccine serotype disease minus non–vaccine serotype pneumnococcal disease increases). See also Appendix B.
b. Base–case scenario.
c. Scenarios were calculated holding all other assumptions similar to the base–case analysis (no net–indirect benefits for PCV7 and 10% for PCV10 and PCV13).
d. Utilities reported by Prosser *et al.* were used for children aged up to 5 years old.[157]
e. Efficacy against acute otitis media was assumed to be 33.6%, as was shown for the precursor vaccine of PCV–10 by Prymula et al. [158]

QALY= quality adjusted life years; PCV7/10/13= 7/10/13–valent pneumococcal conjugated vaccine; NA= Not applicable

Dividing the incremental costs by the incremental health benefits for the 10 valent and 13 valent vaccines produced incremental cost effectiveness ratios of €52,947 and €50,042 per QALY for PCV10 and PCV13, respectively. A 2+1 dose schedule could reduce these incremental cost effectiveness ratios to €37,891 for PCV10 and to €35,743 for PCV13 (Table 4). A 25% reduction in the vaccine price of PCV10 and PCV13 to €50 per dose (the cost of PCV7) would reduce the cost effectiveness ratios to €41,106 and €31,250, respectively. Assuming both a dose (to three doses) and a price reduction (to €50 per dose), the cost effectiveness ratios for PCV10 and PCV13 would be as low as €29,013 and €21,654 per QALY, respectively.

Scenario and sensitivity analyses

Figure 2 shows the parameters that produced the largest variation in the cost effectiveness ratio for PCV7 when varied by 25%. Apart from vaccine efficacy against invasive pneumococcal disease, the most important determinants of the cost effectiveness of PCV were the total vaccination costs, the increase in invasive pneumococcal disease caused by non–vaccine serotypes, and the case

fatality rate for meningitis. In univariate sensitivity analyses for PCV10 and PCV13, generally similar but smaller changes in the incremental cost effectiveness ratio were observed. The changes were smaller because of the relative importance of indirect benefits in the unvaccinated population for PCV10 and PCV13.

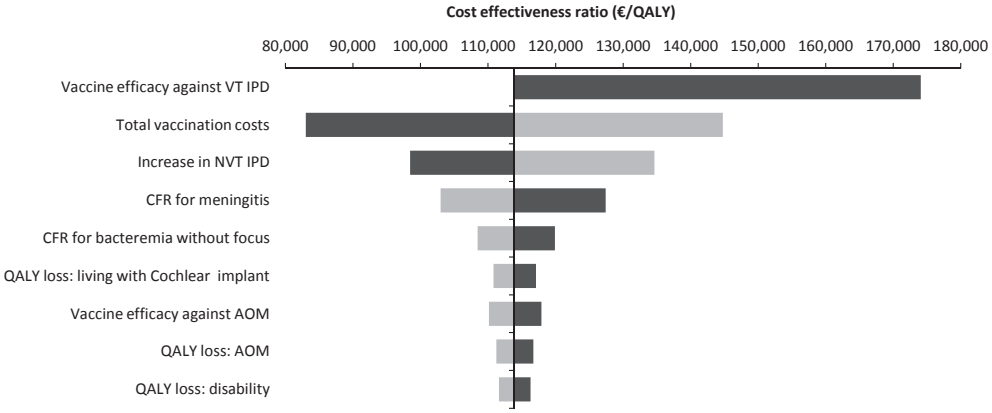

Figure 2. Sensitivity analysis assumptions on base case cost–effectiveness ratio for PCV7. Parameters were varied with 25%. Black bars show the incremental cost–effectiveness ratio for a 25% decrease in the parameter varied, whereas the grey bars show the incremental cost–effectiveness ratio for a 25% increase (note that it was not possible to increase the vaccine efficacy). IPD= invasive pneumococcal disease; AOM = acute otitis media; VT= vaccine serotype; NVT= non-vaccine serotype; CFR= case fatsality rate.

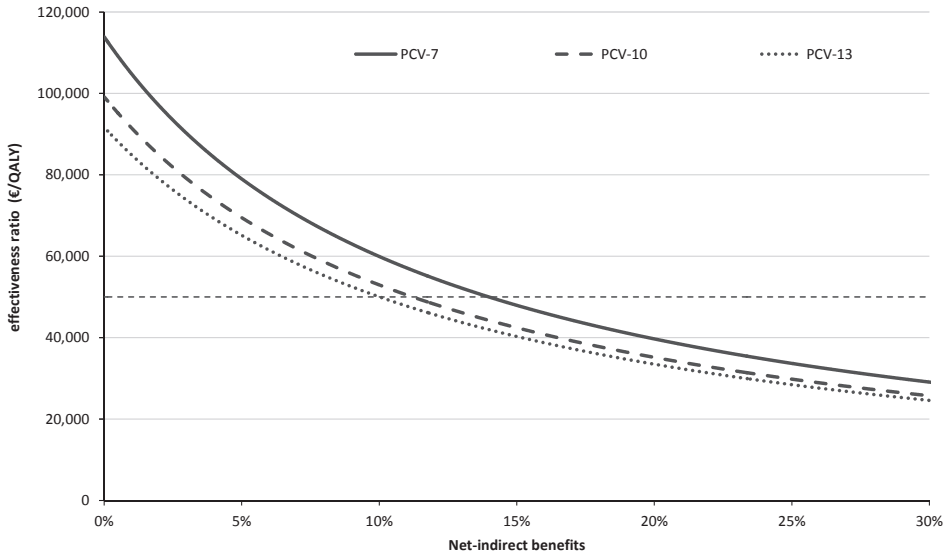

Figure 3. The effect on cost effectiveness ratios of varying the level of net indirect effect of vaccination for individuals aged 5 years or older. The horizontal dashed line shows the threshold at €50,000 per QALY. PCV7/10/13= 7/10/13–valent pneumococcal conjugated vaccine.

Figure 3 shows the impact of varying the level of net indirect effects of vaccination in individuals aged 5 years or over. At least 14% of the estimated net indirect effect would be needed in order to make PCV7 cost effective (that is, less than €50,000 per QALY). Several scenario analyses are displayed in Table 4, which again show the large impact of indirect effects and reduced dose schedules on the cost effectiveness of pneumococcal vaccination.

Finally, Figure 4 shows cost effectiveness acceptability curves for six different scenarios. This figure clearly shows that administering PCV7 in a 3+1 dose schedule cannot be considered as cost effective compared with no vaccination. The incremental cost effectiveness ratios of PCV10 and PCV13 are likely to be more favourable than that for PCV7, yet still the total costs of vaccination should be reduced in order to unambiguously consider vaccination cost effective.

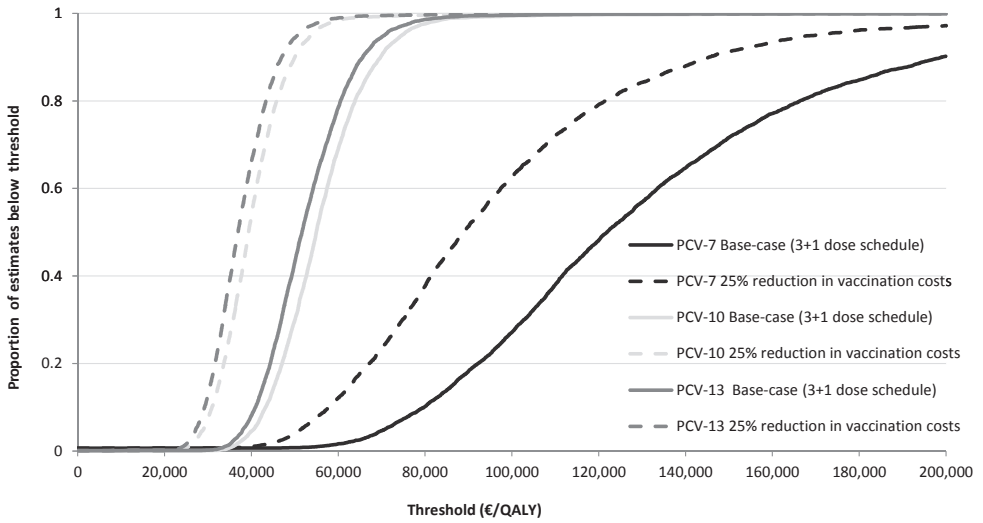

Figure 4. Cost effectiveness acceptability curves for base case vaccination schedules and for alternative scenarios for PCV7, PCV10, and PCV13. PCV7/10/13= 7/10/13–valent pneumococcal conjugated vaccine.

DISCUSSION

Our economic analysis indicates that the current national vaccination programme with PCV7 in the Netherlands is not cost effective. As several papers suggest that lowering the number of doses from four to three will not affect the vaccine efficacy for the pneumococcal vaccine[28,50,54,78], we investigated the potential impact of such reduced–dose schedules. Although a 2+1 reduced dose schedule could lower the total cost of vaccination and, therefore, reduce the incremental cost effectiveness ratio by approximately 30%, it is unlikely that universal vaccination with PCV7 will become acceptable on the grounds of cost effectiveness.

More favourable incremental cost effectiveness ratios were shown for PCV10 and PCV13, as long as net positive indirect effects for individuals aged 5 years or older were included in the analyses. In

particular, scenarios that used reduced total vaccination costs by using a 2+1 dose schedule showed that incremental cost effectiveness ratios would decrease down to €37,891 and €35,743 per QALY for PCV10 and PCV13, respectively. These ratios are likely to be considered as cost effective given various country specific thresholds.

Strengths and weaknesses

This is the first economic evaluation of national vaccination against pneumococcal disease that has included serotype replacement for the analysed birth cohort by using post–vaccination data[81,104]. We estimated the number of cases of invasive pneumococcal disease averted by vaccination and the increase in invasive pneumococcal disease caused by non–vaccine serotypes on the basis of the most recent data available[79]. Given the relatively small number of cases reported during the surveillance period of two years, our predictions regarding the increase of disease caused by non–vaccine serotypes may have limited precision; however, they are based on the best data currently available. In particular, the estimated increase of 100% for invasive disease caused by serotypes not covered by PCV7 was based on national observational studies from the Netherlands and the UK[79,81,104]. On the one hand, this specific assumption may be too conservative. On the other hand, data from the UK show an ongoing increase in the cases of invasive pneumococcal disease caused by non–vaccine serotypes and no plateau has yet been reached in the third year after PCV7 introduction, suggesting that the eventual increase in disease caused by non–vaccine serotypes might even be higher[81]. There are, however, some important differences between the Netherlands and the UK. In contrast to the Netherlands, the UK uses a reduced dose schedule of PCV7 at 2, 4, and 13 months. Also, the introduction of PCV7 in the UK was followed by a catch–up programme for all children aged less than 2 years. In the Netherlands, by contrast, vaccination was implemented without a catch–up programme. Several alternative scenarios regarding serotype replacement were explored in the sensitivity analyses, which showed that our conclusions regarding the incremental cost effectiveness ratios for all three vaccines were quite robust.

In our base case analysis for PCV7, we assumed that there was no net indirect effect of vaccination for individuals outside the modelled birth cohort because no overall reduction in invasive pneumococcal disease in non–vaccinees has been observed in any European country, in contrast to the US[73,81,104]. The difference between results obtained in the US and those recorded in Europe may be partly explained by the 60% to 70% coverage of the seven vaccine serotypes in Europe, compared with the more than 80% coverage in the US[18]. This disparity leaves more room for replacement disease in Europe. Country specific differences in the circulating serotypes causing disease (inclusive of secular changes in time) could also contribute to the lower overall reduction of invasive pneumococcal disease in Europe compared with the US[159]. Furthermore, in the Netherlands, as in most parts of Europe, the baseline incidence rates of invasive pneumococcal disease in children are substantially lower than in the US and almost exclusively based on culture confirmed cases of children admitted to hospital[55,79]. Another potentially relevant difference in the introduction of PCV7 in the Netherlands compared with the US is the high vaccine uptake (>95%)

among all newborns in the Netherlands for all four doses of the vaccination, which could potentially lead to more rapid development of replacement disease[55].

Potential net indirect effects in non–vaccinees were modelled using straightforward calculus. Ideally, the impact of pneumococcal vaccination should have been modelled using a so called dynamic transmission model, in which the transmission and carriage of *S. pneumoniae* is taken explicitly into account. However, because the transition dynamics of *S. pneumoniae* are complex and serotype dependent, and detailed data regarding these transmission dynamics are also quite limited, dynamically modelling all relevant serotypes of *S. pneumoniae* would be very complicated. For PCV10 and PCV13, a net indirect effect of 10% was included in the base case analysis. This estimate of indirect benefit may be conservative if compared with the much higher net indirect protective benefits observed in the US after implementation of routine vaccination with similar or lower vaccine serotype coverage[44-46].

Furthermore, we did not include the benefits arising from the prevention of antibiotic resistance in our model because the impact of this inclusion is expected to be small given that penicillin resistance is less than 0.4% in the Netherlands[79]. Finally, similar to almost all previous cost effectiveness analyses for pneumococcal vaccination, our analytic time frame was equal to the assumed protection period, after which we assumed that health effects and costs would be similar in the vaccinated and unvaccinated group.

Comparison with other studies

The cost effectiveness of PCV7 is worse than that calculated in our previous studies and in other recent health economic studies[131-135,139,147,160]. This disparity is mostly because of the exclusion of herd protection effects and the inclusion of serotype replacement in our study. Other factors contributing to the worse incremental cost effectiveness ratio were the use of a lower death rate for invasive pneumococcal disease and lower indirect costs than in our previous studies[133,135].

Several recently published cost effectiveness studies included net vaccine benefits for unvaccinated adults and elderly people in their base case analysis[131-134,160]. These studies reported vaccination to be cost saving[131,132] or at least cost effective[133,134,160]. The three studies that excluded herd protection in the base case analysis reported relatively unfavourable cost effectiveness ratios for PCV7 compared with other recommended infant vaccinations[135,139,147]. When we excluded the increase in invasive pneumococcal disease caused by non–vaccine serotypes but left all other assumptions the same as in the base case analysis, our results were similar to those of these three studies—that is, we found an unfavourable cost effectiveness ratio[135,139,147].

Our cost effectiveness results show that the current vaccination schedule for PCV7 might be far more expensive per QALY gained compared with other routine infant vaccination programmes recently implemented, such as for human papilloma virus[161], or with other vaccines that have not yet been implemented in a national programme in the Netherlands, such as hepatitis B[162] and varicella[10].

Implications and future research

Administration of PCV7 at 2, 3, 4, and 11 months was introduced to the Netherlands as part of the national immunisation programme in 2006 partially on the basis of favourable cost effectiveness data. The current analysis shows unfavourable cost effectiveness of the PCV7 3+1 dose schedule because of increases in invasive disease caused by non–vaccine serotypes, which offset the herd protective benefits in individuals outside the analysed birth cohort. Although the cost effectiveness of PCV7 is unfavourable from a health economics point of view, it is favourable from a public health point of view—a significant decrease in cases of pneumococcal disease has occurred in the Netherlands over the past two years[104]. Switching to the 10 valent or 13 valent vaccine would extend the serotype coverage to a higher level than that currently achieved with PCV7, which might reduce the potential for disease caused by non–vaccine serotypes and increase the overall benefits in vaccinated children.

Herd protective effects are more likely to occur with broad vaccine coverage, rendering vaccination potentially cost effective. Vaccination would be particularly cost effective if a more valent vaccine is used in combination with dose reductions, price reductions, or both. Our paper should help guide future decisions to potentially reduce doses of pneumococcal vaccine or to shift from PCV7 to vaccines that cover additional serotypes. Further research should be directed to building a dynamic model to entangle and explicitly predict the indirect effects of disease replacement and herd protection on vaccine efficacy and thus further enhance the validity of cost effectiveness approaches applied to pneumococcal vaccination.

Appendixes are online available at:
http://www.bmj.com/content/suppl/2010/06/02/bmj.c2509.DC1

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Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: (1) MHR was funded by an unrestricted grant from Wyeth Hoofddorp; and AJvH was financed by the Netherlands Vaccine Institute, Bilthoven; (2) MJP has received travel grants from GlaxoSmithKline and Wyeth to attend expert meetings in Reykjavik, Iceland, and Istanbul, Turkey; EAMS has received unrestricted grants from Wyeth and Baxter for research, consulting fees from Wyeth and GlaxoSmithKline, lecturing fees from Wyeth, and grant support from Wyeth and GlaxoSmithKline for vaccine studies; and AvdE has received unrestricted grants from Wyeth and Novartis; (3) No spouses, partners, or children with relationships with commercial entities that might have an interest in the submitted work; (4) No non–financial interests that may be relevant to the submitted work.

Results of a cohort model analysis of the cost–effectiveness of routine immunization with 13–valent pneumococcal conjugate vaccine of those aged ≥65 years in the Netherlands

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ABSTRACT

Background: Community–acquired pneumonia and invasive pneumococcal disease are common among older people (ie, those aged ≥65 years). A new 13–valent pneumococcal conjugate vaccine (PCV13) is under study in the Netherlands.

Objective: The aim of this work was to model the cost–effectiveness of PCV13 vaccination among those aged ≥65 years in the Netherlands, both in the total population and in those at increased risk for pneumonia, for various levels of efficacy (30%–90%) assumed.

Methods: Our previously published cost–effectiveness model was updated to include age–specific epidemiologic data and health–care utilization and costs for a hypothetical cohort of adults aged ≥65 years in the Netherlands. This cohort was followed twice—once as unvaccinated and once as vaccinated—over a time period of 5 years, with differences between both analyses reported. Outcome measures included costs, life–years gained (LYGs), quality–adjusted life years (QALYs), and incremental cost–effectiveness ratios (ICERs). All analyses were performed from a societal perspective.

Results: In the model, the ICER for vaccination remained below €80,000/LYG, except when the vaccine was assumed to protect only against bacteraemic pneumonia, with a relatively low effectiveness (40%) in combination with a high vaccine price (€65), and indirect effects of serotype replacement would largely offset the direct effect of vaccination. For various assumptions, introduction of widespread PCV13 vaccination (assuming a 60% efficacy against invasive and noninvasive disease because of vaccine serotypes, and a cost of €50 per vaccinated person) was associated with the ICERs varying from cost–saving to €50,676 per LYG.

Conclusions: In this model analysis of a hypothetical cohort in the Netherlands, vaccination with PCV13 might be considered cost–effective, both for the total population and for the high–risk population aged ≥65 years, from a societal perspective, over a 5–year time horizon. The main limitation of this study was uncertainty regarding how great a proportion of pneumonia could be attributed to pneumococcal disease.

INTRODUCTION

The annual incidence of community–acquired pneumonia (CAP) is estimated between 25 and 44 per 1000 persons in noninstitutionalized patients in Western countries among those aged ≥65 years[163]. It has been estimated that 5% to 60% (depending on the diagnostic test used, geographic region, and health–care setting) of CAP can be attributed to *Streptococcus pneumoniae*[163-165]. In addition, *S. pneumoniae* is responsible for >50 cases of invasive pneumococcal disease (IPD) per 100,000 seniors in industrialized countries.

Although a 23–valent polysaccharide pneumococcal vaccine (PPV23) has been developed to prevent pneumococcal disease[166], the evidence regarding its efficacy has been gathered primarily from nonrandomized, observational studies, and its effects on the occurrence of CAP have not been ascertained[20,166]. Therefore, in the Netherlands, PPV23 is recommended only for those with an increased risk of morbidity and mortality (eg, presence of diabetes mellitus or HIV infection) and not for routine use in everyone aged ≥65 years[167]. Consequently, <1% of those aged ≥65 years were vaccinated with PPV23 between 2004 and 2006, based on information from the University of Groningen prescription database.

In children, the 7–valent pneumococcal conjugate vaccine (PCV7) appeared to be effective against infection with vaccine serotype IPD, both in large vaccine trials and in surveillance studies[25,66]. Also, PCV7 has been effective in studies of CAP and acute otitis media[137,154]. Among those aged ≥65 years, antibody responses after a single dose of PCV7 appeared to be similar to those seen in infants after the primary vaccination, which might imply a high efficacy against pneumococcal disease, although the antibody threshold needed for protection in older patients is unknown[168]. Furthermore, other studies concluded that an initial (double) dose of PCV7 was likely to elicit higher and potentially more effective levels of antipneumococcal antibodies than PPV23[111,169,170]. However, this response was not observed for all of the 7 serotypes common to the PPV23 and PCV7 vaccines[111,169,170].

Besides the possibility of greater efficacy against common serotypes, other possible advantages of PCV7 compared with PPV23 include the possibility of longer duration of protection by revaccination and the expected protection against pneumococcal CAP[171]. Based on these positive expectations, a large trial to determine the efficacy of a successor of PCV7, the 13–valent pneumococcal conjugate vaccine (PCV13), among 85,000 community dwelling adults aged ≥65 years was initiated in the Netherlands in 2008[168]. The primary objective of that trial is to establish the efficacy of PCV13 in the prevention of a first episode of vaccine serotype–specific CAP. The secondary objective is to assess the efficacy of PCV13 against first episodes of nonbacteraemic vaccine serotype–specific CAP and vaccine–serotype–specific IPD. However, in the process of implementing a new vaccine, there is also an increasing focus on economic aspects, particularly cost–effectiveness ratios. Especially in the case of PCV13, with relatively high costs per dose, cost–effectiveness considerations will be important; such considerations have already been important to the introduction of infant schedules for vaccination with PCVs[172]. A preliminary assessment of potential cost effectiveness is therefore

warranted, although definitive results will not be available until after completion of the previously mentioned clinical trial. In the mean time, it is important to estimate the desired efficacy of PCV13 vaccination of older patients in relation to the price of the vaccine. The purpose of the current model analysis, therefore, was to estimate the cost–effectiveness (from the perspective of society) of PCV13 vaccination among those aged ≥65 years in the Netherlands, both in the total population and in those at increased risk for pneumonia, given the assumption of various levels of efficacy (30%–90%).

MATERIALS AND METHODS

Structure of the decision model

Our general decision–tree analytic model structure built on our previously reported models (Figure 1)[47,133,135]. In essence, the model distinguished between IPDs such as meningitis, bacteraemic CAP, and bacteraemia with and without focus, and nonbacteraemic CAP[79]. The model was updated to include age–specific epidemiologic data and health–care utilization and costs for a hypothetical cohort of adults aged ≥65 years in the Netherlands. The model distinguished between individuals without any specific underlying disease (ie, low risk) and those with underlying risk–elevating chronic conditions (ie, high risk) such as HIV, leukemia, or history of splenectomy[79]. This was necessary to enable modeling specific vaccination programs targeted at only those citizens at high risk, given that this group is likely to represent those with shorter life expectancy and lower quality of life[173].

The cohort was followed twice—once as vaccinated and once as unvaccinated—over a time period of 5 years, with differences between both analyses reported. Epidemiologic parameters included the incidence of CAP, the incidence of IPD, hospitalizations, rates of visiting general practitioners, and fatality rates for IPD and CAP. In the model, vaccination was assumed to occur once at age 65 years. A hypothetical cohort of such individuals was followed over a 5–year time frame. Beyond 5 years, no vaccine efficacy was assumed, but long–term impact on life–years gained (LYGs), quality adjusted life–years (QALYs), resource use, and costs were extrapolated over the full lifetime of the individuals in the cohort (until death or age 100 years). For our analysis, therefore, health–economics data regarding individuals aged 65 and 69 years are crucial. Indirect effects (ie, effects in nontargeted age groups) may occur after the introduction of routine PCV13 vaccination; this was previously observed after the introduction of routine infant vaccination with PCV7[66,81]. Furthermore, such indirect effects may have already occurred, given the earlier introduction of infant pneumococcal vaccination in the Netherlands in 2006.

In our analysis, we compared the possible impact of routine vaccination with PCV13 with the current situation. As mentioned, in the Netherlands, the PPV23 is administered only to a few individuals at substantially increased risk of pneumococcal infection (eg, people suffering from asplenia, sickle–cell anemia, or liquor leakage), based on the recommendations of the Dutch Health Council[174]. Therefore, and because data regarding the effectiveness of PPV23 against IPD are limited, we excluded costs (both vaccination costs and costs associated with potentially prevented cases) and potential cases of IPD averted by PPV23 vaccination from our model.

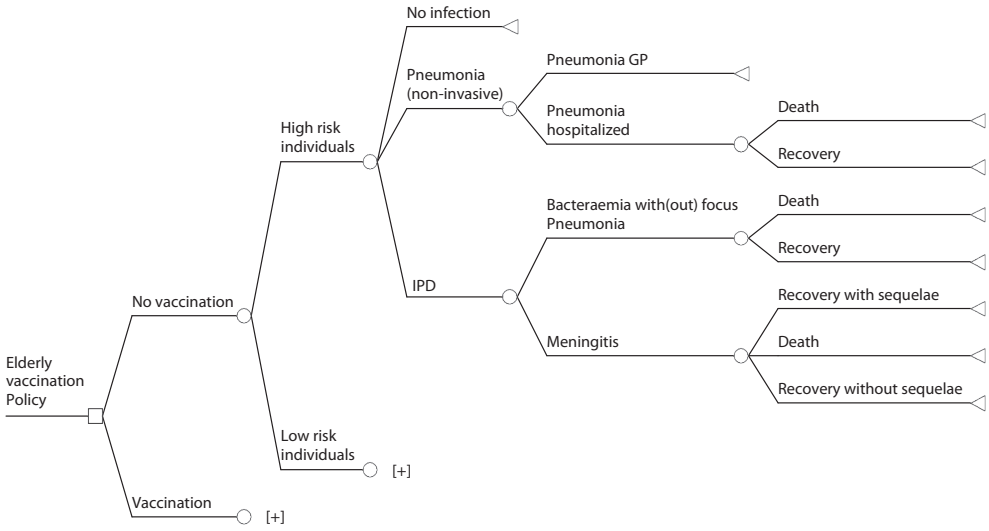

Figure 1. Decision tree used in conjunction with the cohort model for a model analysis of the cost–effectiveness of 13–valent pneumococcal conjugate vaccine in a hypothetical cohort of those aged ≥65 years in the Netherlands. Sequelae for meningitis were not included in base case analyses. IPD= invasive pneumococcal disease.

Epidemiologic parameters

Pneumococcal surveillance data about the incidence and serotype distribution of IPD before national implementation of PCV7 vaccination for the period from 2004 through 2006 have been published, and include information regarding age, primary focus of infection, resource use, underlying conditions, and outcome[79]. In older subjects, many cases of IPD occur among those with an underlying condition (ie, asthma/chronic obstructive pulmonary disease, cardiovascular disease, diabetes mellitus, autoimmune disease, thyroid disease, malignancy, and immunocompromising conditions). According to these criteria, 52% of meningitis incidence, and 81% of other IPD incidence, occurred among those aged ≥65 years with an underlying condition. The fatality rate for IPD is displayed in Table 1[79]. IPD, especially meningitis, may lead to long–term sequelae in children. However, the proportion of patients with meningitis is much lower among older individuals than among infants[175]. Because of this low share of meningitis and the occurrence of sequelae, as well as the absence of data regarding the treatment of meningitis in this population, we excluded the occurrence and impact of sequelae in the base–case analyses. Nevertheless, we explored the potential effect of its inclusion in sensitivity analyses using hypothetical figures (see following subsection).

Baseline risks for pneumococcal–related CAP requiring hospitalization were estimated from national hospital admission data (Table 1). Among those aged 65 to 69 years, 9% of all hospitalized CAP cases were caused by infection with *S. pneumoniae*. However, the causative microorganism was not identified in ~75% to ~80% of cases; therefore, it seems likely that the true proportion of cases caused by *S. pneumoniae* may be higher. In fact, findings in hospital–based studies suggested

that 5% to 60% of all hospitalized CAP cases were caused by *S. pneumoniae*[13,163-165]. To crudely correct for this, we assumed that in 35% of all hospitalized CAP cases, the causative agent would be *S. pneumoniae*. This assumption was also based on 3 Dutch studies that reported that 27% to 38% of all hospitalized CAP cases were caused by *S. pneumoniae*[13,176,177]. However, this estimate is still likely to underestimate the true burden of *S. pneumoniae*, because the causative agent was unknown in ~40% of the cases. In sensitivity analyses, the share of CAP related to *S. pneumoniae* was varied across a wide range. From this same database of national hospital admissions[178], the length of hospitalization due to *S. pneumoniae* CAP was available and subsequently inserted into our model. We assumed that only hospitalized patients would be at risk for death, because severe CAP cases would be referred to a hospital by a general practitioner or admitted to hospital by self–referral (eg, by patient–initiated ambulance transportation to emergency department). A causative organism was reported for few (<5%) pneumonia deaths[179]. Therefore, we calculated fatality rates for hospitalized CAP patients based on the overall hospitalizations and number of deaths due to CAP in the Netherlands, and corrected these for the number of deaths due to bacteraemic CAP[79,178,179]. The estimated fatality rate of 2% for hospitalized nonbacteraemic CAP was low compared with other reported fatality rates[180,181], but it was plausible, given that we were interested in relatively young elderly individuals (beginning at age 65 years) and that antibiotics and other rescue treatments were available. Furthermore, we noted that the overall mortality rate due to hospitalized pneumonia (noninvasive CAP and bacteraemic CAP together) was within the range (4%–29%) reported for CAP in the literature[163].

Table 1. Incidence, fatality rates, and costs for IPD and non bacteraemic CAP related to *Streptococcus pneumoniae* among those aged 65 to 69 years in the Netherlands.

	Case fatality	Incidence[a]	Mean direct costs per case, €	Mean indirect costs per case, €
Invasive pneumococcal disease				
Meningitis	29%	3.4	15,255[b]	302
Bacteraemic CAP	14%	39	10,268	212
Pneumococcal bacteraemia with focus	33%	2	7,105	150
Pneumococcal bacteraemia without focus	43%	3	8,077	197
Noninvasive disease				
Pneumococcal CAP requiring hospitalization	2%	89[c]	5,194	173
Pneumococcal CAP requiring a GP visit	0%[d]	182[e]	17.1	6.50

a. No. of cases per 100,000 elderly persons.
b. Not taking sequelae into account.
c. Assuming that in 35% of all hospitalized Pneumococcal CAP the causative micro–organism is *S. pneumoniae* (ICD–9–CM Diagnosis Codes 488–490were used).
d. Assumed.
e Assuming 20% of all CAP cases are due to *S. pneumoniae.*
IPD= invasive pneumococcal disease; CAP=community acquired pneumonia; GP=general practitioner

Baseline risks for CAP–associated visits to a general practitioner (International Classification of Primary Care code R81) were taken from a national report indicating that the mean incidence of visits for CAP was 91 per 10,000 persons per year for individuals between the ages of 65 and 69 years in 2007 and 2008[182]. For CAP–associated visits to general practitioners, no information was available regarding the causative organism. Based on Woodhead[164], we conservatively assumed that 20% of cases were related to *S. pneumoniae*. Serotype distributions for nonbacteraemic CAP were assumed to be similar to those observed for bacteraemic CAP.

Sequelae not included in the base–case analysis

IPD may lead to long–term sequelae, especially in the case of meningitis. In particular, hearing problems and paresis may occur[79,175,183]. In one specific scenario analysis, we included sequelae due to meningitis. Tetraplegia was assumed to occur in 1% of pneumococcal meningitis cases among those aged ≥65 years[175], which would require lifelong admission to a nursing home. Hemiparesis was assumed in 6% of pneumococcal meningitis cases, resulting in a requirement of lifetime day care[133,175]. Furthermore, it was assumed that after a meningitis episode, 1% of patients would remain in a permanent vegetative state. Hearing impairment was assumed to occur in 15% of the cases[175]. Annual costs due to tetraplegia and hemiparesis were estimated at €81,540, based on the costs of intensive nursing–home treatment[142]. Annual costs due to a permanent vegetative state were estimated at approximately €154,000, similar to the cost previously calculated for children in a vegetative state[184]. Given that no data were available regarding costs associated with hearing impairment, such costs were not included.

Vaccine efficacy, number of doses, duration of protection, and uptake

In our base–case analysis, we assumed that a single vaccine dose would be sufficient to establish a stable vaccine efficacy over a period of 5 years comparable with what was assumed for the PPV23 vaccination in previous cost–effectiveness analyses[173,180,185,186](a single dose is also considered to be effective in children aged 2–5 years[35]). Furthermore, in the base–case analysis, we assumed that the vaccine would be equally efficacious in high–risk and low–risk individuals. In the absence of real clinical data, efficacy was assumed to range from 30% to 90%. Therefore, we explored different scenarios in which we assumed the vaccine efficacy would vary accordingly. Vaccination coverage was assumed to be 83% among high–risk older individuals and 65% among low–risk older individuals, similar to the vaccination coverage against influenza in the Netherlands[187-189].

Indirect effects

Similar to our previous model, we tried to adequately include estimations of indirect effects in our model. Indirect effects can be divided into herd–protection effects (ie, protection of unsuccessfully immunized and unvaccinated individuals because of reduced transmission of the pathogen) and serotype–replacement effects (ie, replacement disease caused by other pathogens)[47]. Indirect effects are likely to occur after the introduction of routine PCV13 vaccination in the older population

because both herd–protection and serotype–replacement effects occurred after the introduction of routine infant vaccination with PCV7[66,81]. However, because vaccination coverage would likely be lower among older people than among infants, and because PCV13 offers broader serotype coverage than PCV7, it is difficult to predict what the indirect effects of PCV13 vaccination on the older population might be. Furthermore, indirect effects on older patients could also occur without the introduction of routine vaccination[66]. Several studies have reported herd–protection benefits for adults after the introduction of routine infant vaccination with PCV7; however, concomitant increases of nonvaccine serotypes were also observed (ie, serotype replacement) [73,74,81,103]. In the United States, herd benefits in adults and the elderly seem to outweigh the serotype replacement[66], but the scarce data available for European countries suggest that the net indirect benefit may be lower than it is in the United States, given that increases in nonvaccine serotypes seem nearly to counterbalance the decrease in vaccine serotypes[73,74,81,103]. Switching from PCV7 to new 10–valent or 13 valent vaccines for use in national immunization programs could complicate predictions regarding indirect effects for older people. Finally, implementation of a vaccination program among the elderly could also influence serotype distribution in children, which could conversely influence serotype distribution among the elderly. All of these factors complicate the consideration of indirect effects.

Because of the uncertainty surrounding the net indirect effects, we explored different scenarios in the base case. In scenario A, we did not include any indirect effects, given the current absence of specific data for those aged ≥65 years in the Netherlands or any other European country. This might be considered too optimistic a scenario from a cost–effectiveness point of view because we assumed no serotype–replacement or herd–protection benefits among older adults as a result of infant pneumococcal vaccination; such benefits might reduce the burden of disease among older people and decrease the potential burden of disease. In scenario B, we assumed that the current PCV7 infant vaccination program would increase the incidence of PCV7 nonvaccine serotype pneumococcal disease to 100%, with a corresponding decrease in PCV7 vaccine serotypes incidence, leaving the overall incidence unchanged[43]. Furthermore, given that the serotypes responsible for replacement are likely to be included in PCV13, we assumed that the 6 additional serotypes in PCV13 would reduce initial serotype replacement by 50%[73,74,81,103]. Also, in scenario B, we modeled an increase of 50% in nonvaccine serotype pneumococcal disease because of the introduction of routine vaccination of those aged ≥65 years. Scenario B might be considered too pessimistic because we included serotype replacement due to infant and elderly vaccination but did not include any potential herd protection benefits of elderly vaccination.

Health care resource use and corresponding costs

The analysis was performed from a societal perspective including both direct medical costs and indirect costs of production losses, all updated to 2008 (source: CPI: Central Bureau of Statistics for the Netherlands). Age specific resource use related to IPD were taken from Jansen *et al.*[79], enabling estimation of direct costs (Table 1). Indirect costs related to IPD were taken into account

for individuals who were unable to perform paid work because of hospitalization, although the impact of these costs is expected to be minimal given the age of the cohort (as only 6% of those aged 65 years and older still work 12 hours or more during a week) [142]. For CAP, age–specific duration of hospitalization was available from the national hospitalization database. For CAP not requiring hospitalization, the costs of primary health care were included. The mean primary health care costs were estimated at €17.1, including the cost of a typical consultation with a general practitioner, antimicrobial treatment, and the pharmacist's fee[148]. Treatment costs were based on official guidelines, recommending doxycycline for a period of 7 days[190].

LYG and QALY estimates

We estimated the years of life lost using the remaining life expectancies, according to standard life tables[180], calculated out over men and women to establish mean values. Life expectancy of those aged ≥65 years may differ between those with and without underlying conditions[172]. In particular, deaths from chronic diseases in conjunction with pneumococcal infection are likely to represent those who are more frail. Therefore, we included a mean 10% reduction in the potential LYGs for those aged ≥65 years with an underlying condition compared with standard life–table estimates, based on a method used previously[191]. To remain consistent with overall life expectancy, we correspondingly increased potential life expectancy by ~15% for the low–risk population. In addition to the cost per LYG, we also estimated the cost per QALY gained. General utility estimates, as well as utility estimates during an IPD episode, were taken from a previous cost–utility study by Sisk *et al.*[192] that used conservative estimates for the general quality of life among older adults. During hospitalization for an episode of IPD, a utility of 0.2 was assumed. Subsequently, the QALY loss due to this episode was calculated by subtracting this utility loss from the mean age–specific utility (Table 2). The high and low–risk group definitions in the Sisk *et al.* study and in the present study were not identical, but they represent the best currently available estimates. In the absence of real data, utility decrements for CAP were not incorporated into the model.

Table 2. Age–specific quality–adjusted life–year weight (QALYs) estimates[a].

Age group	Low–risk individuals[b]	High–risk individuals[b]
65	0.76	0.57
70	0.74	0.54
75	0.7	0.52
80	0.63	0.51
85+	0.51	0.51

a Based on Sisk *et al.* [192]

b Low risk was defined as the absence of any specific underlying disease. High risk was defined as the existence of underlying risk–elevating chronic conditions such as HIV, leukemia, or history of splenectomy.

Outcome measures and economic calculations

Our main outcome measures were the efficacy and the costs of vaccination to determine whether routine PCV13 vaccination in the Netherlands would be cost effective. In the Netherlands, incremental cost–effectiveness ratios (ICERs) above €80,000 certainly reflect unfavorable cost–effectiveness[143]. For LYGs, a threshold of €20,000 defines a situation in which cost–effectiveness would definitely be favorable in the Netherlands[144]. Based on these 2 thresholds, an implicit threshold of €50,000 per QALY for the Netherlands seems reasonable[47]. To calculate cost–effectiveness, the model keeps track of the number of IPD and CAP cases, QALYs, LYGs, and costs among the followed hypothetical cohort of 155,000 people aged ≥65 years (approximately the number of such people in the Netherlands). Dividing the net costs by either one of the health effects (LYGs and QALYs) defined the incremental cost–effectiveness ratio; these health effects and the costs of treatment were discounted according to the Dutch guidelines for cost effectiveness research at 1.5% and 4%, respectively[142]. We investigated the impact of vaccination, starting with the most pessimistic scenario in which only protection against bacteraemic CAP was assumed. In subsequent analyses, we extended the protection to all vaccine serotype IPD and to CAP resulting in general–practitioner visits and hospitalizations.

Sensitivity analysis

To account for uncertainty in point estimates, we performed several sensitivity analyses. In contrast to PPV23, the conjugated vaccines do not cause hyporesponiveness (as observed after revaccination with PPV23)[111,169]. Furthermore, revaccination with the conjugated vaccine or the PPV23 after initial vaccination with a conjugated vaccine may be better tolerated than repeated doses of PPV23. Therefore, we explored a hypothetical situation in which a booster dose of either vaccine (PPV23 or PCV13) was administered 1 year after the initial PCV13 dose to double the protection period. After the booster dose, we assumed an extended efficacy against the serotypes included in the primary PCV13 dose and the PPV23 booster. Nevertheless, inconsistent results regarding the ability of PCV7 to induce immune memory have been reported[193]. In 3 scenario analyses, the impact of less vaccine efficacy in high–risk older people was considered. It has been reported that influenza vaccines are less efficacious in high–risk older patients, so although this model analysis addressed a different vaccine, we explored a relative reduction of 10%, 20%, or 30% in vaccine efficacy among high–risk older patients compared with low–risk older patients, given that these groups are similar to those for whom influenza vaccination is recommended[194]. In a sensitivity analysis, we also explored the impact of the inclusion of meningitis sequelae (see previous subsection for details), the duration of protection after initial vaccination, varying the percentage of hospitalized CAP and general–practitioner visits caused by *S. pneumoniae*, varying assumptions regarding the remaining life expectancy of the high–risk population (maintaining the same overall remaining life expectancy for the whole population), increasing the fatality rate related to CAP, applying different discount rates, and including QALYs rather than LYGs. Furthermore, all outcomes were shown with and without indirect effects (scenario A and scenario B, as previously described).

RESULTS

Burden of disease

Without vaccination, an estimated 358 cases of IPD were projected to occur among those aged 65 to 69 years in the hypothetical cohort. Of these, 295 could be attributed to bacteraemic CAP, with the rest caused by meningitis (26 cases), bacteraemia with focus (11 cases), and bacteraemia without focus (26 cases). The majority of these cases were projected to occur among individuals with an underlying condition. Regarding nonbacteraemic infections, 1387 general–practitioner visits and 679 hospitalizations related to *S. pneumoniae* were estimated. The total number of deaths was estimated at 73, the number of life–years lost at 1083, and the corresponding loss of QALYs at 648.

Effect of efficacy and the vaccine price on the ICER

Figure 2 illustrates the effect on the ICER per LYG of varying the efficacy and the vaccine price. Figures 2A, 2C, and 2E correspond to scenario A (no indirect effects), whereas Figures 2B, 2D, and 2F correspond to scenario B (indirect effects included). Furthermore, Figures 2A and 2B show the effect on the ICER assuming only vaccine efficacy against bacteraemic CAP; in Figures 2C and 2D, it was assumed that the vaccine was effective against all IPD, and in Figures 2E and 2F, an additional efficacy against CAP was assumed.

As shown in Figure 2, with increased efficacy (from 30%–90%), vaccination becomes more favorable. Without a net–indirect effect (Figures 2A, 2C, and 2E) vaccination is likely to be considered cost–effective. Even when the vaccine would only protect against bacteraemic CAP, vaccination may still be considered cost–effective because the ICERs remained below the informal threshold of €50,000/LYG. For example, assuming an efficacy of 30% against bacteraemic CAP and a total cost per vaccinated person of €50, the ICER was estimated at €49,300/LYG. Figures 2B, 2D, and 2F show a more pessimistic scenario in which serotype–replacement effects largely counterbalanced the direct effect of vaccination. However, when the vaccine was assumed to protect against all IPD, the ICERs still never surpassed the threshold of €80,000/LYG (above which an intervention is not certainly considered to be cost–effective), even when vaccine efficacy was estimated at 30%. Nevertheless, if the vaccine offered protection only against bacteraemic CAP with, for example, an efficacy of 40%, the vaccine price would have to remain lower than €65 to remain below the threshold of €80,000 per LYG used.

We made similar graphs for the high and low–risk populations, which were almost similarly shaped (see Table 3 for comparison between the high–risk group and the total population); however, the ICER was lower for the high–risk population and higher for the low–risk population (data not shown). Cost–effectiveness estimates for different scenarios for the total population and the high–risk population are shown in Table 3.

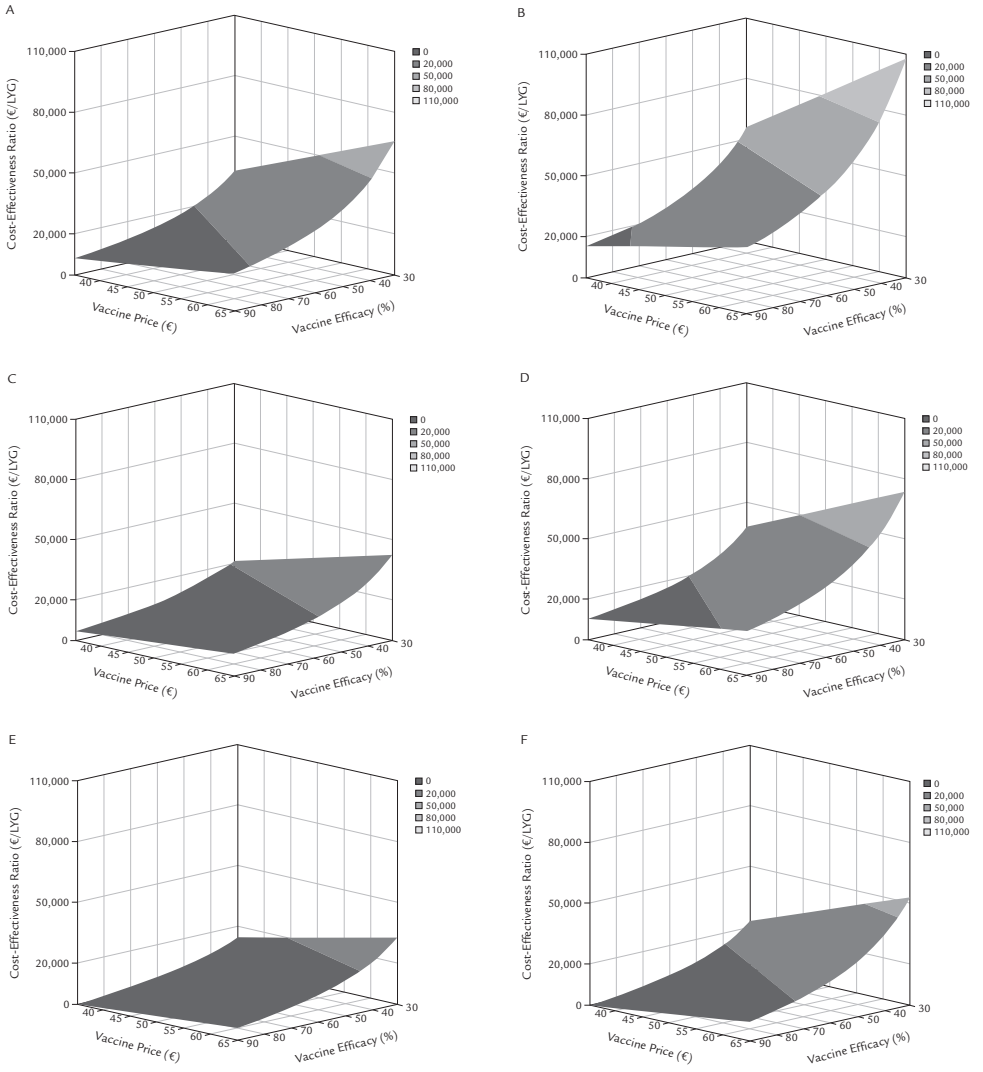

Figure 2. The effect on the ICER of varying the vaccine efficacy and the vaccine price. Vaccine efficacy was not assumed to start at 0%. (A) No indirect effects, with the assumption of only vaccine efficacy against bactereamic CAP. (B) Indirect effects included, with the assumption of only vaccine efficacy against bactereamic CAP. (C) No indirect effects, with the assumption of vaccine efficacy against all IPD. (D) Indirect effects included, with the assumption of vaccine efficacy against all IPD. (E) No indirect effects, with the assumption of protection against all IPD and against nonbactereamic CAP. (F) Indirect effects included, with the assumption of protection against all IPD and against nonbactereamic CAP.

Sensitivity analyses

Table 3 shows several analyses for the total population and the high–risk population. We assumed an efficacy of 60% against both vaccine–serotype IPD and vaccine–serotype non–IPD. Again, all

outcomes are shown with the inclusion of indirect effects (scenario B) and without the inclusion of indirect effects (scenario A). We combined this with a cost of €50 per vaccination. Similar to what was observed in Figure 2, Table 3 shows that the inclusion of net–indirect effects (scenario A vs B) affected the ICER. Calculating the projected costs per QALY instead of the cost per LYG increased the ICER by 70% to 80%. This was due to the relatively lower quality of life of the elderly, particularly those with an underlying condition. A booster dose given in the second year was projected to coincide with more favorable ICERs, especially when PPV23 would be given as a booster because of low vaccine price, combined with an efficacy assumed to be similar to that of a PCV13 booster. Obviously, decreasing the duration of protection would increase the ICER, and increasing the duration of protection would decrease the ICER.

Table 3. Incremental cost–effectiveness ratios (€/QAY) in the base case, sensitivity, and several scenario analyses.

	Scenario A*		Scenario B*	
	Total population	High–risk population	Total population	High–risk population
Base case	8,505	4,723	18,432	12,243
Per QALY	14,416	8,547	31,055	22,152
2 year duration of protection	27,931	20,393	50,676	37,969
10 year duration of protection	722	Cost saving	5,810	2,125
Booster dose (after 1 year) of PCV13 and 10 years protection	7,976	4,717	17,740	12,475
Booster dose (after 1 year) of PVV and 10 years protection†	4,258	1,461	11,583	7,134
Inclusion of meningitis sequalae	6,820	3,550	17,334	11,488
10% of the GP visits related to *S. pneumoniae*	8,520	4,739	18,447	12,259
40% of the GP visits related to *S. pneumoniae*	8,477	4,692	18,402	12,212
25% of the unspecified hospitalized CAP related to *S. pneumoniae*‡	10,500	6,584	21,212	14,701
45% of the unspecified hospitalized CAP related to *S. pneumoniae*‡	6,754	3,096	16,002	10,101
10% lower vaccine efficacy in high–risk elderly	9,793	6,025	20,575	14,389
20% lower vaccine efficacy in high–risk elderly	11,315	7,652	23,111	17,071
30% lower vaccine efficacy in high–risk elderly	13,139	9,745	26,159	20,518
5% case fatality due to hospitalised CAP	6,527	3,587	14,058	9,284
7.5% case fatality due to hospitalised CAP	5,537	3,024	11,894	7,830
Discount rate of 3.5% for both costs and LYGs	10,357	5,668	22,524	14,818
No discounting	6,750	3,543	15,139	9,942
No indirect costs	8,754	5,008	18,684	12,531

* In scenario A, only direct effects were included. In scenario B, indirect effects were also included. It was assumed that the current 7–valent infant vaccination program would increase the incidence of nonvaccine serotype pneumococcal disease to 100%, with a corresponding decrease in vaccine serotype incidence, leaving the overall incidence unchanged.

† No efficacy was assumed for those 10 serotypes not included in PCV13.

‡ In the base case, it was assumed that 35% of all hospitalized CAP cases were caused by infection with *S. pneumoniae*.

PPV= 23–valent polysaccharide pneumococcal vaccine; CAP = community–acquired pneumonia.

The percentage of primary–care visits related to *S. pneumoniae* had virtually no impact on the ICER; the costs related to a primary–care visit were relatively low, and mild pneumonia cases were not assumed to result in mortality. In contrast, the share of *S. pneumoniae* related to hospitalized CAP, and the fatality rate related to hospitalized CAP, had a much larger impact on the ICER in the model analysis. A lower vaccine efficacy for the high–risk population increased the ICER of the high–risk group by 18% to 106%, depending on the decrease in efficacy, but the ICER of the total population (including both low and high–risk elderly) was less sensitive for this variation. Applying a similar discount rate of 3.5% for both costs (4% in the base case) and health effects (1.5% in the base case) to correct for time preference increased the ICER by >20%, whereas not discounting costs or health effects decreased the ICERs to a similar extent. Exclusion of indirect costs, or assumption that a larger share of the CAP–related general–practitioner visits were related to *S. pneumoniae*, had a negligible impact on the ICER.

DISCUSSION

The burden of pneumococcal disease is high among the elderly and, in particular, among those considered to be at high risk for pneumococcal infection[163]. In this model analysis, we present several scenarios to estimate the potential cost–effectiveness of PCV13 for routine use among those aged ≥65 years in the Netherlands. Our results suggest that even in the most pessimistic scenario, vaccination of this population is likely to be cost effective. Despite the fact that we assumed a 10% shorter life expectancy for high–risk people aged ≥65 years, we projected that vaccination of high–risk elderly people would be more cost–effective than vaccination of all elderly people, given that the majority of cases occur in high–risk older people.

Sensitivity analyses revealed that apart from vaccine efficacy and the vaccine price, incidence and fatality rate related to CAP had the greatest impact on ICER. We estimated the share of *S. pneumoniae* related to CAP hospitalizations at 35%, which might well be an underestimate. The literature reports shares up to 60%[163-165], which would further improve the estimated cost effectiveness of PCV13. Future improvements in diagnostics could change understanding of the true burden of disease, given that current diagnostic tests lack sensitivity for the identification of the bacterial etiology of CAP[195]. Furthermore, we estimated the fatality rate due to nonbacteraemic CAP, because a causative organism is reported for relatively few pneumonia deaths. We used general CAP mortality data as a proxy for pneumococcal CAP fatality rates. Because pneumococcal CAP is considered to be more severe than general CAP[196],we may have underestimated the effect of vaccination on both costs and health effects. Our model results suggest that variation in vaccination costs would have a substantial impact on the ICER. If, in the future, PCV13 were used for both routine infant and routine elderly vaccination, it might be possible to reduce vaccination costs because mass quantities of the vaccine would be marketed. In addition, the costs of vaccination could be further decreased if the vaccine could be administered concomitantly with the influenza vaccine without compromising immunogenicity or producing interactions or adverse events. Our model probably provides adequate and mutually consistent estimates for both the high–risk and the

general population of those aged ≥65 years because we corrected the estimated life expectancy among those with underlying diseases[79]. We neglected the beneficial effect that vaccination would have on antimicrobial resistance, further adding to the fact that, in the Netherlands, resistance to antibiotics has traditionally been very low[79]. In other countries with higher levels of resistance, vaccination could result in slightly more favorable outcomes. We also chose to exclude all costs and health effects associated with long–term meningitis sequelae in the base–case analyses, because detailed data regarding costs and quality of life were not available for the elderly population. Finally, we included indirect costs due to paid work in our model. However, because this model considered those aged ≥65 years, this had only a limited impact on the ICER. We did not include unpaid work such as housekeeping and taking care of grandchildren, which one might expect in this older age group. Inclusion of these indirect costs, if valued monetarily, would further improve the cost–effectiveness outcome.

Our model has several limitations. We did not include quality–of–life effects in our base–case analysis because specific data regarding CAP were not available, and because the appropriateness of the data that were available for IPD was questionable. Furthermore, we did not include any possible adverse effects of vaccination because severe reactions to the conjugated vaccines have not yet been observed and because adverse events have mainly consisted of mild local reactions[35]. However, full information about the safety of the use of PCV13 in those aged ≥65 years is still lacking. We also did not include vaccination costs and possible health effects for individuals receiving PPV23 because adverse events would probably consist mainly of mild local reactions that would not require a doctor visit. Because our outcome measure was the cost per LYG, it was not possible to include potential QALY decrements related to these local reactions. Also, we assumed no additional primary care visits, and no additional costs were assumed for mild adverse events. As mentioned, vaccination coverage for PPV23 is very low in the Netherlands[20]. Nevertheless in other countries, routine vaccination with PCV13 might be more cost–effective (assuming no efficacy of PPV23) or less cost–effective (assuming a high efficacy of PPV23) depending on the efficacy of PPV23.

The impact of CAP requiring a general–practitioner visit was limited in our model, mainly because we only assumed that such a case would have costs without any reduction in the quality–of–life. This was assumed because no specific quality–of–life data were available for the elderly population, and because we assumed that severe CAP cases would be referred to a hospital. However, its inclusion would only have further improved our ICERs.

CONCLUSIONS

In this model analysis of a hypothetical cohort in the Netherlands, vaccination with PCV13 might be considered cost–effective, both for the total population and for the high–risk population aged ≥65 years, from a societal perspective, over a 5–year time horizon. The main limitation of this study was uncertainty regarding how great a proportion of pneumonia could be attributed to pneumococcal disease.

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Vaccination of risk groups in England using the 13 valent pneumococcal conjugate vaccine: economic analysis

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ABSTRACT

Objective: To estimate the cost effectiveness of vaccinating people with high risk conditions against invasive pneumococcal disease (IPD) using the 13 valent pneumococcal conjugate vaccine (PCV13).

Design: Economic evaluation using a cohort model from the perspective of healthcare providers.

Setting: England.

Participants: People aged 2 years and older at increased risk of IPD due to chronic kidney disease; splenic dysfunction; HIV infection; a compromised immune system; chronic heart, liver, or respiratory disease; or diabetes.

Main outcome measure: Costs, gains in life years and quality adjusted life years (QALYs), and incremental cost effectiveness ratios (ICERs).

Results: Increasing indirect protection resulting from the infant PCV13 programme means that the burden of disease preventable by targeting high risk groups will diminish in time. Under base case assumptions—that is, no overall impact on non bacteraemic pneumonia in high risk groups and assuming the high risk vaccination programme would be launched two to three years after the infant programme—the ICER was estimated to be more than £30,000 (€37,216; $48,210) per QALY gained for most risk groups. If, however, the vaccine does offer protection against non–bacteraemic pneumococcal pneumonia or the vaccine was introduced concomitantly with the infant PCV13 programme then vaccinating high risk people would (more) likely be cost effective. Sensitivity analyses showed that the cost effectiveness was particularly sensitive to assumed herd benefits and vaccine efficacy estimates.

Conclusion: Under base case assumptions it is unlikely that a pneumococcal vaccination programme aimed at risk groups could be considered cost effective. Uncertainty could be substantially reduced by establishing the effectiveness of the PCV13 against non–bacteraemic pneumococcal pneumonia, particularly in at risk groups.

INTRODUCTION

People with certain clinical conditions such as immunocompromised patients and those with chronic heart or lung disease are at increased risk of invasive pneumococcal disease (IPD) and related mortality[197]. To prevent disease among these high risk groups many countries recommend vaccination with the 23 valent polysaccharide vaccine (PPV23), which has been available since the 1980s. Nevertheless, the efficacy and duration of protection of this vaccine is limited, and the antibody response to revaccination is reduced[20,21]. The use of conjugated pneumococcal vaccines could potentially overcome the limitations of PPV23. In children the seven valent pneumococcal conjugate vaccine (PCV7) has been shown to be highly effective in preventing IPD caused by vaccine related serotypes[198]. Data on the efficacy in adults, elderly people, and high risk groups are, however, scarce, with most studies focusing on immunogenicity rather than on efficacy[21]. The limited data on efficacy that are available suggest that pneumococcal conjugate vaccines are effective in preventing IPD (and possibly pneumonia) in adults and children infected with HIV, a group in whom PPV23 is ineffective[199,200]. As the pneumococcal conjugate vaccines are more expensive, there is a need to assess whether the use of these vaccines is justified. Such an assessment is complicated by the interaction (at a population level) between a targeted risk based programme and vaccination of children. The introduction of the PCV7 in the infant immunisation programme led to a dramatic decline in incidence of IPD due to vaccine serotypes in all age groups (including those in risk groups)[40]. However, these decreases were partly offset by a simultaneous increase in disease caused by non–vaccine serotypes, reducing the impact on overall IPD[36].

In the infant programme in the United Kingdom, as elsewhere, PCV7 has recently been replaced by PCV13. This higher valency vaccine covers six additional serotypes, including the key replacement serotypes 19A and 7F. Similar herd effects for the additional serotypes, as observed for the seven serotypes included in the PCV7 after its implementation, can be expected in time. However, high risk groups could potentially still benefit from the faster and greater effects of direct vaccination with PCV13 compared with waiting for the indirect benefit from the herd immunity against the vaccine serotypes generated by the infant programme.

We estimated the effectiveness, costs, and cost effectiveness of vaccinating high risk groups in England using PCV13, taking into account that herd benefits of the current infant PCV13 programme will diminish the potential impact of a specific programme for high risk groups over time.

METHODS

We estimated the costs, health benefits, and cost effectiveness of vaccination of high risk groups with PCV13 on top of the current risk based vaccination programme with PPV23. This was done because the existing PPV23 programme is likely be continued despite the potential introduction of a risk based PCV13 programme. In addition our risk estimates for pneumococcal disease were estimated in the current situation in which a risk based PPV23 programme is already in place (albeit with a low uptake of vaccination).

As infants are already vaccinated with PCV13, we restricted our analysis to high risk patients aged

2 years and older. The perspective was from that of the National Health Service, as recommended in the United Kingdom[9].

Model and population

We developed a cohort model to determine the cost effectiveness of vaccinating specific high risk groups with PCV13. Groups included in this analysis were based on a recent study among patients admitted to hospital in England with culture confirmed IPD, which compared the prevalence of clinical risk factors in the general population with that in patients admitted to hospital with IPD[40]. The study sample comprised 22,298 patients admitted to hospital between April 2002 and March 2009 with an admission record in the hospital episode statistics database for England that could be linked with the dataset of the national IPD laboratory held at the Health Protection Agency[40].

In the current analysis we differentiate between people who are immunocompromised, such as those with HIV, asplenia, or splenic dysfunction or who respond poorly to the vaccine, such as people with chronic kidney disease; and those in immunocompetent risk groups such as patients with chronic heart, liver, or respiratory disease and people with diabetes[40].

The analytical time frame of the study was until 2021 (we assume that after this time the additional benefits of vaccination would be negligible). However, we extrapolated the long term effects of IPD over the full lifetime of the participants in each cohort—that is, until death or 100 years.

Incidence of IPD and mortality risks

Using the most recent data available we estimated age group and risk group specific incidences. Firstly, we calculated age specific incidences of IPD for the general population, including cases confirmed by polymerase chain reaction and culture from the epidemiological year 2009–10 (in this paper we refer to epidemiological years, which run from July to June, unless stated otherwise)[36]. These incidences were subsequently used to estimate the incidence of IPD in high risk people using the prevalence of clinical risk factors among the general population and the prevalence among the linked patients admitted to hospital with IPD[40]. From the same databases we estimated the age specific share of meningitis and empyema to the total IPD burden to allow the inclusion of specific costs related to these outcomes. We also obtained age group and risk group specific case fatality ratios for IPD from this same study[40].

Invasive pneumococcal disease sequelae

Invasive pneumococcal disease may lead to long term sequelae, especially in the case of meningitis. We obtained the risk of different types of sequelae from a recent meta–analysis[201]. As patients can have multiple sequelae, we assigned all possible combinations on the basis of the prevalence of the individual conditions and reweighted them such that the overall risk to develop any sequela was equal to the pooled prevalence of 31.7% as estimated by the meta–analysis. We obtained the losses in overall quality adjusted life years (QALYs) using the most severe QALY weight in the combination.

Non–bacteraemic pneumococcal pneumonia

To assess whether to include an effect of PCV13 on non–bacteraemic pneumococcal pneumonia in the base case we looked at the impact of PCV7 on the overall incidence of non–bacteraemic pneumonia in high risk children. For this we obtained the number of episodes of non–specified pneumonia (ICD J18.X, mentioned in any diagnostic code) and the number of deaths for the same cases (within 30 days of admission) for the years 1997–98 up to 2009–10 (data from 2002–03 to 2009–10 were used for deaths) from the hospital episode statistics database in children aged less than 5 years. Next, we divided individual cases into risk or non–risk groups based on the same ICD codes (see Appendix 9) as used for IPD, and we calculated incidences. An interrupted time series analysis showed that the incidence of pneumonia requiring admission to hospital in non–high risk children aged less than 5 years (that is, those eligible for vaccination) was significantly reduced after the introduction of PCV7, whereas the incidence in high risk children of the same age was not significantly reduced (see Appendix 1). Based on the striking difference between risk and non–risk groups, and the additional uncertainty about the contribution of *Streptococcus pneumoniae* to non–bacteraemic pneumonia, particularly in high risk children, we decided not to include an overall impact on non–bacteraemic pneumonia in the base case analysis for the high risk groups. We did, however, explore the potential impact of including an effect against non–bacteraemic pneumonia in specific analyses. For this we used the data on age specific incidence for all cause pneumonia for the year 2010 from hospital episode statistics and projected these forward assuming the same incidence as in 2010. Next we assumed that *S pneumoniae* would be the causal agent in 42% of the patients in high risk groups admitted to hospital with non–bacteraemic pneumonia on the basis of the results of the two most recent UK studies available[202,203]. We then assumed that the contribution of the vaccine serotypes to pneumococcal pneumonia would decline in line with the herd effect of the infant vaccination programme on IPD.

Indirect effects

In virtually all countries the introduction of PCV7 was followed by a large reduction in IPD owing to vaccine serotypes in vaccinated and unvaccinated age groups, with the indirect benefits in some age groups partially offset by a concomitant increase in IPD due to non–vaccine serotypes[198]. This was also the case in the United Kingdom in which PCV7 was introduced in September 2006 with a vaccination schedule of 2, 4, and 13 months, and catch–up vaccination for children aged up to 2 years[36]. In April 2010, PCV13 replaced PCV7 in the infant vaccination programme.

To predict the future decrease in IPD due to vaccine serotypes in unvaccinated age groups, we divided the serotypes into those covered by PCV7 and those included in the PCV13 but not in PCV7. In both cases we used age group specific (2–4, 5–14, 15–44, 45–64, and >64 years) UK data on incidence of vaccination before and after the introduction of PCV7. The prevaccination period included the incidence data for the years 2000–06, whereas the post–vaccination period included data up to four years after the introduction of the vaccine (2006–10). Using the age group specific annual incidence (adjusted for underlying trends in case ascertainment) we fitted a Poisson

regression model adjusting for the population size to predict the future reduction in cases of IPD due to the vaccine serotypes (see Appendix 2).

We consequently used the predicted annual decrease in vaccine serotypes to predict the incidence of the additional serotypes (except for serotype 3, see below) in PCV13—that is, we assumed that the herd effects for the additional serotypes in this vaccine would be similar to those observed for the serotypes in PCV7 after the introduction of the routine infant PCV7 programme in 2006[40]. The only difference was that we delayed the herd effects for the six additional serotypes in PCV13 by one year as the introduction of the infant PCV13 programme was not combined with a catch–up programme. This assumption is supported by the most recent data from the Health Protection Agency, which show no indication of any herd effect yet in people aged 5 years and older, 15 months after implementation of the routine infant PCV13 programme[204]. Furthermore, in the Netherlands, where the PCV7 programme was launched without a catch–up, herd effects were not observed in the first year after implementation in contrast with the United Kingdom[105].

We did not include serotype replacement effect in the model as we assumed that it would not affect the incremental cost effectiveness ratio (ICER) because changes in IPD due to non–vaccine serotypes are expected to be the same irrespective of the implementation of the risk group programme.

Vaccine efficacy, number of vaccine doses, duration of protection

Although the efficacy of PCV7 in healthy infants is well established, the available data for risk groups and adults is scarce, with most studies reporting data on immunogenicity rather than efficacy[21]. Data on the efficacy of PCV13 is limited[204]; the current licence for the use in infants and children from 6 weeks to 5 years of age and adults aged 50 years and over was based on immunogenicity rather than efficacy data[35] (see Appendix 3 for an overview of available data).

Considering the limited data available, we carried out a formal elicitation of expert opinion on vaccine related variables to construct a probability distribution that represents the experts' knowledge and uncertainty[205]. The objectives of the elicitation were to estimate the efficacy of PCV13 (against IPD and non–bacteraemic pneumococcal pneumonia) and the duration of protection after one dose of the vaccine (as in the base case analysis) or two doses of the vaccine. Importantly, recent data from our group show that the serotype 3 component of PCV13 seems to be ineffective against IPD caused by this serotype[206]. Therefore, in the model we also assumed no protection against disease or carriage for serotype 3.

Specific details on the method of elicitation can be found in Appendix 4. Briefly, we asked five members of the Pneumococcal Subcommittee of the Joint Committee on Vaccination and Immunisation to give an estimate of the PCV13 vaccine efficacy for risk groups based on the available PCV7 efficacy data and immunogenicity data of both the PCV7 and PCV13. We used the estimates to create distributions for vaccine effectiveness using the Sheffield elicitation framework[205]. Final distributions can be found in Table 1.

Life years and QALY estimates

As the life expectancy between the general population and high risk groups differs[172,209], we calculated specific background mortality for people at high risk (and for the general population for validating purposes). Data were gathered from the Royal College of General Practitioners database (including 0.8 million patients; more than 1% of the UK population) over a period of six years (2005 to 2010). We grouped the patients by risk factor (based on Read codes mapped to ICD–9 codes) and calculated the number of person years and deaths in the high risk group. Using these data we calculated background mortality (see Appendix 5). We also calculated the mortality for non–risk groups and validated these against life tables from the Office for National Statistics[210].

In addition to life years gained we also calculated QALYs gained by vaccination. For patients admitted to hospital for IPD, we used losses in QALYs of 0.0079 per case for bacteraemia and 0.0232 per case for meningitis[150]. We assumed that non–bacteraemic pneumococcal pneumonia resulted in a QALY loss of 0.006 per case[43]. In addition to acute losses in QALYs, we also linked specific losses in QALYs to the sequelae due to meningitis based on a Dutch study[140] (see Table 1 for specific losses in QALYs).

Costs

All costs are reported in pounds sterling at 2009–10 prices. Where necessary we inflated these using the hospital and community health services pay and price index[211]. As the perspective was from that of the healthcare provider, we included only direct costs. We used recommended procedures to estimate the costs for patients admitted to hospital with IPD. The NHS healthcare resource group software was used, which combines procedure codes and ICD–10 diagnostic codes to output the most relevant healthcare resource group code. We subsequently assigned these codes a cost from the National Schedule of Reference Costs for NHS trusts. As the patients included in our analysis are all high risk, we included only those for which it was likely that the IPD episode was the main cause for admission to hospital—defined as those patients who had a primary diagnostic code related to an IPD code (see Appendix 6). Table 1 displays the costs and probabilities related to IPD. The costs of hospital admission for non–bacteraemic pneumococcal pneumonia were based on reference costs for pneumonia. We used the weighted average costs based on the number of non–elective admissions for pneumonia without complications (NHS reference costs code WADZ11C). Patients who had meningitis without sequelae were assumed to have a single outpatient appointment after discharge; we obtained the cost of treatment and care for patients with sequelae after meningitis from a previous cost effectiveness analysis[139].

The total cost per PCV13 dose was estimated at £56.61, consisting of the price of the vaccine (£49.10) and administration costs (£7.51).

Table 1. Variables used in economic model

Variables	Expected value	Distribution	Reference
Age specific incidence	See Appendix 8	NA	See methods
Odds of IPD*	Age and risk group dependent*	Log normal	40, see methods
Case fatality ratio†	Age and risk group dependent†	β	40, see methods
Share of meningitis in total burden of IPD	3–8% (age dependent)	Fixed	See methods
Share of empyema in total burden of IPD	1–5% (age dependent)	Fixed	See methods
Vaccine efficacy against invasive pneumococcal disease‡			
High risk immunocompetent:			
Aged <65 years	0.71	β (α 2.1, β 0.863)	See methods
Aged ≥65 years	0.63	β (α 2.01, β 1.19)	See methods
High risk immunocompromised:			
Aged <65 years	0.53	β (α 1.59, β 1.41)	See methods
Aged ≥65 years	0.43	β (α 1.21, β 1.62)	See methods
Vaccine efficacy against non–bacteraemic pneumococcal pneumonia ‡			
High risk immunocompetent:			
Aged <65 years	0.46	β (α 1.88, β 2.19)	See methods
Aged ≥65 years	0.40	β (α 1.47, β 2.2)	See methods
High risk immunocompromised:			
Aged <65 years	0.33	β (α 1.24, β 2.55)	See methods
Aged ≥65 years	0.27	β (α 1.27, β 3.47)	See methods
Waning immunity (per year)§			
High risk immunocompetent:			
Aged <65 years	0.11	See methods	See methods
Aged ≥65 years	0.25	See methods	See methods
High risk immunocompromised:			
Aged <65 years	0.24	See methods	See methods
Aged ≥65 years	0.26	See methods	See methods
Prevalence of sequelae after meningitis			
Deafness	0.08	β (mean 0.08 SE 0.03)	201
Mild hearing loss	0.21	β (mean 0.21 SE 0.02)	201
Seizures and hydrocephalus	0.07	β (mean 0.07 SE 0.02)	201
Spasticity or paresis	0.09	β (mean 0.09 SE 0.01)	201
Cranial nerve palsy	0.12	β (mean 0.12 SE 0.04)	201
Quality adjusted life year losses			
Hospital admission for meningitis	0.023	β (mean 0.023 SE 0.031)	43, 150
Hospital admission for bacteraemia¶	0.0079	β (mean 0.079 SE 0.083)	43
Hospital admission for non–bacteraemic pneumonia	0.006	Normal (mean 0.006 SD 0.0015)	43, 150

Table 1. Variables used in economic model *(Continued)*

Variables	Expected value	Distribution	Reference
Quality of life weights			
Deafness	0.81	β (mean 0.81 SE 0. 028)	140
Mild hearing loss	0.91	β (mean 0.91 SE 0.015)	140
Seizures	0.83	β (mean 0.83 SE 0.015)	140
Hydrocephalus	0.62	β (mean 0.62 SE 0.021)	140
Spasticity or paresis	0.67	β (mean 0.67 SE 0.023)	140
Cranial nerve palsy	0.67	β (mean 0.67 SE 0.023)	140
Costs (£)			
Case of meningitis**	6509	Normal (mean 6509 SD 405)	See methods
Case of empyema**	7538	Normal (mean 7665 SD 444)	See methods
Short hospital stay for other IPD**	825	Normal (mean 839 SD 3.93)	See methods
Case with long stay for other IPD:			
With excess days in hospital**	8977	Normal (mean 9129 SD 142)	See methods
Without excess days in hospital**	3022	Normal (mean 3073 SD 19)	See methods
Admitted to hospital for pneumonia	661	Normal (mean 672 SD 168)	See methods
Chance of long hospital stay for IPD	0.61	β (α 5075 β 8257)	See methods
Chance of excess days during long stay for IPD	0.46	β (α 2328 β 5075)	See methods
Lifetime costs after meningitis:			
In first year	6591	Log normal (mean 8.7 SD 0.4)	139
In subsequent years	203	Log normal (mean 8.7 SD 0.4)	139
Outpatient follow–up for meningitis	382	Log normal (mean 5.2 SD 0.4)	139
Cost of PCV13	49.10	Fixed	207
Administration costs	7.51	Fixed	207
Other variables			
Herd effect due to infant vaccination	See Appendix2	Normal	See Appendix 2
Life expectancy among high risk groups	See Appendix 2	NA	See Methods
Discount rate for costs and health effects	3.5%	NA	208

* Odds ratio of IPD comparing risk groups to non–risk groups. Specific odds ratios can be found in Van Hoek et al.[40]
† Age specific case fatality ratios can be found in Van Hoek et al.[40]
‡ After single dose during first year of vaccination. Efficacy estimates do not apply for serotype 3 (see method section)[206]. Estimates of vaccine efficacy after two doses are listen in Appendix 4.
§ Annual waning factor was calculated by using the experts estimation of vaccine efficacy during first and third year after vaccination using annual exponential decay of immunity.
¶ Same quality of life year decrement was assumed for invasive pneumonia, bacteraemia with focus, and bacteraemia without focus.
** Mean costs were sampled from a normal distribution with a mean equal to the log normal mean and standard deviation equal to the standard error of the log normal mean.

Scenario and sensitivity analysis

We carried out univariate, threshold, scenario, and probabilistic sensitivity analyses. In the univariate sensitivity analyses, relevant variables were based on the 5% and 95% quantiles to explore the impact of uncertainty around each variable. A threshold analysis was done in which we varied the vaccine price to investigate the effect on the ICER. In specific scenario analyses we explored the impact of changes in vaccine efficacy, vaccine waning, delaying the herd effect of the infant PCV13 programme, assuming life expectancy of the general population (rather than using the life expectancy of people in high risk groups), and the effect of discounting.

For the probabilistic sensitivity analyses, we generated variables using Monte Carlo sampling, with outcome values generated by running the model 5000 times using Latin hypercube sampling. When quantitative data about uncertainty around variables were available we used log normal and β distributions (see Table 1 for specific distributions). When only a single point estimate was available, we assumed a normal distribution with a coefficient of variation of 0.25. For all the sensitivity analyses it was assumed that the vaccination programme would be launched in 2012–13 (two to three years after the infant programme).

Outcome measures and cost effectiveness analysis

The simulation model tracks the incidence of IPD and non–bacteraemic pneumococcal pneumonia, the number of deaths, costs, QALYs, and life years. We calculated the net costs, life years gained, and QALYs by summing all the costs, life years, and QALYs and calculating the differences for the evaluations with and without vaccination. The ICER was calculated by dividing the net costs by either the life years gained or QALYs gained. Health effects and cost were both discounted at 3.5% according to the UK guidelines[208]. In the analyses we compared the possible impact of vaccination using PCV13 with that of the current situation. Currently, adults aged more than 65 years and people in at risk groups aged 2 years or more are recommended to be vaccinated with PPV23[212]; however, uptake of the vaccine is relatively low, especially in those aged less than 65 years (see Appendix 7)[40]. We assumed that PCV13, would be used in addition to PPV23.

Finally, we assumed that the uptake of PCV13 would be similar to the annual influenza programme in the United Kingdom, at 34.5% in the age group 2–16, 53.6% in the age group 16–65, and 72.4% in the age group 65 and older[213] and that vaccination with PCV13 would be offered irrespective of previous vaccination with PPV23.

RESULTS

Invasive pneumococcal disease incidence, vaccine efficacy, indirect effects, and life expectancy

Among high risk groups the highest incidence of IPD was in young people infected with HIV and the lowest in those with chronic heart disease, diabetes, or splenic dysfunction (see Appendix 8 for estimated incidence of IPD among high risk groups). Table 1 shows the estimates for vaccine efficacy based on the elicitation of expert opinion and the estimated costs associated with different

types of IPD. Appendix 2 presents the Poisson regression for IPD due to vaccine serotypes after the introduction of PCV7. Finally, appendix 5 shows the life expectancy for people in high risk groups.

Total burden in high risk groups

Without a vaccination programme based on risk groups, but taking into account the likely herd effects of the infant PCV13 programme, the model predicts that from 2012–13 to 2020–21 about 1333 cases of IPD due to vaccine serotypes would occur in people at high risk. This corresponds to a total loss of about 5900 life years or 6200 QALYs (undiscounted). The herd impact of the infant PCV13 programme is large; preventing an additional 6200 IPD cases due to vaccine serotypes corresponding to an additional 30,400 QALYs lost compared with a continuing infant PCV7 programme.

Table 2. Total burden of IPD due to vaccine serotype (undiscounted) over nine year period (2012–13 to 2020–21) in people at high risk.

Variables	Cases of IPD due to vaccine serotypes	Deaths	Life years	QALYs
Without high risk vaccination and without herd protection benefits of PCV13*	7522	1895	34,251	36,579
Cases prevented by the herd effects of the infant PCV13 programme†	6189	1538	28,397	30,382
Without high risk vaccination and with herd effects of additional six serotypes in PCV13	1333	357	5854	6197
With high risk group vaccination (including herd effects of infant programme)‡	927	247	4033	4274
Averted burden by high risk vaccination (incremental effects)§	406	110	1821	1923

* Only including herd effect due to serotypes included in PCV7 (excluding herd effect due to the six additional serotypes included in PCV13.)
† Herd effects due to the additional six serotypes in PCV13 based on incidence after vaccination with PCV7 (see methods and Appendix 2).
‡ Vaccination uptake to be assumed similar to that of annual influenza uptake (see methods).
§ Numbers may not add up owing to rounding.

Budget impact

A risk based vaccination programme would require 4.1 million vaccine doses (assuming the same vaccine uptake as the annual influenza vaccination programme), resulting in a total cost of around £233m (of which £202m is attributed to the vaccine and the remainder to administration costs). Focusing on specific high risk groups, in whom vaccination would be most cost effective, could reduce the costs substantially. For example, vaccinating people with chronic liver disease would result in a total net cost of £4.6m. Furthermore, Table 3 also shows the impact on budgets of assuming a higher coverage among all risk groups (80% uptake) and the impact assuming the same annual coverage as for the PPV23 (see Appendix 7). If coverage is no higher than that achieved by PPV23, then the impact on budgets would be much reduced, as this programme only achieves poor levels of uptake.

Table 3. Budget impact (total costs) of vaccinating different risk groups (£m) with PCV13 according to assumed uptakes.

Risk group	Assumed uptake*		
	Similar to influenza programme (base case)*	80%	Similar to annual PPV23 programme†
Any risk group	233	290	17.8
Splenic dysfunction	6.3	8.9	0.35
Chronic respiratory disease	34.1	41.5	2.80
Chronic heart disease	116	1411	9.60
Chronic kidney disease	71.5	83.4	6.40
Chronic liver disease	4.64	6.4	0.24
Diabetes	59.2	75.2	4.15
Immunocompromised	17.9	24.0	1.12
Infected with HIV	0.37	0.54	0.01

* Annual influenza coverage 34.5% in 2–15 year olds, 53.6% in 16–65 year olds, and 72.4% in those aged ³65 years[213]. Sum of costs of separate risk groups are higher than total costs of any risk group as people may have more than one underlying condition.

† Annual uptake 4.1% in 2–15 year olds, 1.5% in 16–65 year olds, and 7.2% in those aged ³65 years). See Appemndix 7.

Cost effectiveness

The base case analysis (excluding a possible impact against non–bacteraemic pneumococcal pneumonia) assumed it would be possible to start vaccinating at risk groups in the epidemiological year 2012–13. Using a threshold of £30,000 for a willingness to pay for a QALY gained[208], only vaccination of patients with chronic liver disease (Table 4) would be deemed cost effective. People infected with HIV was the second most favourable at risk group, with an ICER of £61,200 per QALY gained. Vaccinating all other at risk groups would not be considered cost effective, with an ICER of more than £80,000 per QALY gained.

Impact of time on cost effectiveness

The expected indirect benefits as a result of the infant vaccination programme limit the direct effect of targeting high risk groups. As a result the cost effectiveness of vaccinating at risk groups decreases over time as indirect benefits accrue. If a programme targeted at high risk groups had been initiated in 2009–10, then vaccinating immune compromised people and people with chronic respiratory disease and HIV infection could also be deemed cost effective (ICER of ≤£30,000 per QALY). Figure 1 shows the impact of time on the ICER for the years 2009–10 up to 2015–16.

Sensitivity analyses

Table 4 shows the impact on the ICER of assuming an overall impact on non–bacteraemic pneumonia. If included, even vaccinating the whole group at increased risk of IPD might be considered cost effective, with an ICER of £17,500 per QALY. Figure 2 shows the maximum costs of vaccination for it

to be considered cost effective. These costs will decrease with a decreasing net effect of the vaccine in time. In the base case (no overall impact on non–bacteraemic pneumonia) the vaccine costs have to be reduced for all risk groups, except for patients with chronic liver disease, to consider a risk group programme to be cost effective.

Table 4. Incremental cost effectiveness ratios (ICERs) in £/QALY per risk group assuming vaccination will be introduced in epidemiological year 2012–13.

Risk group	ICER (£/QALY)	
	Base case*	Including non–bacteraemic pneumococcal pneumonia
Any risk group	183,680	17,503
Splenic dysfunction	1,204,091	37,686
Chronic respiratory disease	90,243	14,832
Chronic heart disease	161,063	16,043
Chronic kidney disease	493,682	22,641
Chronic liver disease	20,324	10,825
Diabetes	269,750	18,459
Immunocompromised	90,720	24,296
Infected with HIV†	61,239	28,144

* Assuming no overall impact on non bacteraemic pneumonia in high risk group.

† When the assumption was made that life expectancy of people infected with HIV would be similar to high risk immonocompetent people,[43 44] ICERs were estimated at £54 409/QALY in base case analysis and at £25 717/QALY when an effect against non–bacteraemic pneumococcal pneumonia was included.

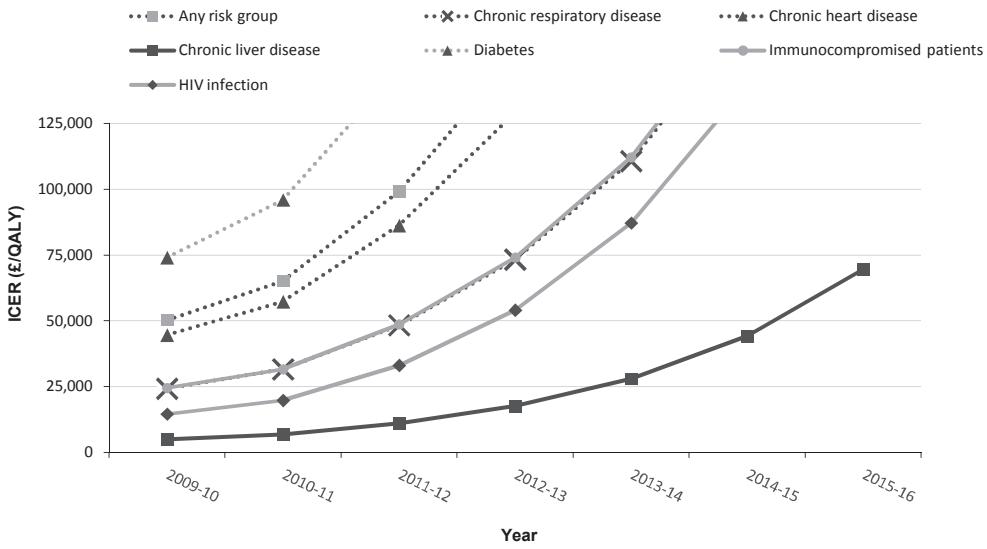

Figure 1. Impact of time on the incremental cost effectiveness ratio (ICER)

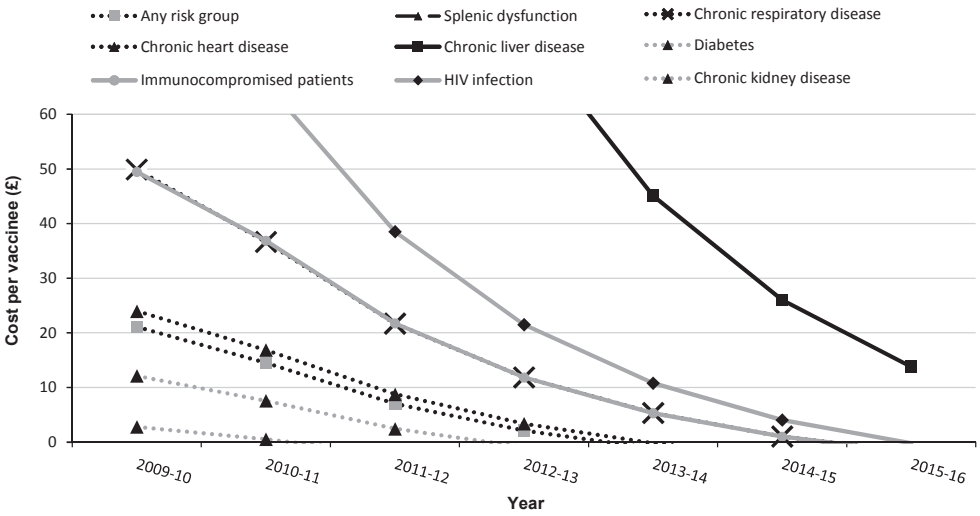

Figure 2. Maximum costs per vaccinee (including costs of vaccine and administration) to consider risk group vaccination cost effective (ICER of ≤£30,000 per QALY)

Table 5. Result of scenario analyses on the incremental cost effectiveness ratio (£/QALY) for those risk groups that had an ICER <100,000 per QALY in base case for epidemiological year 2012–13.

Variables	Any risk group	Chronic respiratory disease	Chronic liver disease	Immunocompro-mised	HIV infected
Base case	183,680	90,243	20,324	90,720	61,239
No herd effects due to any serotypes in PCV13 *	37,687	18,061	2848	20,059	10,059
No herd effects due to six additional serotypes in PCV13 †	46,903	22,715	3529	25,259	12,404
No herd effects due to serotypes 1 and 5†	74,882	36,122	6496	41,115	25,181
Herd effect of infant PCV13 programme delayed by two years	128,603	63,257	13,369	63,301	39,452
Vaccine price 25% reduced	143,564	70,390	15,772	70,720	47,342
Vaccine price 25% reduced and no administration costs	119,021	58,244	12,987	58,484	38,840
No waning immunity	141,999	69,927	17,013	65,107	45,181
No discounting	120,495	60,164	11,570	59,730	34,484
Life expectancy of normal population	163,070	79,937	18,446	81,036	50,331
Double vaccine dose	308,886	153,053	34,429	143,581	97,066
15% higher incidence of invasive pneumococcal disease	159,550	78,302	17,586	78,691	52,880
Assuming PCV13 to be effective against serotype 3	150,326	73,331	17,620	74,099	54,099

* No further reduction as from 2009–10 for all serotypes included in PCV13.

† 20% less herd effects could be achieved when serotypes 1 and 5 were not assumed to provide herd protection and 80% less herd effects could be achieved when six additional serotypes included in PCV13 would not provide any herd effect compared with maximum herd effect (for example, total eradication of all serotypes included in PCV13) calculated by using specific incidence data on serotype for 2009–10 and projecting forward.

The results of the scenario analyses (Table 5) and the univariate sensitivity analysis (Fig 3) show that the predicted herd effects of the infant programme and vaccine efficacy have a large impact on the ICERs. For instance, if there are no herd effects resulting from the additional types now included in the infant vaccination programme then the cost effectiveness of targeting all high risk groups would be reduced from over £180,000 to around £47,000 per QALY gained.

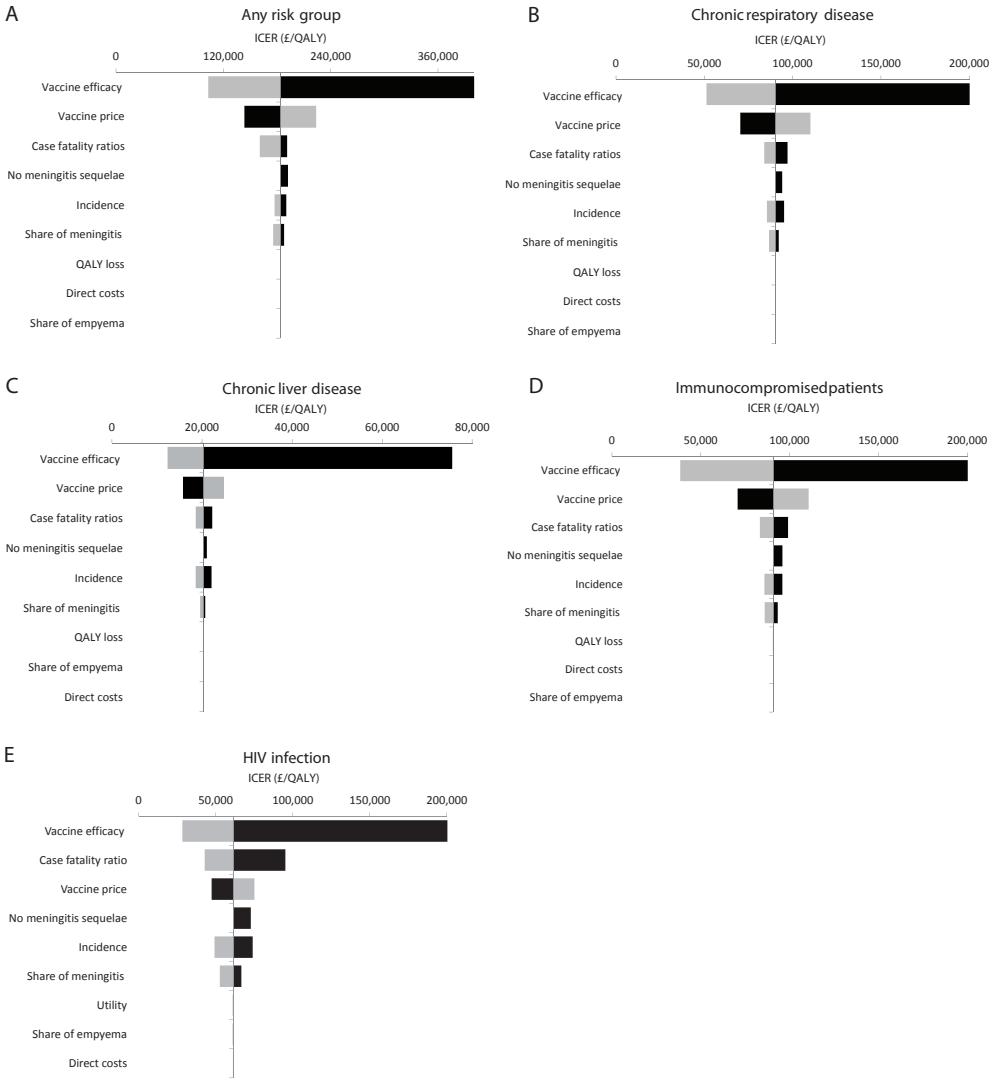

Figure 3. Result of the univariate sensitivity analysis. Variables were changed over their 5% and 95% quantiles, with exception of share of meningitis and empyema, which were varied by 50%. Incidence was altered by varying odds of IPD in those with risk factors compared with those without. Bar for lower vaccine efficacy are cut–off for all at risk groups except immunocompromised patients. Please note that the scales of the figures vary.

Other important factors were the price of the vaccine, the risk and age group specific incidence, and the case fatality ratio. Also, the scenario analysis showed that the additional benefits of a second dose were outweighed by the doubling of the costs.

Probabilistic sensitivity analysis

Figure 4 shows the cost effectiveness acceptability curves for the risk groups in whom the ICER was less than £100,000 per QALY. It is clear that if the vaccine does not offer protection against non–bacteraemic pneumococcal pneumonia then only vaccinating patients with chronic liver disease is likely to be considered cost effective, but by assuming an overall impact against non–bacteraemic pneumococcal pneumonia, vaccinating any of the at risk groups would probably be cost effective.

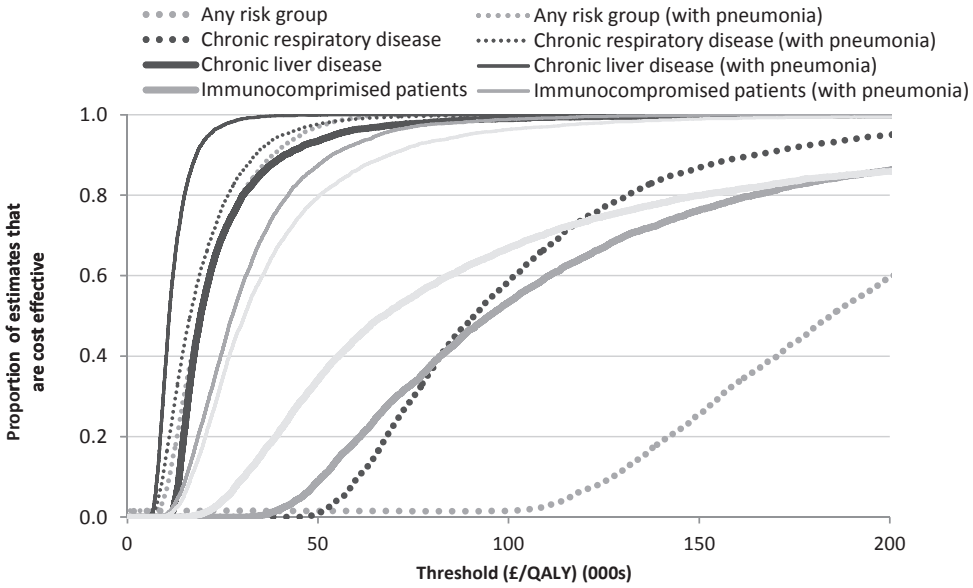

Figure 4. Results of probabilistic sensitivity analysis.

DISCUSSION

Although herd effects of the infant vaccination programme will indirectly protect high–risk individuals in time, the burden of preventable, pneumococcal disease will remain high during the first years after the introduction of the infant PCV13 programme.

Vaccinating all groups at high risk of IPD with PCV13 would have a large impact on budgets, therefore targeting specific high risk groups may be more attractive although this would require general practitioners to identify subgroups among those at increased risk. Our analysis shows that unless PCV13 also offers protection against non–bacteraemic pneumococcal pneumonia, vaccination is unlikely to be considered cost effective for most at risk groups. The assumptions about

vaccine efficacy and effectiveness, and in particular that against non–bacteraemic pneumococcal pneumonia, had a large impact on our results, and a great deal of uncertainty surrounds these estimates. Although evidence from randomised controlled trials would be preferable to expert opinion, by the time results are available[168] the potential benefits of vaccinating high risk groups are already largely limited by the expected herd effects.

Strength and weaknesses of the study

This is the first economic evaluation of vaccination against pneumococcal disease in specific high risk groups using PCV13. The two most influential variables on the outcome were the assumed herd protection benefits from the infant pneumococcal vaccination programme and the vaccine effectiveness against non–bacteraemic pneumococcal pneumonia.

Dynamic models have been used to predict the herd effects of the infant vaccination programme but their reliability critically depends on the structure and underlying assumptions, such as vaccination coverage, difference in case–carrier ratios between serotypes, and the level of competition between vaccine serotypes and non–vaccine serotypes in carriage[209,214]. Hence any such model predictions are subject to considerable uncertainty. Therefore we decided to predict the future herd effects by using Poisson regression models, assuming that the decrease in the additional serotypes (with the exception of serotype 3) would be similar to those observed after the introduction of the PCV7. Nevertheless, the herd effect for the six additional serotypes in PCV13 might be different from those in PCV7 owing to differences in carriage, transmissibility, and the potential to cause disease[80,120]. We also assumed that the herd effects would be similar among high risk and non–high risk groups, as this was previously also observed for IPD due to serotypes in PCV7[40]. However, as the less invasive serotypes primarily affect people at high risk and the additional serotypes included in the PCV13 are the more invasive, people at high risk might benefit less from herd effects compared with healthy people[215]. This may also explain the failure to find a reduction in non–bacteraemic pneumonia in children at high risk compared with healthy children.

Another key assumption was the vaccine efficacy against IPD and non–bacteraemic pneumococcal pneumonia. The main reason for not including an effect against non–bacteraemic pneumococcal pneumonia in the base case analysis was that the time series analysis did not show any measurable effect on admissions due to pneumonia in high risk children eligible for vaccination with the PCV7, whereas a significant reduction was observed in non–high risk children of the same age. This might be explained by different pathogens (viral or bacterial) causing pneumonia in high risk populations and for those with pneumococcal pneumonia, a different serotype distribution in high risk compared with low risk people. As we had the ability to analyse our surveillance data by whether patients had comorbidities, which would seem essential for deciding on a risk based vaccination programme, our assumption of the effectiveness against non–bacteraemic pneumonia differs from two previous analyses[129,216]. We do, however, also note that the effect of being in an at risk group on increasing the risk of IPD is more noticeable in children than in adults[40], which might mean that our assumption of lack of a direct effect of PCV13 on non–bacteraemic pneumonia in

adults may be conservative[199], yet consistent with the *BMJ* guidelines for economic evaluations[40,217].

Finally, we note that the impact of non–bacteraemic pneumococcal pneumonia was high in our analysis despite a relatively low vaccine efficacy being used in combination with a relatively high waning rate (Table 1).

The cost effectiveness of vaccination depends heavily on the probability of developing disease. In our analysis this was based on the observed odds of IPD in risk groups compared with those not in risk groups and the absolute incidence of non–risk group related disease. One of the caveats of the risk factor study was that patients were attributed to risk groups on the basis of the presence of specific discharge codes. Some of the risk groups might not have been consistently recorded. The odds for people with asplenia were low in the study, with no obvious increased probability of developing disease, resulting in unfavourable ICERs. Although this might be explained by successful prophylaxis by antibiotics or polysaccharide vaccine, it is possible that people with asplenia were poorly recorded. Therefore the cost effectiveness of some of the described risk groups might have been underestimated, although sensitivity analyses showed that our conclusions remained valid when we increased the incidence. Also, the future incidence of pneumococcal disease due to vaccine serotypes may be affected by changes in the epidemiology of viral respiratory tract infections, such as happened with pandemic A/H1N1 2009 influenza[218]. This caused a noticeable increase in IPD in the age groups with the highest incidence of H1N1 infection[218], and, given the overlap between the risk groups for influenza and IPD, selective vaccination of high risk groups PCV13 might help mitigate the effects of future increases in such viral infections.

Comparison with other studies

This is the first cost effectiveness analysis of PCV13 focusing specifically on people at increased risk for IPD. As far as we know, two other studies have focused on the cost effectiveness of vaccinating non–infant populations[129,216]. A main difference is that these studies focused on older adults (>50 years[216] and 65 years[129]), whereas our study specifically focused on risk groups of people aged 2 years and older. Both these studies showed that for these specific age groups a vaccination programme could be considered cost effective, whereas we in the base–case analysis conclude that a vaccination programme is unlikely to be considered cost effective. The main driver for this difference is that in the base case analysis we assumed that PCV13 would not have an overall impact on non–bacteraemic pneumonia. This difference was further driven by the assumption that PCV13 would not be effective against serotype 3, as early data from England and Wales suggests that this component of PCV13 does not seem to provide direct protection to vaccinated people[206]. However, this assumption was based on a few cases of invasive disease due to this serotype in children in England and Wales and future data are necessary to answer the outstanding question on the efficacy of this serotype.

Other differences between our study and these two age based studies are that we had detailed data on the risk of disease, the life expectancy of high risk populations, and specific costs per IPD episode available, all based on primary data as opposed to estimates from the literature or databases. Furthermore, compared with the Dutch study we were able to explicitly take herd effects

into account for the unvaccinated population as recent data has become available that could be used for the prediction of these effects[36].

We showed in the current study that these herd effects have a major impact on cost effectiveness. It is desirable that specific cost effectiveness studies from a European perspective become available to guide decision making in European countries rather than using cost effectiveness estimates from the United States. Previous decisions to introduce the infant pneumococcal vaccination programmes in European countries largely relied on herd immunity estimates from the United States that were subsequently shown not to be applicable elsewhere[3].

Implications and future research

We found that the cost effectiveness of a PCV13 risk group based programme will mainly depend on the time of using the vaccine and its effectiveness, in particular against non–bacteraemic pneumococcal pneumonia. Since most countries have replaced PCV7 with PCV13, herd effects are likely to decrease the burden of preventable pneumococcal disease over time rendering any additional preventive efforts less cost effective. If PCV13 does protect against non–bacteraemic pneumococcal pneumonia in high risk groups the programme may be cost effective if introduced early enough before the full effect of herd immunity is manifested, or if the expected herd immunity effect is less than expected. Policy makers may prefer to delay any decision about the use of PCV13 in high risk groups until the results of the trial currently being done in the Netherlands to assess its efficacy against non–bacteraemic pneumonia in elderly people are available[168]. However, such a wait and see policy would possibly reduce the need for the additional vaccination effort. Another option for governments to consider would be sharing the risk with the manufacturer; on the basis of the uncertainty around the cost effectiveness a price reduction could be negotiated that remains valid until the data on efficacy become available. The implementation of a risk based PCV13 programme in the United Kingdom has been considered by the UK Joint Committee on Vaccination and Immunisation, with the final decision being not to introduce such a programme largely dependent on the outcome of our study[219]. As many other European countries lack the various high quality epidemiological data sources available in the United Kingdom or lack the statistical power owing to their population size to conduct their own analyses this study will also provide them with important evidence. Specific cost effectiveness ratios cannot directly be extrapolated from England to other countries but we believe that the general conclusion is informative for those countries that introduced PCV13 around the same time and have a similar uptake of vaccination. Some European countries are, however, already recommending PCV13 for at risk groups or adults. For example, in Austria and Greece PCV13 is recommended for those aged 50 and older[220,221], whereas in France, parts of Germany, and Italy the vaccine is being recommended for (specific) risk groups[222,223].

Finally, we note that in addition to considerations about cost effectiveness, decision makers need to estimate carefully the possible uptake of vaccination, considering the potentially large impact on budgets of a risk based PCV13 programme.

Appendixes are online available at:
http://www.bmj.com/highwire/filestream/611293/field_highwire_adjunct_files/0

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The role of Streptococcus pneumoniae in community–acquired pneumonia among adults in Europe: a Meta–Analysis

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ABSTRACT

Objective: The primary objective of this meta–analysis was to estimate the prevalence of adult community–acquired pneumonia (CAP) caused by *Streptococcus pneumoniae* in Europe, adjusted for possible independent covariates.

Methods: Two reviewers conducted a systematic literature search using PubMed on English–language articles that involved human subjects with CAP during the period from January 1990 to November 2011 across European countries. A mixed–effects meta–regression model was developed and populated with 24,410 patients obtained from 77 articles that met the inclusion criteria.

Results: The model showed that the observed prevalence of *S. pneumoniae* in CAP significantly varies between European regions even after adjusting for explanatory covariates, including patient characteristics, diagnostic tests, antibiotic resistance, and health–care setting. The probability of detecting *S. pneumoniae* was substantially higher in studies that performed more frequently a diagnostic PCR assay compared to all the other diagnostic tests included. Furthermore, *S. pneumoniae* was more likely to be confirmed as the cause of a CAP in studies with ICU patients as compared to those with hospital or community treated patients.

Conclusion: This study provides estimates of the average observed prevalence of *S. pneumoniae,* which could be used for projecting the health and economic benefits of pneumococcal immunization.

INTRODUCTION

Community–acquired pneumonia (CAP) is a common disease, with an annual incidence of 5 to 11 cases per thousand adults in Europe and Northern America[224]. *Streptococcus pneumoniae* is generally accepted to be the most common cause of CAP[163,164,225]. There is, however, no consensus regarding the prevalence of *S. pneumoniae* in CAP, and estimates vary from 5% to 60% between different studies[163,164,225]. This may either reflect a true difference or, rather, a difference in confirmation rates. Two earlier reviews, which focused on the causative agents of CAP, suggested that the frequency of *S. pneumoniae* differs between countries[225] and health–care settings[164]. However, large variations between studies within the same setting and country were observed, suggesting that these differences could be more related to the study methodology than to real differences[164]. Another factor which might have impacted the findings of the previous reviews is that the investigators also included studies in which radiographic confirmation of pneumonia was not an inclusion criterion. As a consequence, part of the study patients can be expected to have had respiratory tract infections other than pneumonia, or entirely other conditions, and the respiratory pathogens detected in those cases might not be relevant to describe the relative contribution of *S. pneumoniae* in CAP[226].

It is important to have a reliable estimate of the share of *S. pneumoniae* in the total burden of CAP, especially now that the results of a clinical trial estimating the efficacy of the 13–valent conjugated pneumococcal vaccine (PCV13) in the elderly are pending and the country–specific health and economic impact of this vaccine will largely depend on the share of *S. pneumoniae* in CAP[129,168].

The primary objective of this meta–analysis is to estimate the average etiological fraction of *S. pneumoniae* in CAP while controlling for potential sources of heterogeneity attributed to regional, health care settings, and other differences.

METHODS

Search strategy and selection criteria

We used PubMed (www.pubmed.com) to search for original study reports during the period between January 1990 and November 2011 on the etiology of CAP among adults using the following search terms: *"Pneumonia" [MAJR] AND ("etiology" [Subheading] OR "epidemiology" [Subheading]) AND ("Pneumonia, Bacterial" [MH] OR "Pneumonia, Viral" [MH] OR "microbiology" [Subheading] OR "virology" [Subheading] OR "Streptococcus pneumoniae" [MH]) AND ("Adult" [MH] OR "aged" [MH]) AND ("Journal article" [PT] NOT "meta–analysis" [PT] NOT "review" [PT] NOT "guideline" [PT])*. We limited the articles to the English language. To ensure that articles actually dealt with the most accurate diagnostic definition of CAP, studies in which the CAP diagnosis was not confirmed with a new or increased infiltrate on a chest radiograph were excluded. Furthermore, we excluded (1) case reports, editorials, reviews, and letters without original data; (2) studies which focused primarily on pneumonia related to sources other than the community; (3) articles that included only specific patient groups such as patients with COPD; (4) studies performed during the 2009 influenza pandemic; (5) clinical trials; and (6) studies which did not report the fraction of CAP being caused by *S. pneumoniae*.

After applying these inclusion and exclusion criteria, the titles of all potentially eligible articles were independently reviewed by two investigators (MHR and EH). Articles were excluded from further review only if both investigators agreed on one or more reasons for exclusion. If a study was not excluded on the basis of the title, the study abstract was reviewed independently by both investigators. Subsequently, all articles judged to meet the inclusion criteria based on the reviewed abstract were retrieved for further evaluations. After reviewing the entire text of the retrieved papers, only those that met all inclusion criteria were included in the analysis and the relevant data were extracted (see below).

Data Extraction

Two reviewers independently extracted the total number of CAP episodes and the number of CAP episodes in which *S. pneumoniae* could be detected. A CAP episode was assumed to be caused by *S. pneumoniae* if it was detected in a normally sterile site, in the nasopharynx, or in sputum. We also recorded the type of diagnostic tools applied and distinguished them between culture, serological or PCR tests, or more invasive sampling methods. Culture tests were subdivided into those performed on either sputum or blood. Serological tests were separated into tests performed on urine and those performed on blood and sputum. More invasive sampling methods included trans–thoracic needle aspirations and bronchoscopic techniques.

Further, the following study–specific data were extracted: health–care setting, country and time period, age (mean or median if the mean is not reported), gender distribution, percentage of included patients with COPD and patients with severe immunosuppression (including patients with organ transplants, HIV/AIDS, chemotherapy and chronic corticosteroids use of >20mg/day). The health–care setting was divided into three distinctive groups: (1) cases managed in primary care; (2) cases admitted to hospital; and (3) cases admitted to the intensive care unit (ICU). Four different geographical regions were defined based on the United Nations geoscheme (North, East, South, and West)[227].

Also, country–specific antibiotic use and resistance of *S. pneumoniae* to antibiotics might have an impact on the observed prevalence of the respiratory agents[228]. To take antibiotic use into account, we used the defined daily dose of outpatient antibiotics (antimicrobials for systemic use, ATC Group J01) per 1,000 inhabitants as reported by Muller *et al* for the year 2002[229]. Since only reimbursement data were available for Spain, we corrected the number of doses upwards to correct for the fact that over–the–counter antibiotic use in Spain stands at around 30% [228]. The *S. pneumoniae*–specific level of antibiotic resistance was based on the percentage of penicillin non–susceptibility using 2010 data of the antimicrobial resistance surveillance in Europe[230] and other sources for Switzerland[231] and Greece[232]. Although shifts in the use of antibiotics and related resistance might occur, it has been shown that antibiotic use and resistance in the selected countries remained quite stable over time[228-230,233].

Statistical Methods

In order to synthesize the collected evidence, we used a meta–regression model framework for binomial outcomes[234]. Given the large expected true variation of prevalence between studies, we decided to use a mixed–effects instead of a fixed–effects meta–regression framework[235]. In this specification, we assumed that the covariate–adjusted log odds of an *S. pneumoniae*–induced CAP is not constant but varies randomly across studies. We further assumed that the additional, study–specific random effects follow a normal distribution with zero mean and variance σ^2_{Study}. It was also assumed that the measure of association between the log odds of an *S. pneumoniae*–induced CAP and countries is random and normally distributed with mean zero and variance $\sigma^2_{Country}$. Additionally to these random effects, the model was corrected for a number of study–and country–specific covariates which were incorporated as fixed effects. From the full set of covariates we sub–selected those that significantly improved the fit of the model. We fitted a variety of models with different covariates included and compared their goodness of fit using the Akaike information criterion (AIC) in order to arrive at the final set of covariates[236,237].

Missing values in the covariates used were handled through multiple imputation[238,239]. We created twenty–five imputed datasets, in each of which every missing value was replaced with a plausible value estimated through a regression model. Next, the meta–regression framework described above was applied for every dataset. The results were subsequently synthesized for statistical inference. All statistical analyses were implemented using the statistical software R (version 2.13.2) [240]. We additionally used the "mi", "lme4", and "meta" R packages for the implementation of multiple imputation, the estimation of the mixed–effects meta–regressions and the visualization of the results, respectively[239,241].

RESULTS

Search results

Of the 3,738 original citations, we excluded 3,290 (88%) based on a review of the titles (Figure 1). Of the remaining 448 selected studies, 277 were excluded after reviewing the abstract. After reviewing the entire text of the remaining 171 studies 73 met eligibility criteria. In addition to the, 73 studies included by the initial search term, four more were identified by scanning of references and subsequently added, resulting in a total of 77 included studies[13,176,177,202,203,226,242-312]. Several studies reported data separately for health–care settings. These studies were, therefore, split into setting–specific "sub–studies" in this analysis.

Study characteristics

The characteristics of the 77 selected studies are presented in Table 1. Of all (sub–) studies included, the majority reported cases admitted to hospital (n=60), 17 were available for cases admitted to the ICU, and 14 for cases managed in the primary care. A total of 24,410 patients were included with an average age of 62.1 years, with 62.3% being male. Most of the studies originated from Southern Europe, with Spain being the most frequently represented country. No studies were found for Eastern Europe. In Figure 2, the crude proportion of *S. pneumoniae* per country is presented.

Table 1. Basic study characteristics of the (sub–) studies included into the mixed–effects logistic regression[$].

First author and reference	Study start and end (year)	Country	European region	Setting	Average Age*	Sex* (% male)	Antibiotic resistance level (%)[#]
Ewig *et al*[242]	1999–2000	Germany	Western	Hospital	68	62	3.7
Ewig *et al*[286]	1985–1993	Germany	Western	Hospital	51	67	3.7
Kruger *et al*[287]	2002–2007	Germany	Western	Community	62	55	3.7
Kruger *et al*[287]	2002–2007	Germany	Western	Hospital	62	55	3.7
Steinhoff *et al*[288]	1991–1992	Germany	Western	Hospital	57	62	3.7
Blanquer *et al*[290]	1985–1986	Spain	Southern	Community	41	70	29.8
Blanquer *et al*[290]	1985–1986	Spain	Southern	Hospital	60	70	29.8
Briones *et al*[291]	2000–2004	Spain	Southern	Hospital	66	64	29.8
Valencia *et al*[292]	1996–2003	Spain	Southern	Hospital	79	69	29.8
Valencia *et al*[292]	1996–2003	Spain	Southern	ICU	79	75	29.8
Cilloniz *et al*[279]	1996–2008	Spain	Southern	Community	66	63	29.8
Cilloniz *et al*[279]	1996–2008	Spain	Southern	Hospital	66	63	29.8
Cilloniz *et al*[279]	1996–2008	Spain	Southern	ICU	66	63	29.8
Falco *et al*[280]	1988–1989	Spain	Southern	Hospital	56	100	29.8
Falguera *et al*[281]	1997–2000	Spain	Southern	Community	51	57	29.8
Garcia–Ordonez *et al*[282]	1996–1998	Spain	Southern	Hospital	76	58	29.8
Garcia–Vazquez *et al*[283]	2003–2003	Spain	Southern	Hospital	63	66	29.8
Garcia–Vidal *et al*[284]	1995–2005	Spain	Southern	Hospital	65	68	29.8
Gomez *et al*[285]	1991–1994	Spain	Southern	Hospital	58	67	29.8
Gutierrez *et al*[303]	1999–2001	Spain	Southern	Community	57	63	29.8
Gutierrez *et al*[303]	1999–2001	Spain	Southern	Hospital	57	63	29.8
Lorente *et al*[304]	1996–1998	Spain	Southern	Hospital	62	61	29.8
Martinez Moragon *et al*[305]	2003–2003	Spain	Southern	Hospital	73	45	29.8
Menendez *et al*[306]	1996–1997	Spain	Southern	Hospital	62	63	29.8
Molinos *et al*[307]	1991–1994	Spain	Southern	Hospital	58	79	29.8
Molinos *et al*[308]	2003–2004	Spain	Southern	Hospital	67	68	29.8
Sopena *et al*[309]	1994–1996	Spain	Southern	Hospital	54	73	29.8
Pachon *et al*[310]	1985–1987	Spain	Southern	ICU	57	67	29.8
Pareja *et al*[311]	1989–1991	Spain	Southern	Hospital	57	67	29.8
Querol Ribelles *et al*[312]	2000–2003	Spain	Southern	Hospital	71	71	29.8
Rello *et al*[293]	1991–1992	Spain	Southern	ICU	72	65	29.8
Rello *et al*[294]	1993–1999	Spain	Southern	ICU	61	79	29.8
Rello *et al*[295]	1988–1990	Spain	Southern	ICU	45	76	29.8
Riquelme *et al*[296]	1993–1994	Spain	Southern	Hospital	79	67	29.8
Ruiz–Gonzalez *et al*[297]	1993–1994	Spain	Southern	Hospital	51	62	29.8
Ruiz–Gonzalez *et al*[297]	1993–1994	Spain	Southern	Community	51	62	29.8
Sorde *et al*[298]	2007–2008	Spain	Southern	Hospital	64	67	29.8
Torres *et al*[299]	1984–1987	Spain	Southern	ICU	53	77	29.8
Zalacain *et al*[300]	1997–1997	Spain	Southern	Hospital	76	63	29.8
Howard *et al*[202]	1999–2000	UK	Northern	Hospital	NS	NS	3.1
Lim *et al*[203]	1998–1999	UK	Northern	Hospital	65	51	3.1
British Thoracic Society[301]	1987–1987	UK	Northern	ICU	54	57	3.1
Venkatasan *et al*[302]	1987–1988	UK	Northern	Hospital	NS	52	3.1
Woodhead *et al*[273]	1988–1989	UK	Northern	Hospital	NS	55	3.1
Boersma *et al*[176]	1987–1989	Netherlands	Western	Hospital	59	64	2.0
Boersma *et al*[274]	1988–1992	Netherlands	Western	Hospital	52	60	2.0
Bohte *et al*[177]	1991–1993	Netherlands	Western	Hospital	NS	58	2.0
Endeman *et al*[275]	2004–2006	Netherlands	Western	Hospital	63	62	2.0

Table 1. Basic study characteristics of the (sub–) studies included into the mixed–effects logistic regression[$]. *(Continued)*

First author and reference	Study start and end (year)	Country	European region	Setting	Average Age*	Sex* (% male)	Antibiotic resistance level (%)[#]
Holloway *et al*[276]	NS–1991	Netherlands	Western	Hospital	58	60	2.0
Templeton *et al*[277]	2000–2002	Netherlands	Western	Hospital	NS	71	2.0
Templeton *et al*[277]	2000–2002	Netherlands	Western	ICU	NS	71	2.0
Van der Eerden *et al*[13]	1998–2000	Netherlands	Western	Hospital	64	54	2.0
Vegalin *et al*[278]	1992–1996	Netherlands	Western	ICU	64	61	2.0
Fantin *et al*[264]	1995–1997	France	Western	Community	52	50	27.6
Fantin *et al*[264]	1995–1997	France	Western	Hospital	52	50	27.6
Georges *et al*[265]	1987–1995	France	Western	ICU	63	66	27.6
Leroy *et al*[266]	1987–1992	France	Western	ICU	63	63	27.6
Leroy *et al*[266]	1993–1994	France	Western	ICU	61	68	27.6
Moine *et al*[267]	1987–1989	France	Western	ICU	58	74	27.6
Paganin *et al*[268]	1995–2000	France	Western	ICU	55	84	27.6
Renaud *et al*[269]	2002–2003	France	Western	Community	71	64	27.6
Renaud *et al*[269]	2002–2003	France	Western	Hospital	71	64	27.6
Laurichesse *et al*[270]	1998–1999	France	Western	Hospital	67	53	27.6
Blasi *et al*[271]	1991–1993	Italy	Southern	Community	42	52	9.2
Blasi *et al*[271]	1991–1993	Italy	Southern	Hospital	42	52	24.4
Cosentini *et al*[272]	1992–1993	Italy	Southern	ICU	68	64	9.2
Farina *et al*[251]	1999–2000	Italy	Southern	Hospital	NS	NS	9.2
Guglielmo *et al*[252]	NS –1995	Italy	Southern	Hospital	63	62	9.2
Michetti *et al*[253]	1991–1992	Italy	Southern	Community	NS	43	9.2
Michetti *et al*[253]	1991–1992	Italy	Southern	Hospital	NS	70	9.2
Burman *et al*[254]	1982–1984	Sweden	Northern	Hospital	NS	52	3.8
Johansson *et al*[255]	2004–2005	Sweden	Northern	Hospital	61	51	3.8
Ortqvist *et al*[256]	NS –1987	Sweden	Northern	Hospital	62	43	3.8
Stralin *et al*[257]	1999–2002	Sweden	Northern	Hospital	0	53	3.8
Hohenthal *et al*[258]	1999–2004	Finland	Northern	Hospital	50	52	14.2
Jokinen *et al*[259]	1981–1982	Finland	Northern	Community	49	58	14.2
Jokinen *et al*[259]	1981–1982	Finland	Northern	Hospital	49	58	14.2
Beovic *et al*[260]	1999–2001	Slovenia	Southern	Community	45	62	15.5
Socan *et al*[261]	1996–1997	Slovenia	Southern	Hospital	57	50	15.5
Melbye *et al*[262]	1988–1989	Norway	Northern	Community	NS	46	15.5
Holm *et al*[226]	2002–2003	Denmark	Northern	Community	NS	58	3.6
Kirk *et al*[249]	1995–1996	Denmark	Northern	Hospital	NS	44	3.6
Ostergaard *et al*[250]	1988–1993	Denmark	Northern	Hospital	65	46	3.6
Leesik *et al*[263]	1996–1998	Estonia	Northern	Hospital	56	77	1.6
Genne *et al*[248]	1999–2000	Switzerland	Western	Hospital	68	57	9.3
Janssen *et al*[247]	1988–1989	Switzerland	Western	Hospital	85	36	9.3
Muller *et al*[246]	2002–2005	Switzerland	Western	Hospital	67	63	9.3
Muller *et al*[245]	2006–2008	Switzerland	Western	Hospital	73	59	9.3
Marques *et al*[243]	2004–2006	Portugal	Southern	ICU	63	74	14.7

$ When studies reported data separately for different healthcare settings, they were split into different sub–studies.

* When average age and sex was not provided across different health settings, the overall average corresponding estimates were used instead.

\# The level of *S. pneumoniae* antibiotic resistance was based on the percentage of penicillin non–susceptibility using the Clinical and Laboratory Standards Institute (CLSI) , the European Committee on Antimicrobial Susceptibility Testing (EUCAST), and national guidelines for clinical breakpoints [230].

NS=not stated

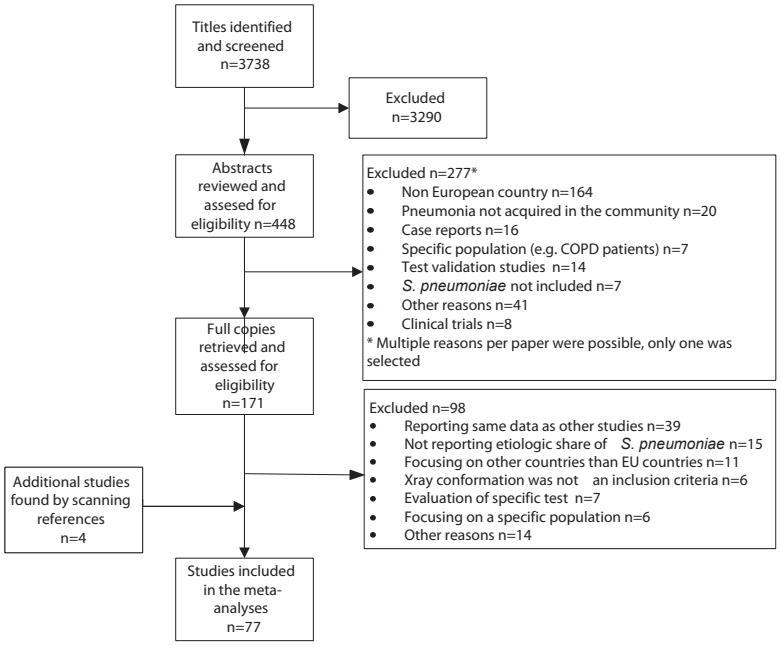


Figure 1. Flow diagram for the selection of studies.

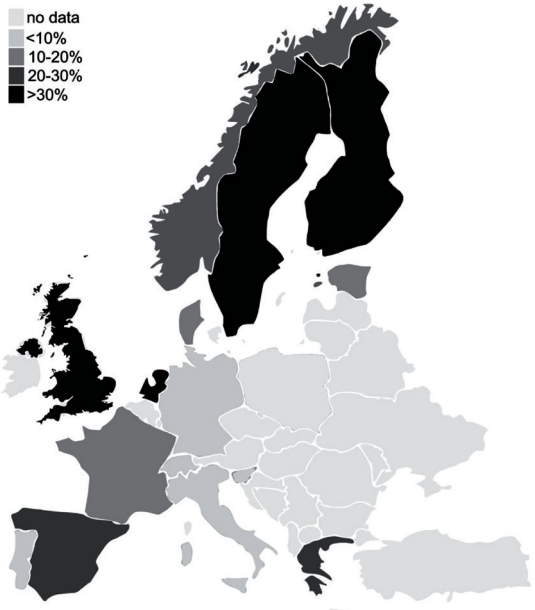


Figure 2. The country–specific, crude proportion of *Streptococcus pneumoniae* as a causative agent for community acquired pneumonia (CAP). Numbers of episodes per country: Germany (1783), Spain (12,804), UK (605), Netherlands (1318), France (2480), Italy (897), Sweden (892), Finland (688), Slovenia (325), Norway (19), Denmark (545), Estonia (439), Switzerland (1,464), Greece (88), Portugal (76).

S. pneumoniae

We identified 24,423 CAP episodes in 24,410 patients (patients could have more than one episode), of which 4,714 (19.3%) were attributed to *S. pneumoniae*. Figure 3 presents the unadjusted, study–specific proportions of *S. pneumoniae* as the causative agent for CAP, together with the proportions' confidence interval (CIs).

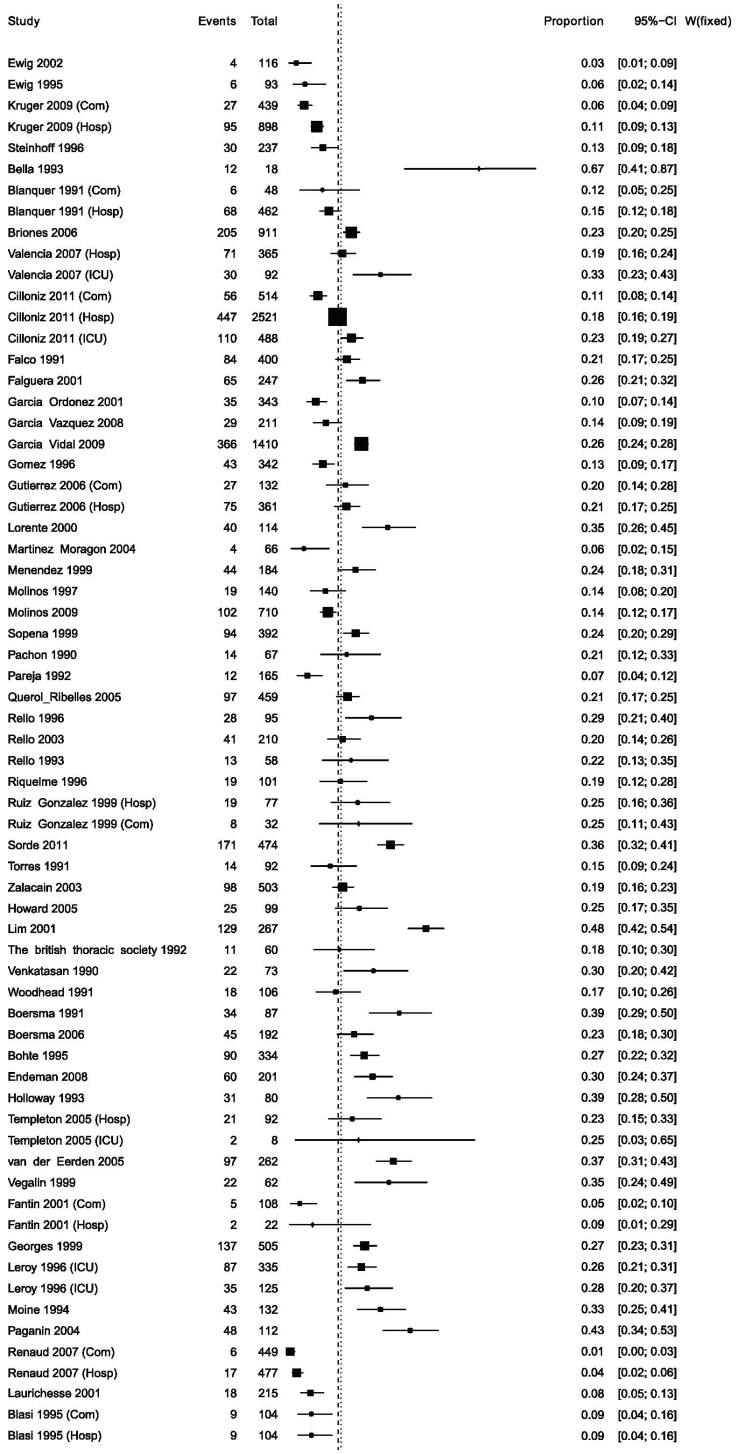
Mixed–effects meta–regression

The results of the final model, in which country and study were estimated as random–effects parameters and the rest of the covariates as fixed–effects parameters, are presented in Table 2. This model assumes as baseline a study with average proportion of blood cultures, urine serology, blood or sputum serology, and PCR tests. Additionally, this baseline study is assumed to originate from a Northern European country with average antibiotic resistance and with CAP episodes that were managed in primary care. Hence, the estimated odds of an *S. pneumoniae*–caused CAP for a study with baseline characteristics was 0.176, which corresponds to a probability of 0.15. The model also showed that, in studies in which the percentage of blood cultures, urine serology, blood or sputum serology, or PCR tests increased, the likelihood of detecting *S. pneumoniae* also significantly increased with the highest increase observed for PCR tests (odds ratio 2.49; 95% CI: 1.39–4.46).

Compared to studies with CAP episodes managed in primary care, the odds of *S. pneumoniae* being the cause of a CAP was 1.45 (95% CI: 1.19–1.77) times higher in studies with episodes treated in the hospital and 2.33 (95% CI: 1.80–3.02) times higher in the ICU. The odds of detecting *S. pneumoniae* as the cause of CAP in studies from Western and Southern Europe were almost two and three times smaller, respectively, compared to studies conducted in Northern Europe, where *S. pneumoniae* was the most frequently observed, independently of the percentage of diagnostic testing, [Western Europe: 0.57 (95% CI: 0.32–1.00); Southern Europe: 0.40 (95% CI: 0.2–0.80)]. Illustratively, a study with baseline characteristics but originating from Southern Europe is expected to identify *S. pneumonia*e as the causative agent in 6.5% of the CAP episodes (since (0.176*0.397)/(1+0.176*0.397)=0.065) .

The estimate of the variance for the study–and country–specific random effects indicated that there was significant heterogeneity among the estimates that was not captured through the fixed–effects covariates. The inclusion of both study–and country–specific random effects significantly improved the goodness–of–fit of the model.

Sputum culture and invasive detection techniques did not have a significant impact on the model or contributed to a better fit of the model to the study data, according to the AIC. Antibiotic resistance also did not significantly affect the probability to detect *S. pneumoniae*, after inclusion of the random–effects term for per–country variations. However, antibiotic resistance was deemed as being useful for the fit of the model and was, therefore, included in the analysis.


Study Events Total Proportion 95%−CI W(fixed)
Ewig 2002 4 116 0.03 [0.01; 0.09]
Ewig 1995 6 93 0.06 [0.02; 0.14]
Kruger 2009 (Com) 27 439 0.06 [0.04; 0.09]
Kruger 2009 (Hosp) 95 898 0.11 [0.09; 0.13]
Steinhoff 1996 30 237 0.13 [0.09; 0.18]
Bella 1993 12 18 0.67 [0.41; 0.87]
Blanquer 1991 (Com) 6 48 0.12 [0.05; 0.25]
Blanquer 1991 (Hosp) 68 462 0.15 [0.12; 0.18]
Briones 2006 205 911 0.23 [0.20; 0.25]
Valencia 2007 (Hosp) 71 365 0.19 [0.16; 0.24]
Valencia 2007 (ICU) 30 92 0.33 [0.23; 0.43]
Cilloniz 2011 (Com) 56 514 0.11 [0.08; 0.14]
Cilloniz 2011 (Hosp) 447 2521 0.18 [0.16; 0.19]
Cilloniz 2011 (ICU) 110 488 0.23 [0.19; 0.27]
Falco 1991 84 400 0.21 [0.17; 0.25]
Falguera 2001 65 247 0.26 [0.21; 0.32]
Garcia Ordonez 2001 35 343 0.10 [0.07; 0.14]
Garcia Vazquez 2008 29 211 0.14 [0.09; 0.19]
Garcia Vidal 2009 366 1410 0.26 [0.24; 0.28]
Gomez 1996 43 342 0.13 [0.09; 0.17]
Gutierrez 2006 (Com) 27 132 0.20 [0.14; 0.28]
Gutierrez 2006 (Hosp) 75 361 0.21 [0.17; 0.25]
Lorente 2000 40 114 0.35 [0.26; 0.45]
Martinez Moragon 2004 4 66 0.06 [0.02; 0.15]
Menendez 1999 44 184 0.24 [0.18; 0.31]
Molinos 1997 19 140 0.14 [0.08; 0.20]
Molinos 2009 102 710 0.14 [0.12; 0.17]
Sopena 1999 94 392 0.24 [0.20; 0.29]
Pachon 1990 14 67 0.21 [0.12; 0.33]
Pareja 1992 12 165 0.07 [0.04; 0.12]
Querol_Ribelles 2005 97 459 0.21 [0.17; 0.25]
Rello 1996 28 95 0.29 [0.21; 0.40]
Rello 2003 41 210 0.20 [0.14; 0.26]
Rello 1993 13 58 0.22 [0.13; 0.35]
Riquelme 1996 19 101 0.19 [0.12; 0.28]
Ruiz Gonzalez 1999 (Hosp) 19 77 0.25 [0.16; 0.36]
Ruiz Gonzalez 1999 (Com) 8 32 0.25 [0.11; 0.43]
Sorde 2011 171 474 0.36 [0.32; 0.41]
Torres 1991 14 92 0.15 [0.09; 0.24]
Zalacain 2003 98 503 0.19 [0.16; 0.23]
Howard 2005 25 99 0.25 [0.17; 0.35]
Lim 2001 129 267 0.48 [0.42; 0.54]
The british thoracic society 1992 11 60 0.18 [0.10; 0.30]
Venkatasan 1990 22 73 0.30 [0.20; 0.42]
Woodhead 1991 18 106 0.17 [0.10; 0.26]
Boersma 1991 34 87 0.39 [0.29; 0.50]
Boersma 2006 45 192 0.23 [0.18; 0.30]
Bohte 1995 90 334 0.27 [0.22; 0.32]
Endeman 2008 60 201 0.30 [0.24; 0.37]
Holloway 1993 31 80 0.39 [0.28; 0.50]
Templeton 2005 (Hosp) 21 92 0.23 [0.15; 0.33]
Templeton 2005 (ICU) 2 8 0.25 [0.03; 0.65]
van der Eerden 2005 97 262 0.37 [0.31; 0.43]
Vegalin 1999 22 62 0.35 [0.24; 0.49]
Fantin 2001 (Com) 5 108 0.05 [0.02; 0.10]
Fantin 2001 (Hosp) 2 22 0.09 [0.01; 0.29]
Georges 1999 137 505 0.27 [0.23; 0.31]
Leroy 1996 (ICU) 87 335 0.26 [0.21; 0.31]
Leroy 1996 (ICU) 35 125 0.28 [0.20; 0.37]
Moine 1994 43 132 0.33 [0.25; 0.41]
Paganin 2004 48 112 0.43 [0.34; 0.53]
Renaud 2007 (Com) 6 449 0.01 [0.00; 0.03]
Renaud 2007 (Hosp) 17 477 0.04 [0.02; 0.06]
Laurichesse 2001 18 215 0.08 [0.05; 0.13]
Blasi 1995 (Com) 9 104 0.09 [0.04; 0.16]
Blasi 1995 (Hosp) 9 104 0.09 [0.04; 0.16]

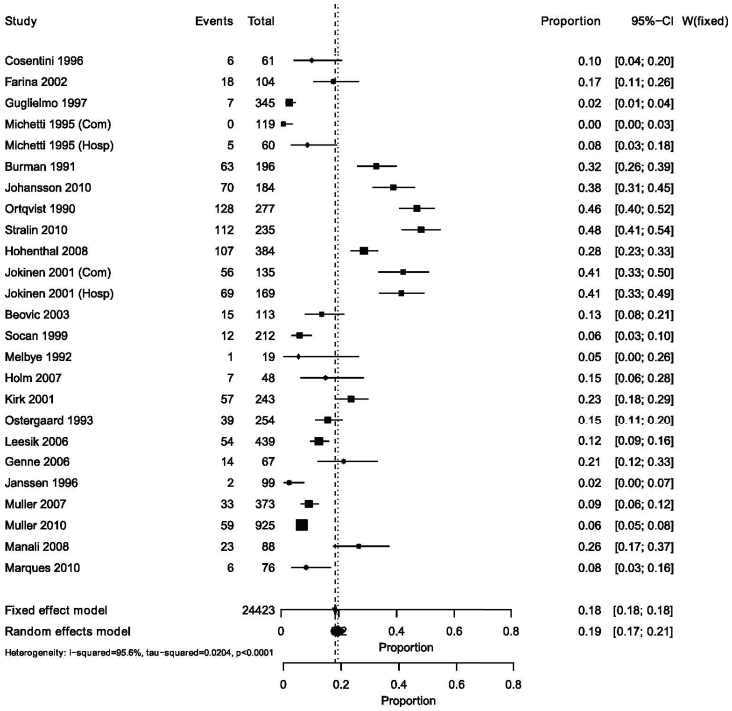


Figure 3. Forest plot showing the unadjusted proportion (with 95% confidence intervals) of *Streptococcus pneumoniae* as the causative agent for community–acquired pneumonia (CAP). CAP cases reported for different health settings are reported separately across studies.

Table 2. Mixed–effects meta regression model results.

	Odds ratios	Lower CI bound	Upper CI bound	*p*–value
Fixed effects estimates				
Intercept[1]	0.176	0.113	0.274	<0.001
Region				
Western Europe	0.565	0.32	0.998	0.048
Southern Europe	0.397	0.198	0.797	0.009
Health Care Setting				
Hospital	1.451	1.191	1.769	<0.001
ICU	2.334	1.804	3.021	<0.001
Blood culture (%)	1.782	1.002	3.17	0.048
Urine serology (%)	1.987	1.283	3.077	0.002
PCR (%)[2]	2.491	1.39	4.464	0.002
Blood or sputum serology (%)	1.836	1.114	3.023	0.017
Antibiotic resistance (%)	1.021	0.995	1.047	0.115
Random–effects estimates				
σ^2_{Study}	0.185			
$\sigma^2_{Country}$	0.094			

[1]Baseline study characteristics: region: Northern Europe; health care setting: primary care; average proportions of blood culture, urine serology, blood and sputum serology, and PCR testing, as well as average antibiotic resistance.

DISCUSSION

In this analysis, we showed that the observed prevalence of *S. pneumoniae* in adult CAP significantly varies between studies conducted in different European regions, even after correcting for effect modifiers, including diagnostic tests used, antibiotic resistance, and health–care setting. The probability of detecting *S. pneumoniae* was also substantially higher in studies that performed more frequently a diagnostic PCR assay compared to all the other diagnostic tests included. Furthermore, *S. pneumoniae* was observed less frequently in studies with CAP cases treated in the community as compared to those with cases treated in the hospital or in the ICU.

In contrast to earlier review studies on this topic, we approached the analysis of the observed frequency of *S. pneumoniae* among pneumonia cases through a mixed–effects meta–regression framework[164,225]. In this respect we not only accounted for the influence of various covariates on the observed prevalence of *S. pneumoniae*, such as the health–care setting, diagnostic tests used, and antibiotic resistance, but we also corrected for other study and country specific unobserved parameters that might also have an impact on this share. This correction revealed that significant unobserved variation exists among countries as well as across studies, regarding the observed share of *S. pneumoniae* in CAP.

The finding that this share differs across health–care settings was also noted previously by Woodhead[164], although this was accompanied with the remark that individual studies showed a wide variety in the frequency of detecting *S. pneumoniae*. Our findings agreed with those observed by Woodhead, but through the use of a meta–regression model and the inclusion of more recent studies, we were able to confirm significant differences that were independent of other covariates.

One of the limitations of the previous reviews was that they did not exclude studies in which a radiographic confirmation of pneumonia was not an inclusion criterion. Without a chest radiograph, a CAP diagnosis cannot be made with certainty[226]. Similar clinical signs and symptoms can also be caused by non–infectious diseases such as congestive heart failure or atelectasis[246]. Therefore, and because the interpretation of clinical assessments are prone to inter–observer variability, we only included those studies in which this was an inclusion criterion.

Our meta–analysis showed that in studies in which the percentage of invasive techniques or sputum culture increased, the likelihood of detecting *S. pneumoniae* did not significantly increase. This finding for invasive testing might be counterintuitive but can be attributed to the underreporting of the proportion of patients tested with this invasive method. In particular, almost all included studies report that invasive tests were performed, but the majority did not report the proportion of the patients tested. In most studies, the use of invasive techniques is likely to be limited to a few patients, as invasive sampling methods for lower respiratory secretions are impractical. This limited the accuracy of the estimate of the impact of invasive tests on detecting *S. pneumoniae*. A sub–analysis in the studies that reported the fraction of invasive testing revealed that the percentage of invasive tests performed had a significant, positive impact on the study's detected fraction of *S. pneumoniae* in CAP (data not shown).

Of course, our study also has some limitations, which can be divided into those related to health–care setting, populations, epidemiological, study methodological, and model–related factors[164]. Our model showed that *S. pneumoniae* was more likely to be prevalent in CAP cases treated in the ICU as compared to those treated in the hospital or in the community. We do, however, note that admission criteria for hospitalization or ICU admission might differ between hospitals and countries and may not always reflect severity. For example, in Spain, many patients seek medical care directly from the emergency service of the hospital rather than after a visit to a primary care physician[281]. Nevertheless, some of the country variation on the detection of *S. pneumoniae* is expected to have been captured through the country–specific random–effects parameter.

Secondly, factors related to the population, such as antibiotic therapy, vaccination status, immunosuppression, and comorbid conditions, might impact the share of *S. pneumoniae* detected. We tried to obtain as much information on the included studies as possible in order to be able to correct for these factors. For example, we obtained information on the proportion of immunosuppressed patients and patients suffering from COPD. However, the fit of the model was best when these factors were excluded. This might be explained by the fact that different definitions of 'immunocompromised' among studies were used or that specific data were just not reported. Additionally, the country–specific random–effects term used in the model might have corrected for enough across–country variation, constituting these variables as redundant. Furthermore, to minimize heterogeneity between studies we decided to exclude clinical trials as patients enrolled in these studies differ from those encountered in daily clinical practice. Considering the long time–span of studies included into the model, we were unable to include PPV23 or influenza vaccination status, as country–specific vaccination coverage over time are not abundantly available. The impact of PPV23 vaccination is probably small as the uptake, the efficacy and the duration of protection of PPV23 are limited[20,21]. Although the influenza vaccine does not protect directly against pneumococcal pneumonia, viral infections may pave the way for pneumococcal infections[32]. We based the level of antibiotic resistance on recent antimicrobial resistance surveillance data[230]. Resistance levels may change over time, but we note that the resistance patterns of the most recent EARSS report[230] are very similar to the earliest EARSS report using data from 1999–2001[233].

Thirdly, epidemiological factors may change the share of *S. pneumoniae* cases. For example, the time of year might impact the frequency of *S. pneumoniae* detected. Most of the studies included in our analysis had a time span of over a year, which might have been long enough to capture the short–term seasonal effects.

Fourthly, methodological factors such as comprehensiveness of sample collection and microbiological investigation performed are important[164]. We explicitly took this into account by correcting for both the type of microbiological investigation performed, as well as for the frequency at which these tests were performed. As previously noted by Woodhead some studies did not explicitly state the percentages of actually performed tests[164].

Finally, a limitation of our analysis is the inability to accurately estimate the true prevalence of *S. pneumoniae* among CAP cases. The main reason for this is that the applied tests cannot detect the

true fraction of *S. pneumoniae* among the CAP cases, and, hence, the *S. pneumoniae* prevalence, due to their limited sensitivity and specificity. It is expected that there will be an undetected fraction of *S. pneumoniae* due to false negative tests, i.e., low sensitivity. However, this undetected fraction might be partly compensated by the false–positive tests, i.e., low specificity.

Recently, the European Commission extended the indication of PCV13 to adults aged 50 years and older to prevent invasive pneumococcal disease caused by *S. pneumoniae*. While there is currently no indication for non–invasive pneumonia, clinical trial data will become available soon[168]. Recent cost–effectiveness studies have shown that, next to the vaccine efficacy, the proportion of non–bacteraemic pneumonia due to *S. pneumoniae* is one of the key determinants of cost–effectiveness[129,313]. Our current study might, therefore, support the decision– making process of the introduction of PCV13[129,313].

In conclusion, our study provides estimates of the average observed prevalence of *S. pneumoniae*, which could be used for projecting the health and economic benefits of pneumococcal immunization.

Part II

Costs and effectiveness of extended vaccination strategies against pertussis

Modelling the impact of extended vaccination strategies on the epidemiology of pertussis

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De Vries R
Le HH
Postma MJ

Epidemiol Infect. 2011 Nov 24:1–12.

ABSTRACT

The aim of this study was to investigate the optimal pertussis booster vaccination strategy for the Netherlands. A realistic age–structured deterministic model was designed. Assuming a steady–state situation and correcting for underreporting, the model was calibrated using notification data from the period 1996–2000. Several sensitivity analyses were performed to explore the impact of different assumptions for parameters surrounded by uncertainty (e.g. duration of protection after natural infection, underreporting factors, and transmission probabilities). The optimal age of an additional booster dose is in the range of 10–15 years, and implementation of this booster dose will reduce both symptomatic and asymptomatic infections, although the incidence of symptomatic infections in older age groups will increase. The impact of the different assumptions used in the model was in general limited. We conclude that over a wide range of assumptions, an additional booster dose can reduce the incidence of pertussis in the population.

INTRODUCTION

Bordetella pertussis is a bacterium that causes the highly contagious respiratory disease pertussis, also known as whooping cough. Despite widespread vaccination, infection with pertussis remains endemic even in countries with high vaccination coverage[314-317]. Moreover, there has been a resurgence of pertussis in many countries during the past decade, particularly in adolescents and adults[314,317-320]. For example, in the Netherlands a clear increase in the incidence of pertussis was apparent from 1996 onwards despite a consistently high vaccine uptake[315,318]. Although infections in adolescents and adults are less severe than those in infants and young children, the increasing incidence in adolescents and adults is still a major concern because adolescents and adults are identified as important sources of transmission to young infants who are not yet vaccinated or only partially vaccinated[321-323]. Therefore, the addition of immunization strategies to the current childhood immunization programme should be considered not only to reduce the disease burden in adolescents and adults but also to prevent transmission of the infection to infants. Indeed, several countries (e.g., Australia, France, USA) have already incorporated adolescent booster doses into their national immunization programmes[324,325]. However, other countries such as the Netherlands, have not implemented adolescent or adult booster immunization programmes even though such programmes would potentially reduce the transmission of *B. pertussis* and potentially lower the incidence of pertussis in infants[323,326,327]. Therefore, the impact of additional booster dose(s) at later age(s) should be explored.

Mathematical models can be used to investigate, for example, the optimal age(s) of vaccination or the impact of different levels of uptake of the vaccine. During the last 10 years several studies have modelled the potential impact of additional booster doses[328-332]. Nevertheless, specific drawbacks make them inappropriate to use for decision making. For example, most studies did not (i) take into account underreporting (for adults), (ii) explore the impact on the epidemiological outcome of transmission–related parameters, or (iii) use contact rates based on 'real life' contact patterns. Also, our previous work had these limitations[329]. We have attempted to overcome these limitations through the use of a realistic age–structured deterministic model, programmed within an environment allowing for high–speed model runs, to determine the optimal vaccination strategy for reducing the number of infections in the population, and to explore the impact of different assumptions for parameters surrounded by uncertainty.

MATERIALS AND METHODS

Several analyses were performed to explore the impact of introducing different types of booster immunization programmes to the current Dutch vaccination strategy in which acellular vaccine formulations are used and infants receive three doses at the ages of 2, 3 and 4 months and booster doses at 11 months and 4 years. In particular, we focused on the optimal age of implementing a single additional booster vaccination. However, we also investigated other potential vaccination strategies to reduce the burden of disease in the youngest age groups such as providing a booster

dose every 10 years. Base–case, sensitivity and scenario analyses were performed. The base–case analysis represented the most plausible assumptions (described below) and was subsequently used as a baseline against which all other scenarios and sensitivity analyses were assessed. The dynamic model was programmed in Berkeley Madonna (R. I. Macey & G. F. Oster, UC Berkeley, CA, USA).

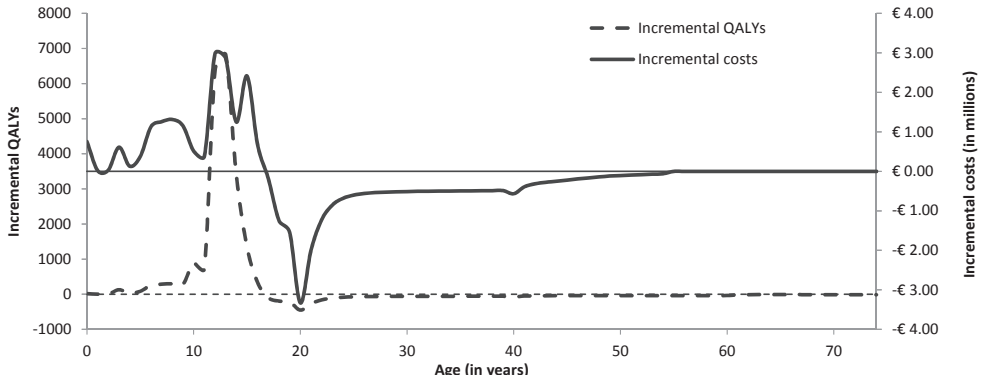

Figure 1. Graphical representation of the possible pathways within the model. The solid compartments represent the different pertussis epidemiological states. Solid arrows represent the flow between these states. Dashed lines and compartments represent events and pathways associated with vaccination.

Model structure

A schematic overview of the deterministic model used to assess the impact of various booster vaccination strategies against pertussis is shown in Figure 1, where mutually exclusive compartments represent the different epidemiological states of the disease and the arrows represent possible flows of individuals between the different states. Note that the underlying structure of the model is the same as our previously published stochastic model[329]. In the model all infants are born susceptible and then face age–specific risks of acquiring a pertussis infection as a result of contact with an infectious person. As shown in Figure 1, the model distinguished between three types of infections: (i) infections in immunologically naive individuals (henceforth called primary infections); (ii) infections in individuals whose immune system has been primed by vaccination or infection (breakthrough infections, sometimes known as 'recidive' infections); and (iii) asymptomatic infections (note that all primary and breakthrough infections were assumed to be symptomatic).

Individuals were assumed to be fully immune (i.e. immunity against transmission and disease) to subsequent infections following either vaccination or recovery from primary infection. Because of waning of immunity, these individuals will become partially immune (i.e. immunity against disease only). Partially immune individuals can acquire the pathogen but will not become ill and only experience asymptomatic infections (and transmit the pathogen). However, partial immunity also wanes with time. As a result, partially immune individuals will again become susceptible. These susceptible individuals are at risk of acquiring breakthrough infections, which were assumed to

be less severe than primary infections because the immune system had previously been primed. Furthermore, we assumed that partially immune and susceptible individuals can re–acquire full immunity as a result of contact with the pathogen through either vaccination or subsequent infection.

Disease characteristics

Although the duration of the infectious period is not precisely known and is likely to vary between individuals, it has been suggested to be dependent on the severity of the disease[329]. Based on expert estimations (see de Vries *et al*[329]), we assumed the average infectious period for individuals with primary infections, breakthrough infections, and asymptomatic infections to be 4 weeks, 3 weeks, and 1 week, respectively (see Table 1 for specific parameter values used)[329].

Similar to the duration of the infectious period, the duration of immunity after a natural infection is not precisely known. However, a recent review suggested that immunity after a natural infection wanes after 4–20 years[333]. Based on these data, we assumed in the base-case analysis that immunity after natural infection wanes after 12 years on average, with individuals being fully protected for 2 years and partially protected for 10 years.

Vaccine characteristics and vaccination schedules

Until 2001, the vaccination schedule in the Netherlands consisted of four doses (currently at ages 2, 3, 4 months and a booster at age 11 months) of the whole cell pertussis vaccine within the combination of diphtheria, tetanus and polio vaccine. From 2001 onwards, an additional acellular booster vaccination was given to 4–year–old children. Starting in 2005 the pertussis component in the combination vaccine was changed from the whole cell to an acellular vaccine. The efficacy of the whole cell pertussis vaccine was estimated at 89%[315,334-336]. Based on clinical trial data, we also assumed that the vaccine efficacy after vaccination in the first year, after booster vaccination at age 4 years[38,337], and after adolescent booster vaccination would be 89%[338-340].

In the model the vaccination scheme was divided into three parts: (i) the vaccinations administrated in the first year (including the first booster dose at age 11 months); (ii) a second booster dose at age 4 years; and (iii) potentially a third booster dose at age 12 years. After vaccination, we assumed that the fraction of the population, defined by coverage multiplied by efficacy, is effectively protected precisely after 4 months. Using a recent estimate for duration of immunity after vaccination with either whole cell or acellular vaccine of 4–12 years[333], we assumed that the immunity acquired by vaccination would be for 8 years, where individuals were fully and partially protected for 2 and 6 years, respectively. Note, that the duration of full immunity after vaccination is identical to the duration after natural infection, while the duration of partial immunity is 4 years shorter after vaccination compared to natural infection.

Based on the actual pertussis vaccination coverage of the Dutch national immunization programme, we applied a vaccine uptake of 96% for the three infant doses and the two booster doses (at ages 11 months and 4 years). Vaccine coverage of 70% was assumed for the adolescent

booster dose(s), which is much lower than the coverage for infants but is still higher than the uptake achieved in girls with the more controversial human papillomavirus vaccine in the Netherlands (50%). In the sensitivity and scenario analyses the vaccination coverage was varied over a much wider range.

Force of infection

The force of infection (FOI) is the rate at which susceptible individuals will be infected within a given time period. Age–dependent FOIs were estimated by using a method developed by van Boven *et al.*[336] (see Supplementary material). The main advantage of this method is that it is able to take different types of infection and waning immunity into account in a consistent manner[336].

Table 1. Epidemiological Data

Variable	Parameter (see also Figure 1)	Base–case value
Annual birth cohort	NA	100,000/75
Force of infection	λ (a)	Age dependent (see Supplement Figure 1)
Rate of recovery from primary infection	ρ_1	13.0 (yr^{-1})
Rate of recovery from breakthrough infection	ρ_2	17.4(yr^{-1})
Rate of recovery from asymptomatic infection	ρ_3	52.1 (yr^{-1})
Rate of loss of full immunity after primary infection	σ_{n1}	0.50 (yr^{-1})
Rate of loss of partial immunity after vaccination	σ_{n2}	0.17 (yr^{-1})
Rate of loss of full immunity after vaccination	σ_{v1}	0.50 (yr^{-1})
Rate of loss of partial immunity after breakthrough infection	σ_{v2}	0.10 (yr^{-1})
Fraction effectively protected by vaccination	V(a)[a]	Age dependent
Vaccination coverage first 4 doses	NA	0.96
Vaccination coverage booster at 12 years of age	NA	0.7
Vaccine efficacy[b]	NA	0.89

[a] (a) = age.

[b] We assumed that a certain fraction of the population (coverage ´ efficacy) is effectively protected precisely after 4 months for vaccinated infants and after 4 years for the first booster. The age of protection after the third booster was dependent on the age at which this dose was administered.

Because an additional booster dose at age 4 years was introduced in 2001, we assumed an endemic equilibrium from 1996 to 2000. For this period, average age–specific incidences were calculated based on case notification data after correction for underreporting[341,342]. Previously, it was estimated that the incidence of pertussis including very mild and asymptomatic cases in the Netherlands was more than 600 times higher than the notified cases for children and adults[342]. In particular, these age–specific Dutch ratios of underreporting were used to correct the number of notified cases[342]. We note that in reality there was probably no endemic equilibrium from 1996 to 2000[341]. Once the FOIs were estimated these were subsequently used to calculate age–specific transmission coefficients. The transmission coefficient denotes the probability that a contact

between a susceptible individual of a specific age and an infectious individual of a specific age leads to transmission. Since the transmission coefficients (β) can be expressed as a function of the number of infectious individuals at a given point in time, the contact function and FOIs, the transmission coefficients can be calculated once the age–specific FOIs are known. The contact function represents the number of contacts between an individual in one specific age group with an individual in another age group per unit of time. We applied the contact function for respiratory diseases in the Dutch population estimated by Wallinga *et al.*[343]. We assumed that the transmission probability would increase with severity of disease and assigned transmission probabilities of 1, 0.7, and 0.05 for primary (β primary), breakthrough (β breakthrough) and asymptomatic (β asymptomatic) infection, respectively[329] .

Population

Simulations were performed for a population of 100,000 individuals with a uniform age distribution (i.e. the age groups were equally sized). The population was divided into 86 age groups, represented by 1–month groups for the first year (0–11 months) and 1–year groups subsequently (1–74 years). The total population size remained constant because newborns entering the model were equal to individuals leaving the model from death (at the age of 75). To mimic reality, the model was started at the steady state of the 1996–2000 endemic period (t=-5 to -1) with a booster vaccination at age 4 years implemented in 2001 (t=0). Additionally, we assumed in the base–case analysis that a booster dose at age 12 years would be implemented in 2011 (t=10) and the impact of this booster vaccination on pertussis incidence and prevalence in the population was assessed over a time period of 35 years. All vaccinations were assumed to be administered at the start of a new year.

Sensitivity analysis and scenario analysis

In the base–case analysis we used the most plausible parameter assumptions. However, as many parameters are surrounded by some level of uncertainty, we performed several sensitivity analyses to explore the impact of this uncertainty on the epidemiological outcome (Table 2a). To explore the impact of vaccination coverage of the booster dose, coverage was varied over a range of 50–90% by increments of 10%. In addition, the impact of applying an alternative contact function based on data provided by Mossong *et al.*[344] was explored. The advantage of using the data of Mossong *et al.* is that it is more recent; however a disadvantage is the much smaller sample size compared to the data of Wallinga *et al.*[343]. Furthermore, the transmission probabilities of the different types of infections, the duration of protection after natural immunity, and the duration of infectiousness were varied[333]. Finally, as the real incidence of pertussis is surrounded by uncertainty, especially in adolescents and the elderly, the impact of lowering the underreporting factor by 25% or 50% was also investigated. In addition, scenario analyses were performed for several other vaccination strategies (Table 2b) including varying the age of the third booster dose between 5 and 35 years, using a combination schedule in which both adolescents (third booster dose) and adults (fourth booster dose) were vaccinated, and giving repeated booster doses every 10 years starting at age 10 years.

Table 2a. Sensitivity analyses performed on the base–case analysis

	Base Case	Sensitivity Analysis
Variation in the coverage of the booster dose	70%	50% to 90% (10%)
Contact function	Based on Wallinga *et al.*	Based on Mossong *et al.*
Different transmission probabilities $\beta_{primary}(a) : \beta_{residive}(a) : \beta_{asymptomatic}(a)$	1: 0.7: 0.05	1; 1; 0.05 1; 0.7; 0 1; 0.7; 0.10
Duration of protection after natural infection	12 (2+10) in years	8 (2+6) in years 16 (2+14) in years
Duration of infectiousness for primary, breakthrough and asymptomatic infections (in weeks)	4, 3, 1	2, 2, 1 3, 3, 1
Reducing the estimated underreporting factors	0%	25% 50%

Table 2b. Scenarios (Variations on base–case analysis)

Scenario´s	Age booster(s) (in years)
Current situation (without adolescent booster dose)	N.A.
Base Case	12 years
Age of the first booster dose (adolescent vaccination)	Between 5 and 35 years[b]
Combined adolescent (1 dose) and adult immunization (1 dose)[a]	Third booster dose between 10 and 18 years and fourth booster dose between 18 and 35 years[b]
A booster dose every 10 years starting at the age of 10 until age 60 years	10, 20, 30, 40, 50, 60, 70[b]

[a] All possible combination were investigated (applying a minimal period between the doses of at least 5 years, and assuming the youngest age at which a adolescent booster dose would be 10 years).

[b] A step size of 1 year was used.

RESULTS

Base–case analysis

The estimated impact of the implementation of two vaccination strategies, childhood boosters alone (at t=0) and childhood boosters in combination with an adolescent booster vaccination (at t=10), on primary, breakthrough and asymptomatic pertussis infections is shown in Figure 2 (note that not all of the axes start at 0). The additional adolescent booster dose resulted in reduction of all types of pertussis infections with the relative decrease being most apparent for primary pertussis infections.

Although a decrease in overall infection was observed, the impact of the adolescent booster dose largely differed between age groups (Table 3). The largest absolute reduction and the largest relative reduction in infections were observed for children (6–12 years) and adolescents (13–19 years). Furthermore, although the total number of symptomatic infections declined as a result of the adolescent booster vaccination, the incidence in the older age groups increased, illustrating an age shift induced by the adolescent booster dose.

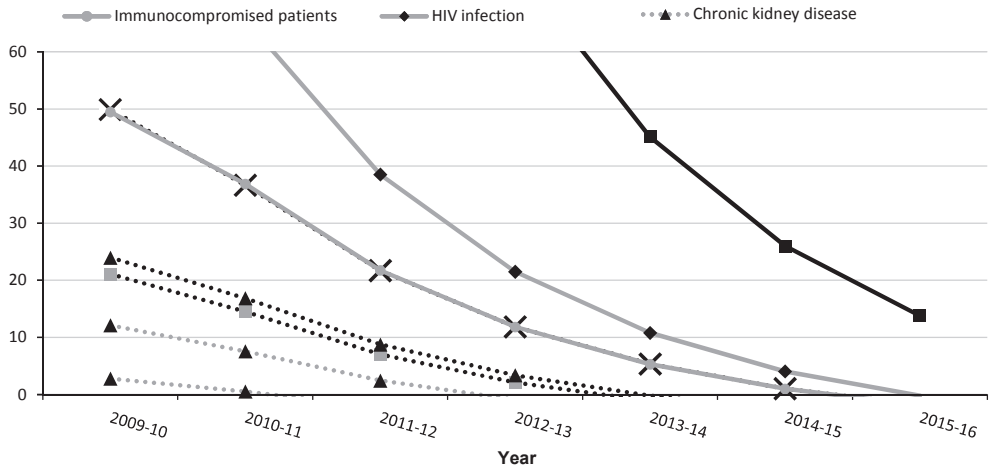

Figure 2. Pertussis incidence per 100,000 population per year applying base–case assumptions. The solid lines show the current situation after implementation of the booster dose at age 4 years (at t=0). The situation regarding adolescent vaccination after t=10 is represented by the dotted lines. Note that the y–axis does not start at 0 in all graphs.

Table 3. Total number of infections per age category per 100,000 population over a time period of 25 years (from t=10 [third booster dose] up to t=35 in model simulated time)

Age group in years	0	1–2	3–5	6–12	13–19	20–39	40–59	60–74	Total
Primary infections, booster at 4 years only (current approach)	1,851	403	10,512	3,999	1,628	8.55	0.00	0.00	983
Primary infections, booster at 4 and 12 years	1,750	381	9,982	3,332	798	9.47	0.00	0.00	821
Averted primary infections	**101**	**21.9**	**529.2**	**667**	**830**	**–0.92**	**0.00**	**0.00**	**163**
Averted primary infections (%)	**5.5%**	**5.4%**	**5.0%**	**16.7%**	**51.0%**	**–10.7%**	**0.00**	**0.00**	**16.5%**
Breakthrough infections booster 4 years only (current approach)	14.9	205	23,735	119,028	155,022	72,358	63,766	85,427	79,918
Breakthrough infections booster at 4 and 12 years	14.1	194	22,586	92,150	120,404	75,338	65,107	85,998	75,399
Averted breakthrough infections	**0.8**	**11.1**	**1,149**	**26,879**	**34,617**	**–2980**	**–1342**	**–572**	**4519**
Averted breakthrough infections (%)	**5.5%**	**5.4%**	**4.8%**	**22.6%**	**22.3%**	**–4.1%**	**–2.1%**	**–0.7%**	**5.7%**
Asymptomatic infections booster at 4 years only (current approach)	441.0	1,106	95,114	197,164	598,860	788,746	817,111	554,833	617,331
Asymptomatic infections booster at 4 and 12 years	416.9	1,045	90,155	156,964	554,735	776,179	808,193	548,523	602,269
Averted Asymptomatic infections	**24.1**	**60.9**	**4,959**	**40,200**	**44,124**	**12,567**	**8,919**	**6,310**	**15,062**
Averted Asymptomatic infections (%)	**5.5%**	**5.5%**	**5.2%**	**20.4%**	**7.4%**	**1.6%**	**1.1%**	**1.1%**	**2.4%**

Sensitivity analysis for base–case

The impact of the different sensitivity analyses on the total number of infections is shown in Figure 3. Overall incidence of all infections decreased with increasing coverage of the adolescent booster vaccine at age 12 years (Figure 3a). Furthermore, with increasing coverage, more primary and asymptomatic infections were averted in generally all age groups, while the shift in age of breakthrough infections became even more apparent.

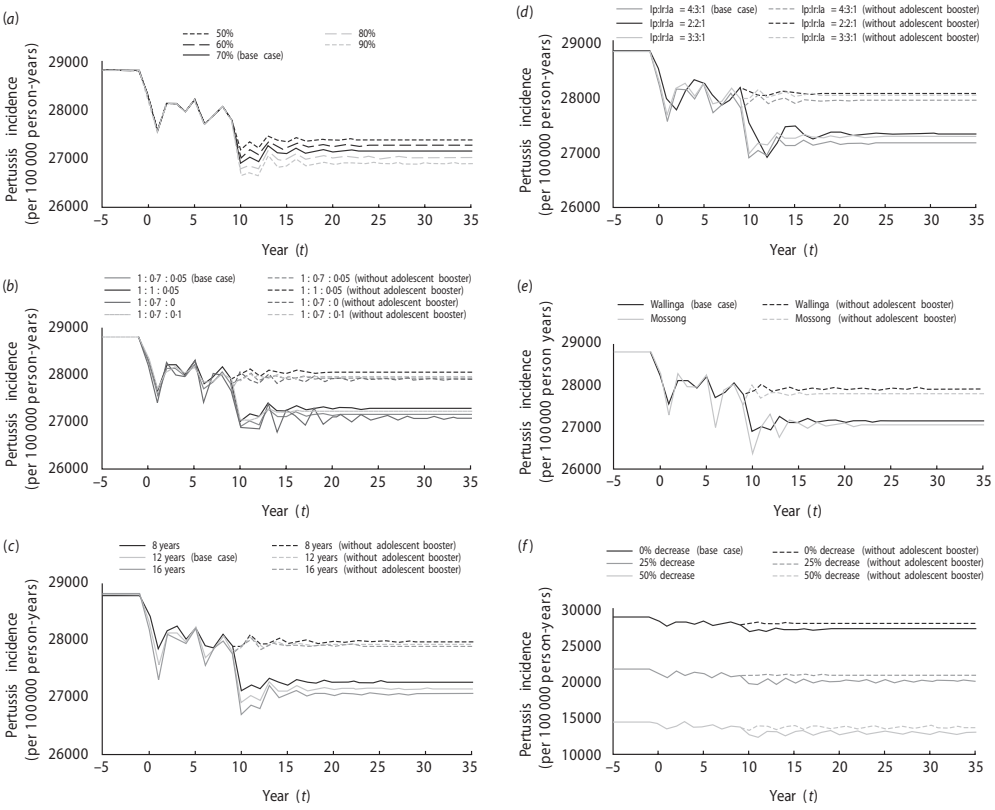

Figure 3. Results of the sensitivity analyses of the base–case scenario (as described in the Methods section and Table 2). (a) The impact of varying the uptake of the booster dose between 50% and 90% (70% in the base–case); (b) the impact of using different transmission coefficients; (c) the impact of assuming a different duration of protection after natural infection; (d) the impact of reducing the infectious period; (e) the impact of applying the contact function is reported by Mossong *et al.* is shown; (f) the impact of lowering the underreporting factor. Note that the y–axis does not start at 0 in any of the graphs.

Varying the transmission coefficients for the different types of infection resulted in a similar post–vaccination endemic equilibrium (Figure 3b). However, in the period between implementation of the booster dose and reaching the post–vaccination steady–state incidence (sometimes referred to as the post–honeymoon period), assumptions on the transmission coefficients, particularly for asymptomatic cases, had the most impact on overall pertussis incidence. For example, assuming

that asymptomatic cases do not transmit infection resulted in stronger annual fluctuations in the incidence of breakthrough and asymptomatic infections, whereas assuming that asymptomatic cases were more infectious than in the base–case analysis resulted in equilibrium being reached earlier.

Changing the duration of partial immunity after natural infection also did not have a considerable impact on the overall post–vaccination endemic equilibrium (Figure 3c). However, the incidence of break–through and asymptomatic cases differed substantially when the overall duration of protection was varied. The post–vaccination endemic equilibria for breakthrough and asymptomatic infections (per 100,000) were 4400 and 22,840 cases, respectively, assuming 6 years of partial protection, and 2360 and 24,660, respectively, assuming 14 years of protection. Nevertheless, the relative change in the number of cases was similar regardless of the duration of protection because, within the methodology used, the pre–vaccination pertussis incidence also differed proportionally to the post–vaccination endemic incidence. Shortening the infectious period for primary and breakthrough cases had almost no impact on the relative decrease of pertussis cases (Figure 3d). In terms of absolute cases it was estimated that for the scenario when the infectious period for both primary and asymptomatic cases was set at 3 weeks, <0.34 cases per 100,000 population could be averted compared to the base case, where this was 0.46 cases per 100,000 population when the infectious period was reduced to 2 weeks.

Using the contact function of Mossong *et al.*[344] instead of the contact function of Wallinga *et al.*[343], resulted in the prevention of slightly more asymptomatic cases, although slightly less breakthrough infections were averted resulting in an overall similar endemic equilibrium (Figure 3e). As expected, reducing the estimated underreporting factors resulted in lower total numbers of infections and in lower age–specific estimates of FOIs (Figure 3f, Supplementary Figure S1). Surprisingly, more pertussis cases were averted when the correction factor for underreporting was reduced by 25% compared to the base case, while slightly less cases were prevented when this factor was reduced by 50% compared to the base case.

Scenario analyses

The impact of varying the age of the third booster dose is shown in Figure 4. The optimal age of administering the third booster dose for the prevention of symptomatic cases was around 10 years, while the optimal age for the prevention of asymptomatic cases was around 12 years. The impact of adding a fourth booster was limited (data not shown). Nevertheless, the most effective combination strategy for the prevention of symptomatic cases would be an additional childhood booster dose at age 10 years and an adult booster dose at age 20 years. However, the optimal strategy for the prevention of pertussis would require a booster dose every 10 years, starting at age 10 years (Figure 5).

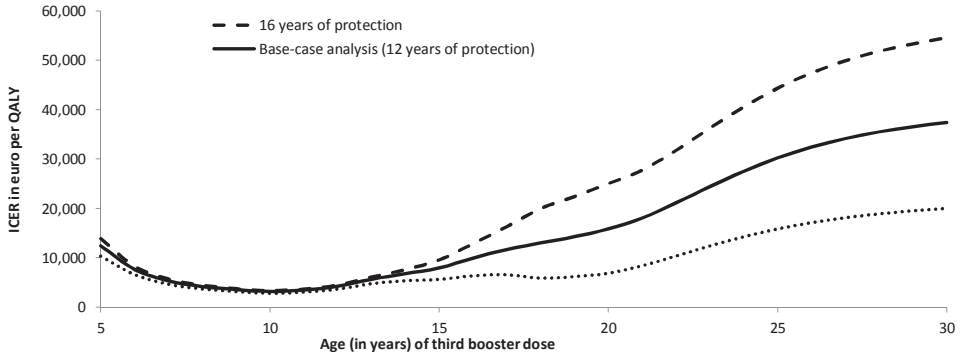

Figure 4. (a, b) Graphs showing the impact of varying the age of the third booster dose on the average number of symptomatic pertussis cases (solid lines) or asymptomatic pertussis cases (dashed lines) per age category per 100,000 populations over a time period of 25 years after the introduction of a third booster dose (t=10 in model–simulated time). Horizontal lines represent the number of symptomatic cases (solid lines) or asymptomatic cases (dashed lines) without a third booster dose; (a) The impact on children aged <3 years ; (b) the impact on the total number of infections in the population.

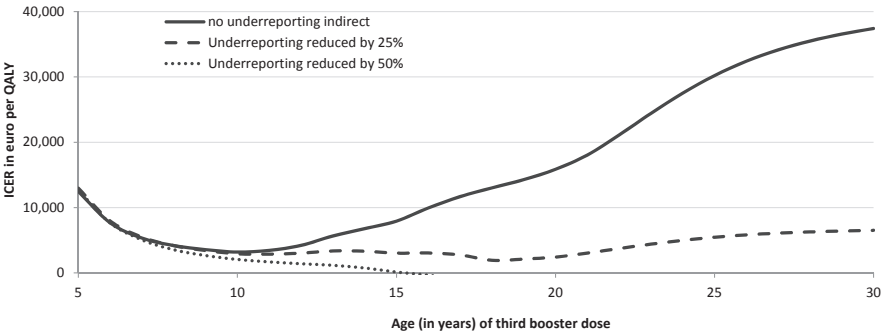

Figure 5. Pertussis incidence per 100,000 population per year showing the effect of a booster dose every 10 years (dashed–dotted line) compared to impact of the current situation (dashed line), the current situation combined with a potential single adolescent booster dose at age 12 years (dotted line, base–case analysis), and two additional booster doses at the ages of 10 and 20 years (solid line).

DISCUSSION

We have presented a realistic age–structured deterministic pertussis model, able to optimally use the scarce data on FOI and age–dependent fractions of symptomatic and notified cases. We have shown that, over a wide range of variations, an additional booster dose can reduce both the incidences of symptomatic and asymptomatic pertussis cases in the population. Furthermore, we propose that the optimal timing for the third booster dose in the Netherlands is between the ages of 10 and 15 years and that the optimal vaccination strategy would be a booster dose every 10 years. Notably, our results confirmed the epidemiological findings of a previous stochastic model in showing similar trends with respect to the prevention of pertussis cases and the induction of age shifts after the introduction of an additional adolescent booster dose[329].

The impact of applying different assumptions on the overall disease burden were limited, although some assumptions (e.g., the duration of protection of natural protection) did change the ratio of asymptomatic and breakthrough cases. Surprisingly, the impact of an additional booster dose on the total reduction of pertussis cases was larger when the underreporting factors was reduced by 25% from base–case level, while slightly fewer cases could be averted when the underreporting factors was reduced by 50% from base–case level. A possible explanation is that the infection pressure is so high in the base–case analysis that the impact of an additional booster dose will have only limited herd effects in the other unprotected individuals. More herd immunity effects may be observed if the FOI is lower (i.e. 25% or 50% lower underreporting), while on the other hand fewer cases can be prevented when the initial incidence is lower (50% lower underreporting).

Several recent modelling studies used a dynamic model to estimate the effect of additional booster doses on the epidemiology of pertussis[326,328-332]. Most of these studies used estimates for FOI

that were based on incidence data from England and Wales before the introduction of widespread vaccination. We used a method developed by van Boven *et al.*[336] to estimate specific Dutch FOIs which allowed waning of immunity and different types of infection to be taken into account. As a result, the FOI estimates of this study, corrected for age–specific underreporting and occurrence of asymptomatic infections, were consistently higher and of different shape than those previously reported[326,328,330-332].

Our model has a number of limitations. First, the method used to estimate the FOI assumed that the population is in endemic equilibrium during the period 1996–2000. Although we are fully aware that this assumption does not reflect reality, we believe that it still represents the best approach currently available and that deviations from the steady state would not relevantly change the findings and conclusions. Second, the estimated incidence during this period and the underlying underreporting factors are uncertain. Our estimates of the incidence of infection are higher than estimated previously by de Melker *et al.* for the period 1994–1996. This is because we used the incidence numbers of notified cases from 1996 to 2000 and increased these with age–specific underreporting factors from 1994 to 1996. As data from 1996 showed that the incidence was about six times higher compared to 7 years previously, our incidence estimates increased about sixfold[345]. As a result our model predicts that, on average, the entire population will be infected every 3 to 4 years, of which 88% will be asymptomatic. Nevertheless, as discussed above, when a lower overall incidence was applied, the number of averted cases increased when the under-reporting rate was lowered to 25% while only a slight decrease in the number of averted case was observed when the underreporting rate was lowered to 50%.

Similar to all previous modelling studies investigating the impact of additional pertussis booster doses[326,328-330,332] we did not include maternal immunity. Indirect evidence from before the introduction of widespread vaccination indicated that maternal antibodies provided some protection against mortality during the first month of life[346]. However, surveillance data after the introduction of widespread pertussis vaccination no longer show this relation between maternal antibodies and protection against pertussis[346]. Furthermore, as there is no serological correlate of protection for pertussis it is not possible to estimate the proportion of infants born with a protective level of maternal antibodies[346]. Therefore, we decided not to include maternal immunity in our model.

We used equally sized cohorts assuming a type 1 mortality, rather than the actual age distribution of the Netherlands. It has been argued in the literature that this approximation represents a valid approach for developed countries[347].

Last, it should be noted that an economic evaluation of our analyses in order to judge the attractiveness of the different strategies from the cost effectiveness perspective is warranted. The most cost effective strategy may certainly differ from the most optimal vaccination strategy (i.e. a booster dose every 10 years), in terms of primary and/or total cases averted. Thus, an economic evaluation, using the epidemiological results reported here, will be the next step in the evaluation of potential additional pertussis vaccination strategies in the Dutch context.

In conclusion, we designed an age–structured deterministic pertussis model with rapid simulation runs, which was used to explore the impact of various parameter assumptions and pertussis booster vaccination strategies on pertussis epidemiology. We showed that the optimum age of an additional booster dose is between ages 10 and 15 years, while the optimal vaccination strategy is a booster dose every 10 years. A sensible strategy representing a compromise between these two approaches may be booster vaccinations at 10 and 20 years.

Supplementary data
Supplementary data associated with this article can be found at:
http://journals.cambridge.org/ hyg.

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Cost–effectiveness of pertussis booster vaccination in the Netherlands

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ABSTRACT

The aim of the current study is to estimate the epidemiological and economical consequences of several extended pertussis booster vaccination strategies and to explore the impact of parameters surrounded by large uncertainty on the cost–effectiveness.

We developed an age structured transmission dynamic model to evaluate the impact of programs targeting (i) adolescents or adults using a single booster dose, (ii) a combination of adolescent and adult vaccination, and (iii) an every 10 years booster dose.

The base case analysis, that is a single adolescent booster administered at the age of 12 years, resulted in a reduction of pertussis infections. However, due to an increase in the number of symptomatic infections in adults, the benefits in terms of QALYs gained and costs saved in children were partly offset. Despite these negative indirect effects in the adult population, administering an additional booster dose could still be considered cost effective with an ICER of €4,200 per QALY gained. Combining an adolescent booster dose at the age of 10 (most cost–effective age for a single adolescent booster dose) with an adult (18–30 years) booster dose always resulted in favorable ICERs (<€10,000/QALY). Finally the every 10 year booster dose resulted in an ICER of €16,900 per QALY. The impact of different assumptions regarding the disease epidemiology, disease–related parameters, and vaccination program–related issues was limited.

To conclude, we show that extended pertussis booster vaccination strategies are likely to be considered as cost–effective.

INTRODUCTION

Pertussis, or whooping cough, is a contagious respiratory tract disease primarily resulting from infection with *Bordetella pertussis*. Pertussis continues to be a public health concern even in countries where a high vaccine coverage for infants and children is achieved[37]. In the past decade, an increase in the incidence has been observed in many developed countries combined with a shift in the incidence towards older age groups which may be related to increased awareness, changes in disease susceptibility and vaccine characteristics, shifting demographics, and genetic variations[348]. Although pertussis is more severe in infants and young children, the increasing incidence in adolescents and adults is a major concern as adults are an important source of transmission to infants, and infection in adults causes significant morbidity and high costs[349-351]. Therefore, extended immunization strategies targeting adolescents and adults should be considered. Several countries, including Australia, Canada, France, and Germany, have already incorporated adolescent booster doses into their vaccination programs[37]. The current Dutch pertussis vaccination schedule consists of three primary doses given at 2, 3, and 4 months and two booster doses given at 11 months and at the age of 4 years. An additional third booster dose could reduce the incidence of pertussis in the population[328,329,352]. However, next to the effectiveness of such programs, also the economical consequences of such programs should be taken into account, i.e., can such programs be considered cost–effective?

Several studies evaluated the cost–effectiveness of extended pertussis vaccination strategies, but most of them used static models[353]. However, as pertussis is a transmissible infectious disease, a dynamic model is required to fully take into account the transmission of the disease in the population[15]. Up to now, only two studies have used dynamic models to estimate the cost–effectiveness of extended pertussis vaccination schedules[328,329]. Although both studies provide plausible insights, they cannot be used for current decision making in the Netherlands. Firstly, because the only study that did focus on the Netherlands was unable to investigate the impact of multiple vaccination scenarios and the impact of different assumptions for parameters surrounded by uncertainty (e.g., duration of protection after natural infection, underreporting factors) due to long computational times[329]. Secondly, the other study focused specifically on the USA with limited options for transferability to other settings. In particular, whereas various vaccination scenarios were analyzed, no transmission related parameters were varied, underreporting for adults was not taken into account, and contact rates were not based on 'real life' contact patterns[328].

Therefore, the aim of the current study is to estimate the cost–effectiveness of several extended pertussis booster vaccination strategies and to explore the impact on the cost–effectiveness of different assumptions surrounded by uncertainty.

METHODS

In this study we compare the current Dutch pertussis vaccination programme (with doses provided at 2, 3, 4 and 11 months and 4 years) with different extended vaccination strategies. In the base–

case (1), representing the scenario in the Netherlands discussed by the Dutch Health Council, we explored the impact of a third booster dose provided at the age of 12 years. In addition to this, we also explore the following strategies:

1. a single (third) booster vaccination with a different timing (between the ages of 5 and 30);
2. a combination of an adolescent booster dose at the age when (1) is most cost–effective with an adult (18–30 years) booster dose (fourth booster dose); and
3. a booster dose every 10 years starting at the age of 10 until the age of 60 years.

Our model (programmed in Berkeley Madonna: R. I. Macey & G. F. Oster, UC Berkeley, CA, USA) consists of two parts: a dynamical transmission dynamic model used to predict the epidemiological impact of the different strategies and an economic analysis, which is integrated into the transmission model, allowing rapid analyses of the economic consequences of epidemiological trends. The epidemiological model and the economical data are described in details in the following section.

Epidemiological model structure

We used an age–structured transmission dynamic model to predict the impact of the extended pertussis programs as presented previously[329,352]. Briefly, the model distinguishes between three types of infections: (I) primary infections in immunologically naive individuals; (II) breakthrough infections in individuals whose immune system has been primed by vaccination or infection; and (III) asymptomatic infections (note that all primary and breakthrough infections were assumed to be symptomatic). Also, four types of immunity are specified: (1 & 2) fully immune (i.e., immunity against transmission and disease) by either vaccination or infection, and; (3 & 4) partially immune (i.e., immunity against disease only) by either vaccination or infection. All epidemiological assumptions and parameters were taken from the base–case analysis in Rozenbaum *et al.* unless stated otherwise[352] and are reported in Appendix 1. The model is able to capture effects at the population level, including herd protection and possible shifts in the average age of infection.

Economical data and QALYs

The analysis was performed from a societal perspective including both direct health care costs and indirect costs of production losses, updated to 2011 Euros when necessary (using the consumer price index from the Netherlands' Central Bureau of Statistics). Direct medical costs included in the analysis were those associated with vaccination, diagnostic procedures, hospitalization, prescribed medicines, prescription fee for the pharmacist, and GP consultation. Specific health quality (utility) scores were assigned to each health state in our model. Assumptions regarding both costs and quality of life are more thoroughly discussed in Appendix 2.

Sensitivity analysis

To test the robustness of the outcomes we performed several sensitivity analysis on various economical and the epidemiological parameters. In the univariate sensitivity analyses, all relevant parameters were varied by 25% to explore the impact of each parameter relative to each other.

Based on our previous modelling exercise[352], we decided to explicitly focus on the duration of protection after a natural infection and on the underreporting factors as these are extremely important to drive conclusions about the epidemiology of pertussis after the introduction of an additional booster[352]. Age–specific Dutch factors were used to calculate the incidence of unnotified cases given that it was estimated that the incidence of pertussis including (very) mild and asymptomatic cases in the Netherlands was more than 600 times higher than the notified cases for children and adults[342]. As these ratios are surrounded by uncertainty, especially for adolescents and elderly people, the impact of reducing the underreporting factors by 25% or 50% (ie, reducing the number of unnotified cases) was also investigated. The duration of protection after natural infection was assumed to be on average 12 years (fully protected for 2 years and partially protected for 10 years) in the base case scenario[333], similar to our previous estimate[352]. In one scenario, we reduced this period to 8 years (fully protected for 2 years and partially protected for 6 years) while in another scenario we increased it up to 16 years (fully protected for 2 years and partially protected for 14 years). Finally, the impacts of excluding direct costs, varying the vaccine uptake and the discount rates were explored.

Cost–effectiveness analysis

In the model, cohorts of 185,000 newborns, representing Dutch birth cohorts were followed, once using the current pertussis booster programme, and once with an extended pertussis vaccination programme implemented. In the model it was assumed that it would be possible to implement a potential booster in 2013. Finally, the time horizon used in the model was 25 years.

The model tracks the cases of infections, costs, life years (LYs) and quality–adjusted life years (QALYs). Summing all the costs, LYs and QALYs and consequently calculating the differences for the respective outcomes with and without the extended programme rendered net costs, LYs gained and QALYs gained. Dividing the net costs by either one of the health effects defined the incremental cost–effectiveness ratio. Future health effects and the costs of treatment were discounted according to the Dutch guidelines for cost–effectiveness research at 1.5% and 4%, respectively[142].

RESULTS

Result base case

The implementation of an adolescent pertussis booster dose resulted in a reduction of all types of pertussis infections with the relative decrease being most apparent for primary pertussis infections. In total 22,400 cases of primary infections, 628,200 of breakthrough and 2.1 million asymptomatic infections could be avoided (see Table 1). Around 25,200 QALYs could be gained in children. However, due to an increase in the number of symptomatic infections in adults and elderly as described previously in more detail[352], 4400 QALYs would be lost resulting in a net overall number of 20,800 QALYs. Similar to the QALYS, both the overall direct and indirect costs would increase in adults and elderly (see Figure 1). This increase in direct costs did only partially offset the savings obtained in

children. However, due to indirect costs, productivity losses in adults outweighs the limited benefits obtained by prevented cases in children (work loss due to mothers taking care of their children), there is a net overall increase in productivity losses. The total net costs of an adolescent booster program is €107.4 Million. Dividing the incremental costs by the incremental health benefits results in an incremental cost–effectiveness ratio of €5600 per QALY (undiscounted) or €4200 per QALY when discounted.

Table 1. Undiscounted base–case analysis results (numbers in thousands).

	Primary infections	Breakthrough infections	Asymptomatic cases	Cost of vaccination	Direct costs*	Indirect costs	QALYs
Without vaccination	135.9	11,088	85,640	736,592	28,387	1,189,260	289.1
With vaccination	113.5	10,460	83,523	844,006	26,821	1,199,390	268.3
Incremental effect	22.41	628.20	2,117	–107,414	1,567	–10,130	20.84

*Excluding vaccination costs

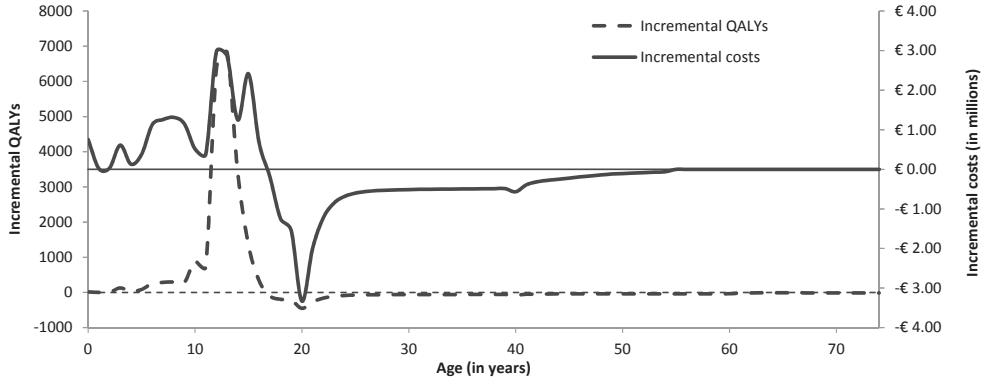

Figure 1. Age specific impact of a pertussis booster dose administered at the age of 12 years on the incremental QALY (dashed line) and total incremental costs (solid line). Horizontal lines show the zero axis for QALYs (dashed line) and costs (solid line).

Other vaccination strategies

Vaccination at the age of 10 years was the most cost–effective vaccination strategy (solid black line in Figure 2). Increasing the age of the third booster dose also gradually increased the ICER. Excluding indirect costs resulted in a slightly more favorable ICER when the third booster was given between the 12 and 14 years of age. However, if the third booster was provided from 15 years onwards, the inclusion of indirect costs would result in more favorable ICERs. Combining a third booster dose at the age of 10 with an adult (18–30 years) booster dose always resulted in favorable ICERs (<€10,000/QALY). Finally the every 10 year booster dose resulted in an ICER of €16,872 per QALY.

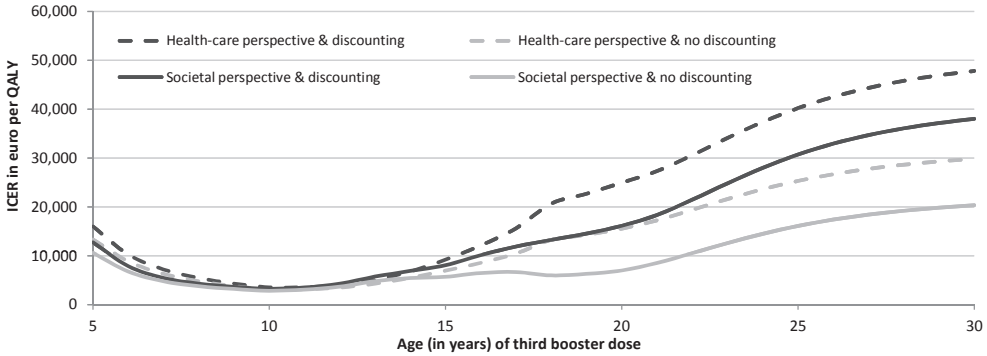

Figure 2. Impact of age of the third booster dose, discounting and indirect costs on the incremental cost–effectiveness ratio (ICER) in the base–case analysis. The solid black line shows the base–case ICERs (societal perspective combined with Dutch discount rates) while the dashed black line shows the ICERs from the health care perspective (ie only direct costs). The solid gray line shows the ICERs without discounting from the societal while the dashed gray line shows the ICERs without discounting from the health care perspective (ie only direct costs).

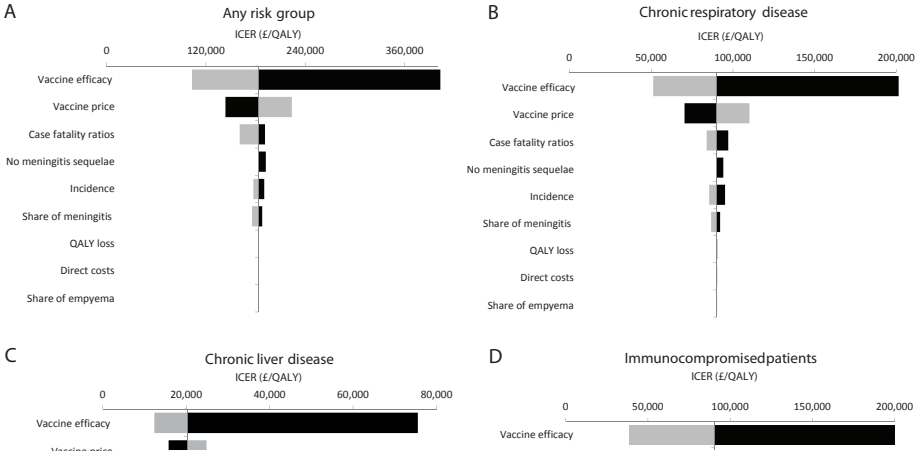

Figure 3. Sensitivity analysis on the base–case cost–effectiveness ratio. The parameters were varied by 25%. Dark bars show the ICER after a 25% decrease in the parameter (note that it was not possible to increase vaccine efficacy), whereas light bars show the ICER after a 25% increase. # cases notified but not hospitalized; QALY=Quality Adjusted Life Year; GP=General Practitioner

Scenario and sensitivity analyses

Apart from varying the vaccine efficacy of the booster dose, the QALY losses associated with unnotified pertussis cases and the vaccine price, the impact of the other parameters was very limited (see Figure 3). Varying the duration of protection after natural infection had only a negligible influence on the ICER when the third booster was given around the age of 12 (Figure 4). However, above the age of 15 a reduction in the duration of natural protection resulted in a more favorable ICER, while an increase resulted in a less favorable ICER as compared to the base case. Decreasing

the underreporting factor resulted in more favorable ICERs (Figure 5). In the base–case the impact of the vaccine uptake was very limited as the incremental costs of the booster programme linearly increased with the QALY gains (data not shown). This was related to the high pressure of infection which resulted in only minimal herd effects. The impact of the coverage was much larger when a booster dose was given every 10 years. Surprisingly, when health and costs were not discounted in the base-case analysis the ICER became less favorable, i.e., discounting made the ICERs more favorable.

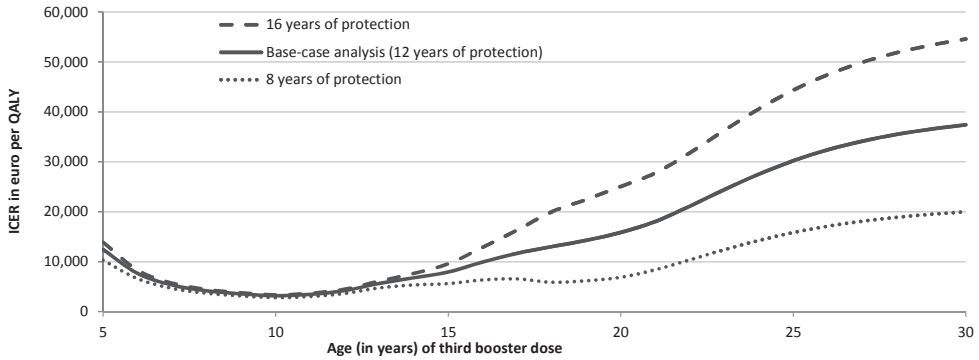

Figure 4. Impact of age and duration of natural protection on the incremental cost–effectiveness ratio (ICER). The solid line shows the ICERs for the base–case analysis (12 years of protection), the dotted line corresponds to the case of natural duration of 8 years of protection, and the dashed line corresponds to 16 years of protection.

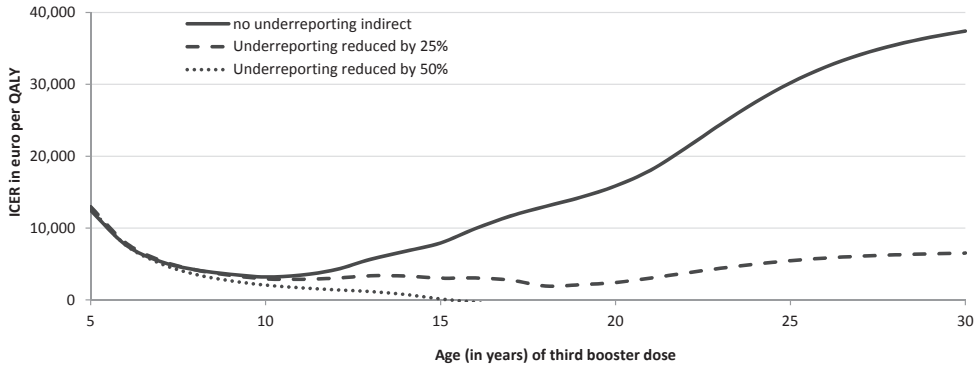

Figure 5. Impact of age and underreporting on the incremental cost–effectiveness ratio (ICER). The solid line shows the ICERs for the base–case analysis, the dashed line in case the underreporting factor is reduced by 25%, and the dotted line when the underreporting factor is reduced by 50%.

DISCUSSION

In this paper, we show that an additional booster dose against pertussis is likely to be considered as cost–effective by using an age–structured deterministic pertussis model integrated with a health economical model. Furthermore, by using this model we were able to show that the impact of different assumptions, regarding the disease epidemiology, disease–related parameters, and vaccination program–related issues, does not change the main result: vaccination is likely to be considered cost–effective.

Only two previous studies estimated the cost–effectiveness of an additional pertussis booster dose by using a dynamic transmission model[328,329]. The most recent model was also developed for the Netherlands, and was used to estimate the cost–effectiveness of an additional pertussis booster dose at the age of 12 years. It was a stochastic and individual–based model, while our model is a population–based model. The main advantage of our model is the running time, which made it possible to explore, within a reasonable time, the impact of different assumptions on disease epidemiology (e.g., underreporting factors), on disease–related parameters (e.g., duration of protection after natural immunity), and on vaccination program–related issues (e.g., age of the booster and vaccine uptake). Moreover, in this paper we used the most recent cost data available. Despite these differences both models showed that an additional booster dose at the age of 12 years can be labeled as cost–effective, as interventions with an ICER of less than €20,000/QALY are considered favorable in the Netherlands[43,47]. The second study[328] used a dynamical compartment model to estimate the cost effectiveness of pertussis vaccination strategies in the USA. This study showed that implementation of booster vaccination could be considered as cost effective or even cost saving. Unfortunately, this study did not take underreporting cases in adults into account, which could potentially overestimate the ICER as we showed in this paper. An advantage of the USA study was that it also modeled the impact of cocooning. That is protecting infants indirectly by vaccinating their parents. Unfortunately, specific household contact patterns for parents and infants were not available for the Netherlands which made it impossible to consider such strategy with our dynamic model. However, previous work based on a static model showed that cocooning was likely to be considered as cost–effective[354].

One of the advantages of our model was the possibility to investigate the impact of several scenarios. We showed that the impact of non–disease related parameters such as cost parameters and utility decrements had only a very limited impact on the ICER. Also, the impact of different disease related parameters was very limited. However, the impact of these parameters became more apparent with an increase of the age of the third booster. Surprisingly, discounting resulted in more favorable ICERs as compared to no discounting. The reason for this is related to the future increase in pertussis infections in the older age groups (age shift) resulting in a doubling of the productivity losses. These productivity losses are more heavily discounted (4%) compared to the health effects (1.5%). Furthermore, also the future incremental vaccination costs are 50% higher, when the outcome measures were not discounted. Both factors contribute to the fact that discounting the outcomes resulted in a more favorable ICERs. Decreasing the underreporting factors resulted in

more favorable ICERs. With a lower underreporting rate, the pressure of infection decreased resulting in the prevention of relatively more symptomatic cases by herd effects in younger individuals. In addition, the relative increase in the number of symptomatic cases in the older individuals was reduced. Finally, we note that exclusion of indirect costs resulted in a more favorable ICER when the booster was given at 12–14 years of age, but inclusion of these costs resulted in a more favorable ICER when the booster was provided at 15 years of age and onwards. This is directly related to the fact that when a booster is provided at 15 years productivity losses are prevented leading to cost saving, while if the vaccine is provided at the age of 12 years this would result in an increase in productivity losses and costs. This difference is indirectly caused by the waning immunity of the vaccine. If a booster dose was provided at the age of 12 years, the increase in the number of breakthrough infection would start at an earlier age than when the booster was provided at the age of 15 years. Furthermore, with regard to productivity losses we assumed that individuals start to have productivity losses at the age of 15 years. As a consequence, when a booster was given at the age of 15 years, more productivity losses would be avoided in the "targeted" population.

An assumption of our model structure is that pertussis, or pertussis immunization, induces immunity against transmission and disease. As a consequence vaccinating individuals against pertussis can prevent the transmission of pertussis to other individuals resulting in herd protection. Although, the exact duration of this immunity against transmission is not known, there is evidence that vaccinations does induce herd protection. For example, in Sweden after the re–introduction of the pertussis vaccine in 1995 after 16 years, a significant reduction in the number of isolates in unvaccinated infants was noticed[355]. Also, several other observational studies[355-357] have demonstrated a decrease in *B. pertussis* incidence rates in unvaccinated subgroups (when the vaccination uptake was higher than 80%). Furthermore, a decrease in the transmission of *B. pertussis* infection from vaccinated through household contacts was observed in several vaccine efficacy studies[358-361].

In this analysis we estimated the cost–effectiveness of a pertussis booster vaccine. Given that a single pertussis booster vaccine is not available, we assumed that the pertussis booster would be given in the formulation together with diphtheria and tetanus toxoids (dTpa vaccine). We explicitly looked at the cost–effectiveness of a pertussis booster dose without taking into account the potential effects of the booster dose for diphtheria and tetanus. To fully evaluate the health economic consequences of this combination vaccine, all three diseases should be taken into account in the model.

We did not consider deaths due to pertussis infections because in the last decade in the Netherlands on average less than one death per year was reported[362]. Including deaths might have resulted in a slightly more favorable ICER as deaths are assumed to occur most frequently in the youngest age groups. On the other hand, if (unreported) deaths occurred more frequently as a result of breakthrough infections in adults and elderly, that could result in a slightly less favorable ICER.

In conclusion, we developed a flexible dynamic model and showed that a pertussis booster vaccination given at approximately the age of 12 years is cost–effective given a wide range of assumptions. Our results can be used to support decision makers on the introduction of a pertussis booster into the Dutch national immunization programme.

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Dynamic models for health–economic assessments of pertussis vaccines; what goes around comes around…

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ABSTRACT

Despite childhood vaccination programs, pertussis remains endemic. To reduce the burden of pertussis, various extended pertussis vaccination strategies have been suggested. The aim of this review is to evaluate dynamic models used to assess the cost–effectiveness of vaccination. In total, 16 studies using a dynamic model were included in our review, of which four also studied the cost–effectiveness of extended pertussis vaccination strategies. Generally, adolescent vaccination was found to be cost effective, but not highly effective in protecting infants too young to be vaccinated. The models also predicted that owing to age shifts, reduced pertussis disease in adolescents and young adults comes with an increase in later stages of life. This underpins the use of dynamic transmission models for interventions directed against pertussis. In future, dynamic transmission models for pertussis should be used widely to further enhance understanding of pertussis epidemiology and of extended pertussis vaccination programs that are currently considered in various countries.

INTRODUCTION

Pertussis, or whooping cough, is a highly contagious infection of the respiratory tract. It is caused by the bacteria *Bordetella pertussis* and it was one of the main causes of morbidity and mortality before the introduction of widespread vaccination against pertussis. With mass vaccination programs, the incidence and severity drastically dropped. However, resurges of epidemic episodes, infections in infants too young to be vaccinated, and pertussis disease in adults and adolescents remain, resulting in renewed attention by authorities in the recent decade to further improve pertussis control and optimize the system of protection rendered by vaccination[363]. In this respect, extended vaccination strategies are often mentioned[354,363,364], including cocooning, adolescent–and adult booster vaccination or even maternal vaccination to directly protect newborns.

The cornerstone of pertussis vaccination is provided with a schedule that comprises at least three doses within the first year of life. A fourth dose is often given as a first booster somewhere between the first and second year of life. Sometimes, a second booster is provided preschool or during the first years in school. Various vaccine formulations exist and often the pertussis (P) component exists within a combination vaccine with diphtheria (D), tetanus (T), inactivated polio virus (IPV), *Haemophilus* type b (Hib) and hepatitis B virus (HBV). For example, existing formulations comprise DTP, IPV–DTP and IPV–DTP–Hib–HBV. Within these formulations, the P–component can be either cellular (whole cell; wP) or acellular (aP), with the latter reflecting the newest technology. Many countries have shifted from vaccines with the P–component to those with an aP–component in the last decade, in particular, owing to the superior safety profile of the latter.

Some countries have already introduced an adolescent booster in the schedule, primarily with the notion to reduce spread and indirectly protecting those very young yet to be vaccinated[348]. Among these countries are France, Germany, Canada and the USA; however, most countries are reluctant in implementing this owing to health economic reasons and the potential shift in the age of infection up to the childbearing age. Moreover, it has already been argued to extend boostering beyond the adolescent age and all throughout life[348,364].

Since the 1990s, there have been increases in the number of cases of pertussis reported and of outbreaks, including in countries with a very high coverage, such as the Netherlands (coverage of 95%)[365-367]. This is a concern as adults are identified as an important source of transmission to children, including very young infants with potentially severe disease[321,323,368-371]. Notably, it is suggested that, particularly, those aged between 19 and 39 years play an important role in pertussis transmission in households[372], and therefore, pertussis vaccination in adolescents/young adults may decrease the dissemination of pertussis in households. The potential for adults and adolescents to transmit the bacteria to infants[319,320,348,373], together with the increasing number of cases in these groups might pose a continued spread for severe disease in infants. Moreover, pertussis seems to be poorly controlled in older age groups in the absence of boostering due to waning vaccine–induced immunity after the often high–coverage initial infant vaccination schedules[314,374]. Finally, it has been noted in these same studies that the incidence of pertussis in vaccinated infants has increased significantly, which might be related to an increase in awareness, changes in vaccine characteristics

and disease susceptibility, shifting demographics, variations in vaccinations coverage and genetic variations of *B. pertussis*[348]. The shift to acellular vaccines might not have resolved this as the primary difference between wP and aP is related to safety rather than efficacy[37]. The efficacies of aP vaccines and wP vaccine differ, with the best aP vaccines being more efficacious than low–efficacy wP vaccines but the former may have a lower efficacy than the most efficacious wP vaccines[37].

Health economics is important in assessing new technologies in health. Therefore, new strategies to control pertussis are also prone to health economic evaluation. Recently, Millier *et al*. have reviewed the health economic analyses in pertussis[353], updating some previous reviews on the topic[375,376]. They noted a general lack of studies into the health economics of pertussis booster vaccination, with only 13 studies examining the economics of vaccination strategies into adolescence, every–10–year adult or cocooning (mothers and fathers). However, the lack of studies deploying dynamic models within such contexts is even more startling as dynamic models seem to reflect the only class of models that are actually suitable to validly analyze the issue. Notably, dynamic models take the spread of the infection explicitly into account, whereas the so–labeled static models do not. As such, only dynamic models are able to predict herd–protection effects of protective vaccination efficacy in unvaccinated populations. As the major issue of pertussis boostering is reducing spread and protecting the infants too young to be vaccinated or being only partially vaccinated, the need for the deployment of dynamic models is eminent. Out of the models identified by Millier *et al*., only three models involved transmission dynamic models[328,329,377].

The aims of this paper was to review the dynamic transmission models developed for pertussis, their application in health economic analyses and to update the landscape of health economic studies with special reference to those deploying dynamic models.

METHODS

Literature search

We searched PubMed and EMBASE for modeling studies of pertussis booster vaccinations. For this purpose, the authors inserted the search term 'pertussis', in combination with any of 'cost(–)effectiveness', 'cost(–)utility', 'cost' and/or (pharmaco–)economic evaluation. Moreover, the authors analyzed 'pertussis' combined with any of 'compartmental model', 'dynamic(al) model' and/ or 'mathematical model', to adequately cover the regularly used synonyms of dynamic models in the literature. Out of the list generated, the authors selected those studies that predicted the impact of extending or changing currently used pertussis booster programs. Snowballing was performed on all studies found in the first or second stage of the literature search to potentially identify further studies. Not unexpectedly, the approach resulted in only a limited number of papers, generally focusing on epidemiology alone and hardly any including the economics as well[326,328-332,336,352,377-384]. In particular, the authors identified four studies deploying dynamic models with the final purpose of health economic analysis[328,329,377,378].

Reporting

In the following section, the authors report their findings separately regarding dynamical models that have been developed for analyzing the epidemiology of pertussis vaccination and for those that have extended these models to health economic analysis. Next to a narrative approach to both aspects, the authors analyze the results on epidemiology and economics to explain the specific features on adolescent and adult booster vaccinations. For this purpose, the authors have tabulated several study characteristics including, the duration of natural and vaccine–induced protection, the mixing pattern used, the potential correction for underreporting. Notably, for underreporting, a difference should be made between non–notified symptomatic cases and asymptomatic cases that are obviously not prone to notification at all but may drive the epidemiology[329].

RESULTS

First–generation dynamic models

The first dynamic mathematical models for pertussis were developed by Knox and Shannon, and Grenfell and Anderson[381,384]. A decade later, Hethcote *et al*. developed a model for the USA where multiple doses of pertussis vaccine were given to young children[379]. It was an age–dependent compartmental model that included 12 different epidemiological classes over 32 age groups with very small age classes for infants and adolescents up to age of 19 years. The demographic structure of the American population was carefully taken into account and a demographic equilibrium in the age distribution was assumed. The 12 compartments corresponded to a class of susceptible individuals, three disease classes according to the infectivity (weak–disease class when infectivity is low because people cough less and are less likely to infect; mild–disease class; full–disease class), four recovered classes that capture the decrease in the immunity and four vaccination classes. In the model, the assumption of proportionate mixing was assumed for the contact matrix. The authors performed a sensitivity analysis changing demographic and epidemiologic parameters, vaccine efficacy, vaccine coverage and duration of protection.

Hethcote's initial model has been further developed to cover the option of analyzing adult and adolescent booster vaccination, in particular an adolescent/adult booster every 10 years (from the age of 10 years onwards) was assumed[380]. In analyses for the USA, it was shown that although the program had a profound effect on overall pertussis incidence with the potential of decreasing it by 30–60% over a period of 50 years, incidence in infants and young children was only modestly affected. Van Rie and Hethcote extended further on the modeling by including the potential of a cocooning strategy within a methodological mix of the initial dynamic approach and some static properties[332]. The study reinforced previous conclusions that adolescent/adult vaccinations could only modestly contribute to the control infants and young children, whereas the cocooning had clearly visible effects on the incidence of typical pertussis in children up to the age of 5 years. Notably, for example, in 1–month old infants, cocooning had the potential to reduce incidence by up to 75%. Finally, the model was applied to the Australian setting[330], with the aim of analyzing a

potential transfer of the infant booster at 18 months to an adolescent booster between 12 and 17 years. Slightly differing results were found, compared with the USA analyses, in particular, regarding a 30% decrease in pertussis cases aged 0–23 months old, suggesting an impact of adolescent vaccination on the very young. This advantage was partly offset by an increase in incidence in the age group of 2–4 years. However, with the very young being most prone to severe disease, this shift seems favorable. Moreover, the study did not reinforce the general concern on adolescent pertussis boosters in shifting the peak incidence from adolescence to young adulthood, with potentially higher contact intensity with infants in the latter. One might doubt, however, whether the contact patterns inserted in the model were specific enough to adequately capture such details.

None of the analyses with the initial Hethcote generation of models was extended with economic analysis, although the papers generally stated the need[330,332,379,380]. However, recently, Coudeville *et al*. have developed a compartmental, age–structured mathematical model on US pertussis data, using the van Rie and Hethcote version of the model with the explicit aim of subsequent economic evaluation[326,328,380]. With the cocooning strategy being analyzed as well (using a static approach within the dynamic model), the authors state that routine adult vaccination may exhibit the greatest impact on pertussis incidence in all age groups, but the resources needed may be high compared with that for cocooning. The authors have shown that applying the van Rie and Hethcote model, adolescent vaccination can potentially impact on pertussis in the very young infants 0–3 months. In particular, nationwide pertussis incidence in this group may drop from approximately 1000 cases to less than 400 owing to adolescent vaccination. Addition of either cocooning or routine adult booster vaccination every 10 years would almost eliminate pertussis in these very young infants. The latter is probably mostly due to vaccination in the childbearing decades of life. The authors note the lack of reliable data on contact patterns, while illustrating the major impact on the results of the exact specification of the contact matrix (assortative, proportional or constant mixing).

Subsequent model approaches

Some years later, another relevant dynamic model for pertussis was developed by van Boven *et al*. [336]. The aim of the paper was to study the outbreak of pertussis that took place in the Netherlands in 1996–1997. The model had less compartments than Hethcote's model, with only six in total (immune naive, primed susceptibles, protected after vaccination, protected after natural infection, primary infection and secondary infection). The goal of the paper was to investigate the subclinical infection and waning immunity in the transmission dynamics. Two types of infections were distinguished: infection in immunologically naive individuals or primary infections, and infection in individuals whose immune system had been primed before by vaccination or infection, labeled secondary infections. People could recover and become immune after primary or secondary infection or vaccination. The duration of infection was assumed to be 2 weeks, shorter than the 3 weeks in Hethcote's model. The duration of protection was instead assumed to last 20 years on average, whereas in Hethcote's model, it was 15 years. However, for both the durations, van Boven *et al*. considered different scenarios as sensitivity analysis. An important aspect of this model was

the formal estimation of the age–specific force of infection, estimated from age–specific Dutch incidence data and the stable age distribution of the endemic equilibrium in the model being assumed. Moreover, in later specifications of the Hethcote model, the estimates of the age–specific forces of infection were based on those available in the literature, mainly fitted to data from England and Wales[347,384,385]. Finally, van Boven *et al*. also assumed a proportionate mixing.

A next model by the same group extended the six compartments to seven by separating those protected by natural infection into those protected after primary infection and after secondary infection[331]. The analyses reinforce pervious findings that there exists a relevant contribution of adults to the spread of pertussis and that the duration of protection after vaccination had decreased from pre– to post–1995 periods. Notably, the idea is expressed in the van Boven *et al*. paper that immunity for pertussis disease might last 10–20 years after natural infection and only 5–10 years after vaccination. Others have expressed that immunity for (subclinical) infection might even be significantly shorter[329].

Finally, two dynamic models for Latin American countries have been developed[382,383]. The first model focused on Rio de Janeiro (Brazil) and was divided into two submodels, one capturing the demographic and the other the epidemiological dynamics. The structure of the epidemiological model was drawn from previous published papers and consisted of nine compartments including one susceptible compartment, one primary and one secondary infection compartment, three immunological stages (full immune, intermediate immune and minimum immune), and three levels of vaccination depending on the number of doses received. Furthermore, the model consisted of 12 age groups; the rate of interaction between individuals was stratified as a function of their age. The aim of this paper was to reconstruct the impact of the introduction of pertussis vaccination and to optimize the currently used strategy consisting out of three doses before the age of 1 year and two boosters at 15–18 months and 4 and 5 years. One of the conclusions was that it might be more effective to eliminate one of the boosters if it could be guaranteed that coverage of the other booster would increase (as the current coverage is <30%). Another conclusion was that a better understanding of the social contact structure is urgent especially that of the very young people. The other paper assessed the impact of a booster at 11 years for Argentina[382]. An age–structured compartmental model was developed based on Hethcote's model[379]. The population was divided into nine classes including susceptibles, three classes of infections, two classes of complete protected individuals (after vaccination and natural infection) and four classes of partial protected individuals, and 30 age groups. As no specific contact patterns were available for Argentina, three different sets of contact patterns were used. They found that although a booster at 11 years significantly reduces the incidence of disease, the impact on infants of less than 1 year was very low and that the impact of a higher coverage of the first dose would be much larger.

Points of uncertainty

As described earlier, there are several mathematical modeling studies that assess the effectiveness of different pertussis vaccination strategies. However, none of them explicitly considers subclinical

infections, and the studies may partly neglect the difficulties in interpreting notification data. Notification data report only (part of) symptomatic cases, whereas pertussis is characterized by mostly subclinical/asymptomatic or mildly symptomatic cases in older age groups[314,374]. Kretzschmar *et al*. have used different methods to estimate the incidence from individual data on pertussis titers rather than notification data[386]. In their approach, they estimate basic reproduction numbers that are remarkably similar across countries at approximately 5.5.

Several studies, including the first being published on this topic, describe that the current generation of vaccines with limited duration of protection cannot eliminate pertussis from the population. Owing to vaccination, the pertussis burden of disease is shifted forward from infants and children to adolescents and young adults, potentially requiring new control strategies. Notably, the debate on duration of immunity continues with analyses being performed on notification data and based on models for infections, regarding natural infections and/or vaccination, and concerning infection or disease[329,333,387]. Recent studies, for example, indicated a duration of immunity of 7–20 years after infection and 4–12 years after vaccination[333], or even long lasing after infection beyond 30 years[387]. The authors also note that differentiating between immunity against infection versus disease might help clarifying some of the issues in this discussion[329].

Another point of concern is the increase in the age of infection to women of childbearing age, which might infect their children as shown by several studies[328,329,332,378,383]. Current contact parameters are unable to capture these within household contacts. Although studies show that additional booster dose (slightly) reduces the incidence in infant, conclusions should be made carefully as an increase in women at childbearing age might result in an overall increase in pertussis cases in these infants.

Health economic studies

As mentioned, four health economic studies could be detected that explicitly applied dynamic models to get to the results[328,329,377,378]. Studies have in common that they are all directed towards analyzing adolescent vaccination, potentially extended with adult vaccination or even further strategies. Notably, in the studies, adolescent vaccination is studied in contexts where the vaccination is already in place (e.g., the USA) or where it is compared with potentially highly cost–effective comparators not yet in place, such as toddler booster vaccination[388] (e.g., the UK). In addition, in most papers, adult vaccination strategies on top of, or instead of, adolescent boostering are analyzed. Notably, the two studies for the Netherlands both build on a similar modeling approach and are integrated in the reviews below.

Brief descriptions of the four health economic studies

Edmunds *et al*. analyzed the potential cost–effectiveness of introducing acellular pertussis booster doses at either 4 or 15 years, using the equilibrium state of a transmission dynamic model to estimate the indirect protection of those too young to be vaccinated[377]. In particular, the latter referred to those infants aged <3 months, prior to the protective effect of the infant vaccination schedule

in place in the UK around the turn of the century. Obviously, herd protection was an important parameter in the analysis – if not the most important – however, the authors acknowledge the uncertainties surrounding the potential acellular vaccines to confer herd protection, as compared with the whole–cell vaccines. Rather than extensively elaborating on this discussion, the authors present extensive sensitivity and scenario analysis on this aspect. Whereas some other studies had the period until indirect protection occurs as a result of the modeling, Edmunds *et al*. assumed this parameter at 5 years (range: 2.5–7.5 years). The exact rationale of the study was to analyze which strategy outperformed in protecting the young (partly) unvaccinated infants: either vaccinating at 4 years or at 15 years? A major part of the epidemiological model was unpublished by the time the study was reported and referred to as 'Gay, unpublished materials'. Analyses were targeted at the specific situation in the UK.

Coudeville *et al*.[328] built an economic analysis following up their epidemiological analysis[326]. In particular, they wanted to address the economic issues on pertussis adolescent and adult boostering, given the lack of consensus in the literature[389-393]. In view of the explicit recommendation of the US Advisory Committee on Immunization Practices for routine adolescent booster vaccination[394], Coudeville *et al*. exhibited a specific interest in analyzing the incremental value of adult booster strategies over and above adolescent vaccination. However, next to this approach, the authors also analyzed the cocooning strategy. Supposedly though, the full benefit of the population dynamic approach is present in the adolescent and adult vaccination strategies rather than in the cocooning approaches. For that purpose, we focus on the analyses on adolescent and adult booster strategies in the following section. The study was performed using data and assumptions for the USA.

The publications by de Vries *et al*.[329] and Rozenbaum *et al*.[378] are both based on the same model structure described in the former and separately in yet another paper[352]. In particular, the second report extended on the first by using a more user friendly and less computational–intensive version of the same model structure, allowing extensive scenario and sensitivity analyses that the initial version was lacking. Underlying this was a reprogramming of the model into another type of software. In particular, the follow–up paper[378] analyzed several adult vaccination strategies in the Netherlands in addition to adolescent vaccination, whereas the former analysis only allowed analysis of the latter.

Table 1: Results and key features of the studies selected

	Edmunds *et al.*	Coudeville *et al.*	De Vries *et al.*/ Rozenbaum *et al.*
Comparison(s)	Booster at 4 years vs. 15 years both compared to initial infant schedule only	Adolescent vs. adolescent+ adult booster compared to initial infant schedule	Adolescent and adult booster both compared to initial infant + 4-years booster
Perspective	Health care and societal	Primarily societal	Primarily societal
Discount rates	Money: 3%; Health: 3%	Money: 3%; Health: 3%	Money: 4%; Health: 1.5%
Diff. discounting in SA?	Yes	No	Done in base case
Cost-effectiveness(utility)			
Health care	<£50,000 vs. <56,000/LYG	dominant vs. dominant	€4400 and <16,900/QALY
Societal	<£37,000 vs. <47,000/LYG	dominant vs. dominant	€5100/QALY (adolescent)
Probabilistic SA	Yes	No	No

LYG: Life-year gained; QALY: Quality adjusted life years; SA: Sensitivity analysis.

Results & key features of studies

Table 1 lists some of the results and key features of the four studies. In particular, the authors consider the exact comparison(s) made, costs per quality–adjusted life years (QALYs) or life–year gained (LYG), the perspective, discount rates used, whether differential discounting was used in sensitivity analysis and whether probabilistic sensitivity analysis was included.

Edmunds *et al*. analyzed the cost–effectiveness of boostering at 4 versus 15 years, both compared with the initial set of infant doses only[377]. Costs per LYG were reported from the healthcare and societal perspectives, which presented an important difference. In particular, work days lost for the society was set at 7 days with average wages taken from the Office for National Statistics[350]. Profound impact of the perspective was illustrated in cost–effectiveness still <£50,000 per LYG for boostering 4–year olds from the healthcare perspective, but always <£37,000 per LYG for that same strategy from societal point of view. Equal discounting was used to derive these results: 3% for costs and 3% for health outcomes. The results appeared sensitive to differential discounting (costs at 6% and life years at 1.5%), grossly reducing cost–utility rates by a thirds. From the probabilistic sensitivity analysis, it appeared that for boostering at 4 years, 50% of simulations would be <£10,000 per LYG from the healthcare perspective, whereas this would be 75% from the societal perspective, with even 20% consistently indicating cost savings. Results were reported to be sensitive to the assumptions on indirect costs of production losses, in particular related to assumptions on this aspect for mild cases.

The US study found that compared with the initial infant vaccination strategy, both adolescent and adolescent+adult boostering dominate from both perspectives[328]. In addition, the incremental analysis of adolescent+adult over and above adolescent only indicates dominance of the former over the latter. The extra vaccination costs at approximately half a million dollars per million population are more than offset by savings on disease costs from both perspectives. Notably, the sensitivity

analysis was only done from the societal perspective, with however, the general picture reflecting direct and indirect costs, and savings at grossly similar orders of magnitude. The study assumed plausible coverage rates for the different strategies investigated comprising close to 100% coverage for the initial infant schedule, 75% for adolescent vaccination, 65% for cocooning and 40% for routine adult vaccination every 10 years. Higher coverage – in particular, for the latter – analyzed in the sensitivity analysis did not change the conclusion of the study. Most strategies and combinations of strategies remained highly attractive from the economic point of view. As not specified in any US guidelines on health economic analysis, the US study lacked differential discounting in the sensitivity analysis. However, the authors analyzed different percentages for equal discounting: as is the case for most vaccination strategies, higher discount rates deteriorate cost–effectiveness ratios, lower ones improve[395]. As most strategies were dominating, the subsequent comparators were only reported for the strategy of 'childhood+adolescent+routine adult' compared with the 'childhood+adolescent+cocooning+1 adult dose at 40 years' strategy at $678,500 per LYG in the base case, $482,100 at 0% discounting and $837,400 at 5%. The authors note the similarities in the set of strategies investigated compared with Lee *et al*. [391,392], whereas inferences differ. In neglecting herd immunity and potential resurgence of pertussis incidence, Lee *et al*. found that addition of adult vaccination to adolescent boostering unlikely to be cost effective. Neglecting herd immunity is obviously related to the model approach chosen: static versus dynamic.

Primary focus in the first paper on the Dutch analysis[329] was the adolescent vaccination strategy at the age of 12 years, with an aim to protect infants too young to be (fully) vaccinated. It appeared that this strategy had only limited impact in this respect given the Dutch mixing patterns modeled. However, the strategy was cost effective in the preferred Dutch societal perspective primarily owing to direct QALY gains, and inclusive age shifts and related changing indirect cost patterns. In particular, indirect costs seem to be shifted from adolescents and young adults to childbearing and parental ages and beyond. A similar pattern can be observed for QALYs; that is, adolescent vaccination lowers QALY losses in the former group at the expense of increased QALY losses in the latter groups. Related to the age shift explicitly modeled and related effects on indirect costs, lower discount rates worsened the cost–effectiveness: €4400–6400 per QALY in the base case at differential discounting using 4% for money and 1.5% for health, €5200–7400 per QALY for equal discounting at 4% and even up to €7900 per QALY in the absence of discounting. Notably, this result is seldom seen but can occur as a result of age shifts in dynamic models. No probabilistic sensitivity analysis was performed; however, the respecification of the model for the second paper[378] would allow probabilistic sensitivity analysis in the future to be embarked upon. All in all, the Dutch analyses indicated favorable cost–effectiveness for adolescent vaccination due to QALY gains in adolescents and shifts in indirect costing patterns, with an optimal age of vaccination of 10 years from the economic perspective[352,378]. In particular, reduced pertussis disease in adolescents and young adults comes with an increase in later stages of life. Thus, age shifts might increase pertussis in the childbearing and parental ages, providing potential for additional booster strategies in adulthood. Rozenbaum *et al*. found both one–off and every–10–year adult vaccination on top of

adolescent boosting to be cost effective in the Netherlands[378].

Table 2: Specific characteristics of selected cost-effectiveness studies.

	Edmunds *et al.*	Coudeville *et al.*	De Vries *et al.*/ Rozenbaum *et al.*
Underreporting explicitly taken into account?	Yes	Yes	Yes / varied in scenarios
Asymptomatic cases included?	No	Yes	Yes
Duration of protection			
Natural infection	5 years	8 years	13 years/ 8, 12 and 16 years
Vaccination	5 years	4 years	8 years
Direct and indirect effects separately reported			
Herd protection	Yes	No	Yes
Age shift	No	No	Yes
Contact matrix used	Unpublished material[#]	[332]	[343]

Extensive sensitivity analysis was performed (personal communication)

Specific characteristics of studies

Table 2 lists some further specific characteristics of the studies. In the following paragraph, these aspects are described in detail.

The UK model was built to validly analyze epidemiology using registration systems for GP visits (Royal College of General Practitioners Weekly Returns Service) and hospitalizations. The Royal College of General Practitioners Weekly Returns Service was corrected for non–notified cases; a multiplier of 2.5 was specifically used for this purpose. Notably, if higher, but still plausible, underreporting was assumed, cost savings became within the realm of potential results if the societal perspective was taken. Duration of protection was set at 5 years for both natural and vaccine–induced protection, although in scenario analyses sets of protective durations with consistently lower vaccine–induced durations than natural at half of the natural duration were analyzed (e.g., 5 years after infection and 2.5 years after vaccination or 10 and 5 years, respectively). Owing to the design of the model, results were not highly sensitive to this specific assumption. Five different mixing matrices were specified and analyzed, reflecting different levels of mixing between age groups. Direct and indirect effects were analyzed separately in the study by focusing once on herd protective effects on infants <3 months only. Generally, this analysis illustrated that these indirect herd protective effects drove the model results and that inclusion of the direct vaccination effects on the toddlers and adolescents in the respective vaccination strategies had only modest impacts. Inclusion of the direct effect was relatively more important in adolescent vaccination and in the societal perspective.

The US model explicitly included asymptomatic disease. After waning of natural or vaccine–induced immunity, subsequent infections may result in asymptomatic manifestations in approximately 50% of cases. Inherent to the dynamic nature of the models considered and the crucial age–structured element in this, all models included both age shifting and herd protection in the

epidemiology. However, in the reporting on the US model, these specific aspects were not explicitly addressed, which is a pity as reporting would provide important insights in the relative contributions of the various dynamical effects involved. Moreover, indirect costs could not be separated in the reporting on the sensitivity analysis. Ideally, reporting would allow specification of herd protection and age–shifting effects with corresponding changes in direct medical and indirect non–medical, respectively. The mixing pattern in the contact matrix was taken from the previous analysis by van Rie and Hethcote[332] that analyzed, within an extensive sensitivity analysis, all from assortative mixing to proportional mixing in the epidemiological analysis[326]. However, in the economic analysis on the original, van Rie and Hethcote matrix was used[332]. Specific attention was directed at the contribution of household members to pertussis transmission to allow detailed scenarios on cocooning strategies. In particular, this relative contribution ranged from almost 40% to just up to 50% for preschool children, and approximately 25% for children 5 years of age. Beyond 5 years, no impact of cocooning was assumed anymore.

In some aspects, the Dutch studies did benefit from some more recently published specific materials. For example, the Dutch study could make use of an extensive analysis on underreporting, estimating infections to be in general 660–fold of symptomatic diseased and notified cases, obviously with age–specific patterns underlying the overall estimate[332,342]. A specific study for contact patterns could be used, estimating recent European contact patterns[343]. Furthermore, a cost–of–illness study was available, facilitating the parameterization of the costing modules in the overall design. A specific feature of the Dutch study was to differentiate between immunity against infection and disease. As all dynamic models were considered, both herd immunity and age–shifting patterns were included in the analysis; however, reporting was done much more extensively. In particular, the Dutch study explicitly reported the age shift simulated with the model in more detail than both other studies analyzed here. As mentioned, the age shift clearly illustrates how reduced pertussis disease in adolescents and young adults comes with an increase in later stages of life, providing potentials for adult strategies. In pertussis, what goes around seems certainly to come back around.

DISCUSSION

Pertussis vaccines have been licensed in the USA since the second world war, both as monovalent vaccine and combined with diphtheria and tetanus. Its widespread use has become eminent, supported by WHO recommendations and initiatives[396,397]. Despite widespread use, pertussis disease and infections are still around and periodic resurgences occur. One of the reasons is that immunity induced by pertussis vaccination or even natural infection is relatively short and heterogeneous. In particular, immunity might protect significantly longer against disease than against infection, enhancing potentials for continued spread despite relatively high vaccination coverages in infants and toddlers. Notably, it is yet to be determined how effective vaccine coverage will be for the potential new additional control strategies of adolescent vaccination, adult vaccination and cocooning.

Dynamic models are becoming increasingly important in analyzing the control strategies for infectious diseases[398]. Notably, whereas still control strategies may exist that can sufficiently be analyzed with static models, such as travelers' vaccinations, the vast majority of issues can be more validly addressed with dynamic models[10,399,400]. Adolescent and adult strategies should ideally be analyzed using dynamic models with their aim of influencing epidemiology rather than directly protecting the adolescents and adults targeted with the vaccine. Non–dynamical approaches to these strategies might fail to provide insight into these indirect protections and may fail to adequately mimic the age shifts incurred through vaccination programs[401-403], although they might provide valuable first gross insights[391,392]. Finally, areas for in–between types of models certainly exist. For example, cocooning strategies require insight into transmission dynamics in households but may be analyzed with models lacking the full contact matrix structures within the full populations. Such quasi dynamic approaches have indeed been applied to cocooning as a control strategy, limiting the contact pattern to parents, siblings and potentially others without the comprehensive population approach[328,354,404]. Notably, these analyses indicate potentials for cocooning to be highly cost effective, but also indicate the practical issues concerning effectively and broadly implementing such strategies outside the routine structures provided within existing immunization programs. In particular, for example, Westra *et al*. found cost–effectiveness for cocooning at €4600 per QALY for the Dutch society taking the healthcare perspective, whereas from the societal perspective cost savings were even indicated[354]. Similar superior profiling of cocooning, as from the Dutch societal perspective, was indicated by Coudeville *et al*. for the USA[328].

Dynamic models should capture recent insights in pertussis epidemiology and spread on differing types of models suggested, induced immunity provided and transmissibility[405,406]. A recent paper focuses on the different types of models to be used, in particular, SIR versus potential extended compartmental approaches[405]. Notably, the vaccine is considered to better protect against pertussis manifest disease than to (subclinical) infection, providing an immune escape and continued circulation despite high infant coverage – or even – adolescent vaccination[329,386,406]. In addition, the models should consider differing transmissibility of the bacteria depending on the disease manifestation in the host: symptomatic disease might certainly lead to higher transmission than asymptomatic disease does. Exact coverage needed to achieve cost–effectiveness is another issue that can be addressed with dynamic models. However, this will crucially depend on country–specific issues in health economics (costing, discounting and perspective chosen), surveillance, reporting and epidemiology.

The exact roles of all relevant factors in pertussis epidemiology remain uncertain, however, evidence is accumulating. It is obvious that with regard to the major issue of pertussis transmission to young infants too young to be (fully) vaccinated, both the household and the community play their roles[323,372,407]. For example, it was found that at least 34% of cases in young infants was infected through casual community contacts in a study in France, Germany, Canada and the USA[323]. Furthermore, regarding close contacts, parents accounted for 55%, siblings for 16% and other family members (and close friends) for 27%[407]. In this specific study, part–time caretakers only accounted

for just 2% of the transmissions. In another study conducted in the Netherlands, for those infants where the source could be detected, siblings contributed to 41% of cases, mothers 38% and fathers 17%[327]. All these studies contribute to further understanding mixing patterns, populating assumptions in dynamic and quasi–dynamic pertussis cost–effectiveness models. For full dynamic models analyzing adolescent and adult strategies, recent initiatives on establishing comprehensive contact matrices in populations will further help in targeting and validating these models[344,390]. Failing to adequately integrate information from age–structured contact patterns probably results in misunderstanding epidemiological patterns, enhancing the wrong control strategies rather than focusing on the right ones and invalid inferences on cost–effectiveness profiles[408].

Dynamic models have up to now focused on adolescent vaccination strategies and adult strategies on top of those. Adolescent vaccination was investigated at the age of 10, 12 and 15 years, although a study even analyzed the whole spectrum during teenage years initially[378]. Notably, adolescent vaccination was generally found to be cost effective, as well as adult boostering on top of it. In the reporting of the results of the dynamics models so far, the exact contribution of such strategies on protection of the very young infants yet too young to be (fully) vaccinated. Only de Vries *et al*. report extensively on this and show the limited effect[329]. Indeed, it has been argued, found and seems highly plausible that age–mixing patterns are such that contacts between adolescents and young infants are infrequent, rendering the adolescent strategy as unsuitable for indirect protection of (partly) unvaccinated infants[344,406]. Obviously, cost–effectiveness of adolescent vaccination is driven by other factors such as direct protection and age shifts. Actually, for the former even no dynamical models would be required, for the latter dynamical models are still crucial. In particular, reduced pertussis disease in adolescents and young adults comes with an increase in later stages of life. In pertussis, what goes around comes around.

We conclude that dynamic model approaches in pertussis are highly valuable in analyzing adolescent and adult vaccination strategies. We recommend continued and extended use of dynamic models for these strategies, inclusive separate analysis of the cost–effectiveness of adult boostering strategies.

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General Discussion

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Pneumococcal and pertussis vaccination programs

Vaccination is considered to be one of the most effective methods of preventing infectious diseases. In the Netherlands, a routine infant pertussis vaccination programme has been in place since the 1950s while a routine pneumococcal programme was initiated more recently in 2006. Inclusions of pertussis and pneumococcal vaccination into national immunization programmes (NIPs) had a tremendous impact on the mortality and morbidity in the Netherlands and other countries worldwide[36,84,409-411]. Nevertheless, extending pertussis vaccination to other age groups, replacing the currently used pneumococcal vaccine to one with a broader coverage, introducing a risk-groups-targeted or elderly pneumococcal vaccination programme, could reduce the morbidity and mortality due to these bacteria even further.

This thesis deals with both the epidemiological and economic impact of such new pneumococcal and pertussis vaccination strategies. This chapter summarizes and discusses the main results, findings and ideas described in the previous chapters, including some future perspectives.

PRINCIPLE FINDINGS AND FUTURE PERSPECTIVE

PART I: EPIDEMIOLOGY AND ECONOMICS OF PNEUMOCOCCAL VACCINATION.

Chapter 2 described a literature review aiming to address the following aspects: first, to provide a descriptive overview of the available epidemiological post–marketing data and experience with 7–valent pneumococcal conjugate vaccine (PCV7) in different countries and populations; second, to explore potential factors that could explain observed differences; and third, to discuss issues related to the use of national data in (cost–)effectiveness modeling. It showed that there are large differences in the observed disease epidemiology after implementation of pediatric pneumococcal immunization programs between the USA and Europe, but also between European countries and even between regions within countries. Possible factors responsible for these differences may include vaccine–serotype coverage, implemented vaccination schedules, antibiotic resistance rates and pneumococcal disease incidence prior to vaccination. A potential limitation can be found in the installation or enhancement of existing surveillance systems as well as other potential factors possibly causing confounding bias, which may have influenced observed disease rates in the included observational studies. Based on the findings in **Chapter 2**, it was concluded that the health and economic impact should be addressed in the light of the country–specific pneumoccocal disease epidemiology to support decisions on national immunization programs.

Several published European cost–effectiveness studies on PCV7 have included net–indirect vaccine benefits (herd protection minus serotype replacement) in their analyses. These net–indirect benefits were often extrapolated based on a specific observational study from the USA, after the introduction of PCV7[46]. In **Chapter 3** the impact of including indirect effects on the cost effectiveness of PCV7 vaccination in the Netherlands (3+1 dose schedule) was calculated. Also, 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 was estimated. Using a previously developed cohort model[133,135], updated with the most recent Dutch costs and epidemiological data, it was shown that without net–indirect benefits for non–vaccine protected groups included the incremental cost–effectiveness ratio (ICER) of a routine infant PCV7 program was €72,360 per QALY. Full inclusion of indirect effects would lower this ICER to €16,750 per QALY. Furthermore, it was shown that in order to obtain ICERs below a threshold of €50,000 per QALY the net–indirect protective effect should at least be 16% of those observed in the USA after the introduction of PCV7.

Given that net–indirect effects considerably affect the cost effectiveness of the current Dutch vaccination program, the cost–effectiveness estimates of PCV7 vaccination were updated using recent data on these indirect vaccination effects in **Chapter 4**. In this same chapter also the cost effectiveness of reduced dose schedules and vaccine price reductions combined with the implementation of PCV10 and PCV13 were estimated. At the time of the study only a relatively small number of IPD cases were reported during the surveillance period of two years after the introduction of PCV7 in the Netherlands. It was therefore necessary to partly base the estimations for indirect

effects on epidemiological data from the UK, a country with a similar pneumococcal epidemiology before the introduction of PCV7[79,81,104]. In particular, an increase of 100% for NVT IPD for children less than 5 years was included combined with the absence of an overall net indirect effect for individuals aged 5 years and older. Nevertheless, a recent study from the UK, which corrected the incidence for underlying trends and case ascertainment, showed net–indirect benefits in older age groups and less serotype replacement than previously assumed in children aged less than 5 years[36]. This suggests that the base–case results, which showed that vaccination with PCV7 in the Netherlands was unlikely to be considered cost effective, might be too conservative, although specific Dutch data would be required to confirm this. Finally, the study concluded that vaccinating with the 10–or 13–valent pneumococcal vaccines would result in cost-effectiveness estimates which are likely to be considered as cost effective.

Next to infants, elderly and individuals with specific conditions are at increased risk of pneumococcal infections[40,163,412,413]. Therefore, the cost effectiveness of PCV13 vaccination among (high–risk) elderly and individuals with specific high–risk conditions was explored in **Chapter 5** and **Chapter 6**, respectively. To estimate the cost effectiveness of elderly vaccination (**Chapter 5**) a cohort model in which vaccination was assumed to occur at the age of 65 years was developed. Because of the uncertainty surrounding the net–indirect effects, different scenarios were explored in the base case. In a first scenario indirect effects were excluded, given the absence of specific data for those aged ≥65 years in the Netherlands or any other European country at that time. This might be considered too optimistic a scenario from a cost effectiveness point of view because it assumed no herd–protection benefits among older adults as a result of infant pneumococcal vaccination. In a next scenario, it was assumed that the PCV7 infant vaccination program would increase the incidence of NVT IPD (replacement) while reducing the incidence of VT IPD. Furthermore, as there is much uncertainty regarding the efficacy, first the cost effectiveness was estimated by only assuming protection against bacteraemic community acquired pneumonia (CAP). In subsequent analyses, the protection was extended to other IPD and to CAP resulting in general–practitioner visits and hospitalizations. The model showed that the ICER remained below €80,000 per LYG, except when PCV13 was assumed to protect only against bacteraemic CAP, with a relatively low effectiveness (40%) in combination with a high vaccine price (€65), and indirect effects of serotype replacement would largely offset the direct effect of vaccination. Based on these outcomes it was concluded that vaccinating elderly with PCV13 might potentially be cost–effective.

The aim of **Chapter 6** was to estimate the cost effectiveness of vaccinating individuals of 2 years and older with high–risk conditions for IPD using PCV13. In contrast to the previous chapters, in which the cost–effectiveness analyses were performed from a societal perspective for the Netherlands, this study was performed for the UK from a National Health Service (NHS) perspective. A cohort model was developed which differentiated between individuals who are immunocompromised, such as those with HIV, asplenia, or splenic dysfunction or who respond poorly to the vaccine, such as people with chronic kidney disease; and those in immunocompetent risk groups such as patients with chronic heart, liver, or respiratory disease and people with diabetes[40]. As there is much

uncertainty around the potential impact of non–bacteraemic pneumonia no net effect against non–bacteraemic pneumonia was assumed in the base–case analysis. The model showed that increasing indirect protection resulting from the infant PCV13 program means that the burden of disease preventable by targeting high risk groups will diminish in time. Assuming that a vaccination campaign could be launched in 2012/13, the ICER was estimated to be >£30,000 per QALY for most risk groups, with the exception being patients with chronic liver disease. If, however, the vaccine program would be effective against non–bacteraemic pneumococcal pneumonia or the vaccine would have been introduced concomitantly with the infant PCV13 program, vaccinating high risk individuals would (more) likely be cost–effective. It was concluded that without an assumed effect against non–bacteraemic pneumococcal pneumonia, a risk–group pneumococcal vaccination program is unlikely to be considered cost effective. It should be noted that the results of this analysis cannot directly be transferred to the Netherlands. Firstly, the health-economic methodological requirements differ between the Netherlands and the UK. For example, in the UK an equal discount rate should be used and analyses are performed from the NHS perspective while in the Netherlands differential discount rates for costs and health are used and studies are performed from the societal perspective[142,208]. Secondly, in the Netherlands PCV10 has been introduced rather than PCV13. In contrast to PCV13[414], PCV10 has not demonstrated herd effects (yet), and does not cover serotype 19A, which is one of the key replacement serotypes. Therefore, it is likely that a high–risk group vaccinating strategy in the Netherlands will be more favorable as compared to the UK.

Next to the assumed vaccine efficacy and the assumed herd protection effects from the infant vaccination program the main driver of the ICERs in **Chapters 5 and 6** was the proportion of pneumonia that could be attributed to *Streptococcus pneumoniae*. Therefore, a meta–analysis to estimate this fraction and the factors influencing this fraction was performed in **Chapter 7**. Using a systematic literature search, 77 articles were assessed that covered human subjects with CAP over the period January 1990–November 2011 across European countries. A mixed effects regression model was developed and populated with 24,410 patients obtained from 77 articles that met inclusion criteria. The model showed that the observed prevalence of *S. pneumoniae* in CAP significantly varies between European regions even after adjusting for explanatory covariates, including patient characteristics, diagnostic tests, antibiotic resistance and health–care setting. The probability of detecting *S. pneumoniae* was substantially higher in studies that performed more frequently a diagnostic PCR assay compared to all the other diagnostic tests included. Furthermore, *S. pneumoniae* was more likely to be confirmed as the cause of a CAP in studies with ICU patients as compared to those with hospital or community treated patients.

PART II: EPIDEMIOLOGY AND ECONOMICS OF PERTUSSIS VACCINATION

Despite widespread vaccination, there has been a resurgence of pertussis in many countries during the past decade, particularly in adolescents and adults[314,317-320]. Although infections in infants and young children are more severe than in adolescents, the increasing incidence in adolescents and

adults is a major concern because adults are identified as important sources of transmission to young infants, and infection in adults causes significant significant morbidity and high costs[349-351]. Therefore, we explored the optimal vaccination strategy for reducing the number of infections in this population in **Chapter 8.** It was shown that, over a wide range of variations, an additional booster dose can reduce both the incidences of symptomatic and asymptomatic pertussis cases in the population although the incidence of symptomatic infections in older age groups can increase due to an age shift. A similar age shift was observed after the introduction of a pertussis booster vaccination in 2001 for 4–year–old children in Netherlands. The introduction of this booster dose reduced the number of hospitalizations among infants less than 4 months of age, while the incidence in adolescents and adults increased[318]. Furthermore, it was shown in **Chapter 8** that the optimal timing for the third booster dose in the Netherlands is between the ages of 10 and 15 years. However, this strategy only offered limited indirect protection to the (partly) unvaccinated infants with potentially most serious disease which might be a primary aim of extended pertussis vaccination. The most optimal strategy explored in terms of primary and/or total cases averted was a booster dose provided every 10 years. However, this strategy may certainly differ from the most cost–effective strategy.

Two previous studies used dynamic models to estimate the cost effectiveness of extended pertussis vaccination schedules[328,329]. Although both studies provide plausible insights, they could not be used for decision making in the Netherlands. Firstly, because the only study that did focus on the Netherlands was unable to investigate the impact of multiple vaccination scenarios and the impact of different assumptions for parameters surrounded by uncertainty (e.g., duration of protection after natural infection, underreporting factors) due to long computational times[329]. Secondly, the other study focused specifically on the USA with limited options for transferability to other settings[328]. Therefore, an economical model was developed which was integrated into the dynamical transmission model. The advantage of this model is the short running time after reprogramming, which made it possible to explore, within a reasonable time, the impact of different assumptions on disease epidemiology, on disease–related parameters, and on vaccination program–related issues[328,329]. This model showed in **Chapter 9** that an additional booster dose against pertussis would result in QALYs gained in children. However, the QALYs gained in children were partially offset due to an overall loss in QALYs in adults and elderly as a result of an increase in the number of symptomatic infections in these groups. Similar to the QALYs, both the overall direct and indirect costs would increase in adults and elderly. It was found that vaccination at the age of 10 years was the most cost–effective vaccination strategy (€4,200 per QALY gained). A booster dose provided every 10 years could also be considered as cost effective (ICER of €16,872 per QALY).

Chapter 10 described a literature review aiming to provide an overview of dynamical transmission models developed for pertussis, their application in health–economic analyses, and to update the landscape of health–economic studies with a special reference to those deploying dynamic models. Various studies using a dynamical model predicting the epidemiological effects were obtained while only four studies deploying dynamic models with the final purpose of health–

economic analysis (with 2 studies actually using the same model structure) were found. Notably, use of dynamical models is yet scarce in this area. The studies show that adolescent and adult vaccinating strategies may be cost–effective, but lack the desired effectiveness in indirectly protecting the infants too young to be vaccinated, where the major risks for serious pertussis disease and mortality exists. It was concluded that dynamic model approaches in pertussis are highly valuable in analysing adolescent and adult vaccination strategies. Furthermore, the continued and extended use of dynamic models for these strategies, inclusive separate analysis of the cost effectiveness of adult boostering strategies was recommended.

GENERAL DISCUSSION

Advanced technologies resulted in the development of a number of vaccines that can enhance the possibility to prevent and control infectious diseases[415]. However, as new vaccines, as well other health–care technologies, become more expensive the pressure on health care budgets is rapidly increasing. Cost–effectiveness analyses can be used as a tool to inform decision makers who have to determine where to allocate the limited healthcare resources. These kinds of analyses compare the costs and (health) effects of an intervention to assess the extent to which such an intervention can be regarded as providing value for money. In this thesis several cost–effectiveness analyses which can be used to support decision making were presented. Indeed two of these analyses presented in this thesis were already used to support the decision making process in the Netherland and in the UK[43,313].

In contrast to most medical interventions that are directed to ameliorate the health of specific individuals, one of the primary goals of NIPs is to decrease transmission of an infectious disease to prevent disease in a whole country or even supranational. Vaccination against a specific infectious disease not only lowers the likelihood that the vaccinated individual will become infected and infectious but can also reduce the exposure of the potential infection to others. Especially, when a sufficiently large part of a population is vaccinated, the likelihood of an individual to contact an infectious individual will decrease. In most cases, reducing the transmission of infectious diseases in the population will bring overall benefits although in some circumstances there can also be indirect negative effects for some groups.

A positive indirect effect of vaccination is that individuals with little or no protection can be indirectly protected if the chance of meeting an infectious individual is reduced sufficiently[146,416]. This indirect protective effect is labeled 'herd protection' and can be achieved by mass vaccination against infectious diseases that are transmissible from person–to–person (e.g., pneumococcal, pertussis, measles) and for those for which humans are an important reservoir (e.g., polio, malaria)[16,146,416]. To induce herd protection on a population level, the proportion of the population that needs to be vaccinated should exceed a specific threshold which differs among infectious diseases. This threshold depends on the basic reproduction number, which specifies the average number of secondary infections generated by one typical infectious case in a fully susceptible

population over the course of its infectious period. The higher the basic reproduction number of an infectious agent the higher the vaccination coverage must be to eradicate the disease[146]. Theoretically, pertussis could be eliminated with the current vaccine uptake in the Netherlands as pertussis is less transmissible than other childhood infections such as measles and rubella[386]. Unfortunately, vaccination–induced immunity against *Bordetella pertussis* is relatively short, with estimations ranging from 4 to 12 years[333]. This waning immunity causes that, as illustrated with our estimations, the desired elimination of pertussis cannot be reached even when an every 10 year booster would be introduced into the population[352].

Next to positive indirect effects, vaccination can also have negative indirect effects. For example, the introduction of a varicella infant vaccination program, to avoid generally mild infections, could potentially prevent the boosting of natural immunity against the varicella zoster virus, possibly resulting in an increased herpes zoster incidence in elderly[417-420]. Furthermore, vaccination might result in an increase in the average age of infection[421]. This effect has been observed in Greece, as a result of a very low vaccine uptake (50%), with rubella vaccination[422]. Also, our model predicted an increase in the incidence of symptomatic pertussis infections in older age groups after the introduction of adolescent pertussis booster. Due to this increase in symptomatic secondary infections in adults and elderly it was predicted that there would be an overall loss in productivity and QALYs in adults and elderly. Nevertheless, introducing a booster was considered highly cost effective due to the benefits (both costs and health) obtained in infants, children, adolescents and young adults.

Another potentially negative indirect effects of vaccination is an increase in the prevalence of certain strains of bacteria as a result of vaccination against other strains[423]. After the introduction of the infant immunization program against *S. pneumoniae* (using PCV7), reductions in carriage and disease caused by serotypes included in the vaccine have been observed[57-60]. However, near eradication of these vaccine serotypes (VTs) in asymptomatic carriers has created an ecological niche for NVTs, which has led to rapid increase of colonization by NVTs[57-60]. This indirect effect is known as serotype replacement. However, even if the carried pneumococcal serotypes are completely replaced by pneumococcal serotypes not included into the vaccine, the overall disease incidence would be reduced as these replacement serotypes have less invasive potential[36,84]. In addition to serotype replacement, it might also be possible that the carriage of other bacteria such as *Staphylococcus aureus* could increase as a result of PCV7 vaccination although conflicting results have been reported[424,425].

All the indirect effects discussed above are only assessable with so called dynamic transmission models[14,15,426]. In these kinds of models the risk of acquiring a transmissible infection is related to the number of infectious individuals in the population enabling us to predict the effects of reduced transmission (see TEXT BOX 1 for more technical details about dynamic modeling). A key concept in a dynamic model is the force of infection, which denotes the rate at which susceptible individuals will be infected within a given time period. In this thesis, a dynamical model was presented which was used to predict the costs and effectiveness of extended pertussis booster programs. However, dynamic models are not always required. If infections are (generally) not transmissible from person–

to–person or if humans are not an important reservoir of infection (e.g., tetanus, rabies and West Nile virus) dynamic models are not required, as vaccination will not lead to any indirect effects. Also, for interventions targeting small groups, such as screening and treatment programs against Chlamydia in pregnant women or offering hepatitis A vaccination for travelers, transmission models are not required[426,427]. So in general, a dynamic model is not required if the vaccination program is not expected to have any influence on the transmission dynamics of an infection disease[426]. Also, it might not always be feasible to develop a dynamic model as dynamic models are analytically more complex and time consuming to develop and require specific epidemiological data such as detailed information regarding mixing patterns, carriage, transmissibility, and the potential of an infection to cause disease[80,120].

In case a dynamic model is not required or it is not possible to develop one, a so called static model can be used. The key difference between dynamic and static models is that static models assume that the force of infection is a fixed parameter while in dynamic models this is dependent on the number of infectious individuals in the population[426]. Although, static models cannot predict indirect effects, these effects can be included into models by making assumptions. These assumptions could, for example, be based on a similar population that has undergone the same intervention or on previously implemented vaccination programs. This latter approach was used to predict the herd effects in the unvaccinated population due to PCV13 in the UK. In this analysis it was assumed that the herd–effects for five out of the six additional serotypes in PCV13 would be similar to the observed herd effects for the serotypes in PCV7 after the introduction of the routine infant PCV7 program in 2006[40]. Also in Chapter 6, a static model was used to calculate the cost effectiveness of implementing a routine PCV7 vaccination program in the Netherlands. Previously it was already shown that the cost effectiveness of PCV7 vaccination would be critically dependent on the level of herd effects and serotype replacement included into the analysis[47]. To predict these effects, a dynamic model would be required. However, as the reliability of a dynamic model for *S. pneumoniae* is dependent on the structure and underlying assumptions such as the serotype specific carriage, transmissibility, and the potential to cause disease and because at the time of the analysis detailed data regarding these parameters were only very limited it was decided to use a static model[209,214]. Indeed, a more recent study showed that the impact of an infant program is extremely sensitive to assumptions regarding the level of competition between VTs and NVTs, even predicting an increase in the overall incidence of disease depending on the level of protection for VT from NVT acquisition[209].

Models always are a simplification of reality and all models are based on assumptions. Dynamic models are not necessarily better than static ones as greater uncertainty is introduced as the number of assumptions and parameters increase and data to validate the developed model become scarce. In the light of model limitations, the cost effectiveness can be most accurately estimated by using observational data after the introduction of vaccination programs. To make this possible, it will however be required that comprehensive surveillance systems will be in place (even before the introduction of the program to avoid bias) closely monitoring the epidemiology of specific infectious diseases under study.

TEXT BOX 1: Dynamic modeling[428]

The first dynamic epidemiological model was probably developed in 1906 by Hamer, being used for understanding the recurrence of the measles epidemic[428,429]. Since then, mathematical models have slowly increased in complexity and are currently able to include aspects such as, maternally–derived immunity, gradual loss of vaccine efficacy (waning immunity), disease–acquired immunity, different stages of infection, age structures and social and sexual mixing patterns.

A frequently used type of dynamic model for economic evaluations of vaccination programs is the so–called SIR model (Susceptible–Infected–Recovered). This model basically assumes that the population is divided into three mutually exclusive subpopulation or compartments (Figure 1). The first compartment contains that part of the population being susceptible to a particular disease, the infected and infectious part of the population is included in the second compartment, and the last compartment consists of those who are removed from the infected population, through death or recovery from infection resulting in immunity to subsequent infection. Depending on the type of infectious disease, additional compartments can be included into the model. For example, when infant varicella vaccination is modeled, it should be taken into account that neonates are protected during the first months after birth due to maternal antibodies, and a corresponding compartment 'maternally–derived immunity' should be added for newborns (Figure 1). After a few months when the maternal antibodies have waned, the infant would move to the susceptible compartment. Between the susceptible and the next (infected) compartment, an additional compartment can be added, including that part of the population being infected but not being infectious. In this way multiple compartments can be added to the SIR model, enlarging its complexity to a level depending on the disease being modeled and the purpose of the model. Furthermore, the dynamics of infectious disease are not only time dependent but also age dependent. For example, the risk of infection may be related to age as different age groups mix heterogeneously rather than homogeneously, and the fraction of the population recovered from infection usually increases with age. Using an age–structured model is also necessary when vaccination programs are focused on specific age groups. Thus, realistic infectious disease models should often include both time and age as independent variables. Further information on dynamic modeling can be found in the extensive review by Hethcote[428] or the comprehensive textbook of Anderson and May[430].

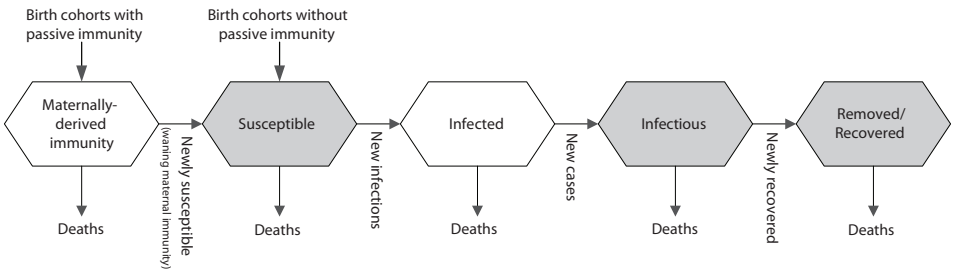

Figure 1. The MSEIR model (basic SIR model shaded in grey); M=Maternally derived immunity, S=Susceptible, E=infEcted, I=Infectious, R= Removed/ Recovered.

Extrapolation of epidemiological data

In the Netherlands, as in many other European countries, the decision to introduce PCV7 in 2006 into the Dutch NIP for infants has in part been driven by cost-effectiveness considerations[131-134,139,145]. The Dutch Health Council estimated the cost–effectiveness ratio (CER) of vaccination with PCV7 compared with no vaccination at €70,000 and less than €20,000 per quality adjusted life year (QALY) in 2001 and 2005, respectively[11]. Crucial factors responsible for the change from a potentially unfavorable CER in 2001 to a favorable ratio in 2005 were the inclusion of data on observed herd protection effects in adults after nationwide implementation of PCV7 in the USA in 2000, yet limited disease development caused by pneumococcal serotypes not present in the PCV7 replacing pneumococcal serotypes eliminated by the vaccine (replacement disease) and a change in the discount rate for health effects[44-46]. However, as argued in Chapter 2, extrapolating these effects from the USA was deemed inappropriate on the longer run and resulted in too favorable CERs in later years. To avoid over– or underestimation of the impact of potential new vaccination programs future cost effectiveness, analyses should preferably not extrapolate the epidemiological impact of a vaccination program from one country to another. However, if there are no other possibilities, first the pre–vaccination epidemiology (e.g., incidence, coverage by the vaccine etcetera) and differences between populations (e.g., vaccine uptake, age distribution, mixing patterns), and other parameters such as the (expected) vaccine uptake and immunization schedules should be compared in order to judge whether extrapolation of data can be deemed appropriate or specific corrections should apply and are feasible. In Chapter 4, the estimations for indirect effects were also partly based on epidemiological data from the UK. In contrast to the US data, the UK data seemed more relevant for the Netherlands because the UK has a comprehensive surveillance system, comparable IPD rates, and a similar serotype coverage by PCV7[79,139]. Furthermore, the Dutch data available at that time showed a similar increase in IPD caused by non–vaccine serotypes as observed in the UK two years post–vaccination[81,151].

Further issues in health economics of vaccination

The conclusions drawn from our analyses largely depend on the specific cost–effectiveness thresholds applied. Very recently the Dutch Healthcare Insurance Board (CVZ) advised the Ministry of Health to use a threshold of €80,000 per QALY gained which can be lower or higher depending on the context[431]. This context might, for example, be dependent on the severity of disease or on the age of the population involved. Applying the threshold, as suggested by the CVZ, all interventions investigated for the Netherlands in this thesis are likely to be considered as cost–effective.

The cost effectiveness of preventive interventions largely depends on discounting[395,432]. Discounting is used to devalue future costs and health outcomes relative to current ones. This is done to reflect the time preference of individuals and societies, due to uncertainty about the future and the growing (economic) wealth in particular[433,434]. In contrast to discounting future costs, which has a clear basis in economics, discounting health outcomes has been subject of much debate[152,395,435]. Especially, the cost effectiveness of preventive interventions is influenced by discounting, and led

some to argue for specific discounting rules for preventive interventions[152,395,435]. In particular with vaccination, the costs of the program are incurred at the time of vaccination while the benefits can occur in the middle–to long term. This is in particular true for HPV, where the benefits of vaccination, i.e. the prevention of cervical cancer, occur several decades after the initial vaccination[395]. However, the impact is also significant for vaccines which prevent mortality in young children such as the pneumococcal vaccine, as future life years saved are also discounted.

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines state that the time horizon of an analysis should be long enough to capture all the differential effects of the interventions compared. Especially with vaccination programs, where costs are incurred immediately, while potential savings and health benefits are spread out over a prolonged period of time, a long time frame seems to be necessary on the one hand. On the other hand, very long time horizons may not be very informative for decision makers and uncertainty is high. Indeed, it is very unlikely that models are able to predict disease impact in 50 or 100 years, due to the uncertainty regarding the disease dynamics, and because external factors such as demographic changes and the developments of new medical technologies are difficult to predict. Despite that, costs and benefits occurring far in the future will be so heavily discounted that the effects are likely to be marginal[395]. An interesting approach used sometimes is to report the outcomes at the equilibrium state (i.e. when the full impact of vaccination has been reached)[328]. Similarly, indirect effects can also be included in a static model by using equilibrium outcomes of a separate dynamic model[377]. Again, given the discussion on the time horizon, the validity of these outcomes might be questioned because the time to reach an equilibrium state may take more than a century[328] and because using the outcomes at the equilibrium state ignores the (potentially more relevant) period between the start and reaching the steady state, when disease prevalence may fluctuate[398]. The impact of the chosen time horizon depends on the infectious disease being modelled and should be explored in the sensitivity analysis, in particular if a steady state has not been reached within the chosen time horizon. If a steady state has not been reached, cost effectiveness can change in time as has been shown for varicella vaccination[398]. In conclusion, the issue of the time horizon warrants specific attention in the area of vaccine health economics.

Specific groups can be at increased risk of infection compared to healthy population[40,436]. For example, the majority of the IPD cases in individuals aged 2 years and older occur in those with specific underlying conditions[40]. As characteristics between the general population and high–risk groups differ, this group warrants specific attention. It is, for example, essential that cost–effectiveness analyses focusing on preventative interventions use the life expectancy of the targeted at risk population rather than using the life expectancy of the overall population (see also Figure 2) as such differences will impact on the cost effectiveness of preventive interventions[172,173,209].

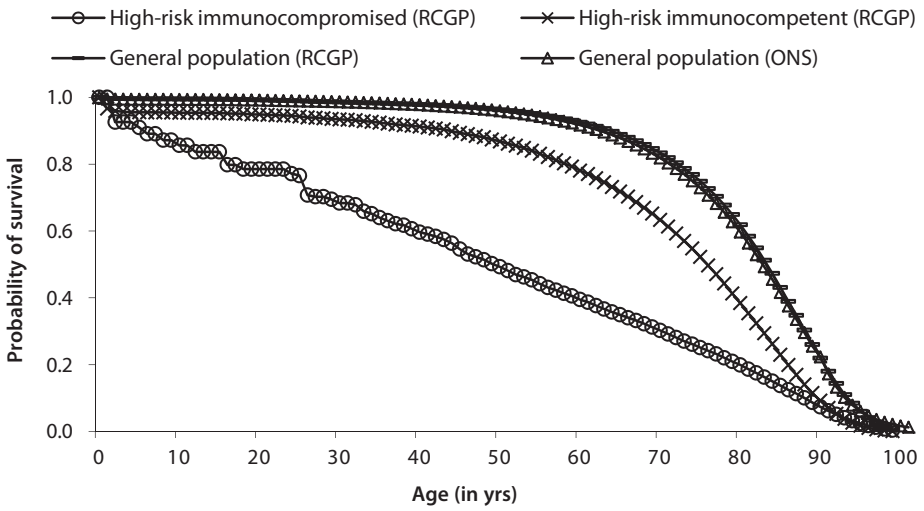

Figure 2. Survival curves for high–risk immunocompromised individuals, high–risk immunocompent individuals (based on Read codes mapped to ICD–9 codes) and the general UK population. Data taken from Royal College of General Practitioners (RCGP) database (including 0.8 million patients; more than 1% of the population of the UK) and collected for the years 2005 to 2010. The RCGP data was validated by comparing the calculated survival curves with the survival curve of the general population based on mortality data obtained from the Office for National Statistics (ONS) for the year 2008[210].

Notably, any extension of the NIP should be carefully considered because since the early introduction of vaccines, opponents have claimed that they are ineffective, dangerous (e.g., compromising the immune system), and unnecessary (e.g., attribute success in controlling infectious diseases to social and environmental developments rather than vaccination). These arguments may lead to a reduction in vaccination coverage in certain communities, increasing the risk of preventable outbreaks of infectious diseases[437-439]. For example, while the compliance with the Dutch NIP is high (95%), a large rubella outbreak occurred in the Netherlands in a population subgroup with religious objections to vaccination[437]. Next to these known clusters, the anti–vaccine lobby and the media can have a considerable impact on the vaccination coverage in general. For example, the initial coverage of the HPV vaccination program in the Netherlands was only 53% with regional uptakes varying from 40%–61%[440]. The debate on the HPV vaccine's safety and efficacy was widely relayed in the national media, inclusive skepticism of some Dutch scientists and the anti–vaccination lobby, resulting in mixed messages and a feeling of confusion in the population[441]. Several other events demonstrated the impact of the anti–vaccine movement in the past. In the 1970s the diphtheria–pertussis–tetanus (DPT) immunization was disrupted by anti–vaccine movements in several countries resulting in much higher incidence of pertussis compared to countries where high vaccine coverage was maintained[442]. Another example of the impact of media was the decrease in vaccination rates after the publication of a paper implying a link between the measles, mumps and rubella (MMR) vaccine and autism and bowel disease[443]. Although, the scientific limitation of this

paper was clear when it appeared, vaccination rates in the UK dropped to 80% in the years following the study and as a result measles was declared endemic again in England and Wales in 2008 for the first time in 14 years[444,445]. After being heavily criticized on scientific and ethical grounds, in 2010 *The Lancet* retracted the paper[446,447]. This illustrates the relevance and potential impact of the media, but also the general lack of valid scientific arguments to underpin such standpoints.

OTHER (FUTURE) POSSIBLE VACCINATION STRATEGIES

Pneumococcal vaccination

Several countries have already introduced infant pneumococcal vaccination schedules of which most are currently using the 13–valent vaccine in either a 2+1 or 3+1 dose schedule. To prevent disease among high–risk groups and elderly, with the highest burden of disease, many countries recommend vaccination with the 23–valent polysaccharide vaccine (PPV23) which has been available since the 1980s. Nevertheless, the efficacy and the duration of protection of this vaccine is limited, and there is a reduced antibody response to revaccination[20,21]. The use of conjugated pneumococcal vaccines could potentially overcome the limitations of PPV23[199,200]. Indeed, efficacy data that are available suggest that PCVs are effective in preventing IPD (and possibly pneumonia) in HIV infected adults and children, a group in whom PPV23 is ineffective[199,200]. As the indication for PCV13 was recently extended to adults aged 50 years and over[35] some European countries are already recommending PCV13 for risk–groups or adults. For example, in Austria and Greece PCV13 is recommended for those aged 50 years and older[220,221], while in France, parts of Germany and Italy the vaccine is being recommended for (specific) risk groups[222,223]. This thesis showed that the cost effectiveness of such programs will be crucially dependent on the effectiveness of PCV13 against non–bacteraemic pneumonia and on the time since the introduction of the infant PCV13 program. Interestingly, in the Netherlands the government decided to switch to PCV10 rather than PCV13. As PCV10 has shown mixed effects in nasopharyngeal carriage and has not demonstrated herd effects after the introduction of routine infant pneumococcal programs the cost effectiveness of a risk–based PCV13 program might not decrease (as fast) in time as was predicted for the UK[158,448]. Another difference is that economic evaluations in the Netherlands should include indirect costs and future health gains are discounted with a lower rate which could also result in more favorable ICERs.

In many countries, the decision on switching from PCV7 to either PCV10 or PCV13 was largely driven by the observed increase in disease due to serotypes not included in PCV7 and the sheer fact that PCV7 is not available anymore (i.e. Pfizer replaced PCV7 by PCV13). In particular, after the introduction of routine infant PCV7 vaccination serotypes 19A, 7F, 3, 22F, 10A and 33F have become the most important causing disease[116-118]. In addition to PCV7, PCV10 also contains serotypes 1, 5 and 7F, while PCV13 includes the PCV10–serotypes and adds serotypes 3, 6A, and 19A. The broader serotype coverage of the 10– and 13–valent vaccines might reduce the potential for disease caused by serotypes not included in the vaccine in both children and the elderly[215]. However, it can still be expected that serotypes not included in the vaccine will emerge in time. Considering

the immunogenicity issues, it seems unlikely that vaccines will eventually include all serotypes. Therefore, it might be necessary, depending on the level of serotype replacement, to revise the composition of the protein conjugated vaccines in the future. The expenses of developing such new conjugated vaccines prompted the consideration of novel vaccines including those targeting broadly conserved proteins or killed whole–cell pneumococcal vaccines[449]. Until these new vaccines will become available, it is important to continue IPD surveillance in order to identify the emergence of new relevant strains and to switch to vaccines with the broader or otherwise different coverage.

Pertussis

Despite widespread vaccination, infection with pertussis remains endemic even in countries with high vaccination coverage[314-317]. Moreover, there has been a resurgence of pertussis in many countries during the past decade, particularly in adolescents and adults[314,317-320]. Therefore, several countries, including Australia, Canada, France and Germany, have incorporated adolescent booster doses into their vaccination programs[37]. Our dynamic model showed that extension of the current pertussis vaccination program in the Netherlands could be considered cost–effective. Nevertheless, it was also shown that even with an every 10 year pertussis booster it was unlikely that pertussis would be eliminated from the population. This means that neonates and infants too young to be vaccinated will still be at risk of infection. Additional strategies, aiming to protect unvaccinated or incompletely vaccinated infants that can be considered, include, vaccination of the mother in the third trimester of pregnancy (maternal immunization), vaccination of family members after or before birth of the child (cocooning), vaccinating infants directly after birth, or administering the first dose already at six weeks of age.

Family members present a substantial source of infection in newborn babies and young infants[321,323,327,450]. Vaccinating these family members (and other close contact persons) could avoid transmission of pertussis to the non–immune and/or incompletely vaccinated infant. A recent Dutch cost–effectiveness analysis showed that vaccinating the parents directly after birth could be considered as cost–effective[354]. A disadvantage of this strategy is that the infant can still be infected by infectious individuals as cocooning does not offer direct protection for the infant. Direct protection of the infant may be conferred by maternal or neonatal vaccination. Maternal vaccination potentially offers both direct protection to the mother and temporary protection to the neonate due to placental transferred maternal antibodies[451-453]. Preferably, maternal vaccination should take place in the third trimester taking into account the immune response of the mother, the maternal–fetal IgG transport[454,455], and potential side–effects[456]. An additional advantage of maternal vaccination is that breastfed infants may passively acquire IgA antibodies after birth[457]. Potential disadvantages of this strategy might include the temporarily antibody interference with the infant immunization schedule[453,458]; yet limited availability of efficacy data hinders to adequately analyze this. Nevertheless, maternal vaccination studies carried out in the 1930s to 1950s using the high–dose whole–cell vaccine showed no serious side–effects in mothers or children. In addition, maternal vaccination against tetanus has been shown to be effective and safe over long periods

of time[454,459]. Notably, also the Advisory Committee on Immunization Practices (ACIP) recommends (partly based un yet unpublished literature) to vaccinate pregnant women who previously have not received Tdap[404]. Two clinical trials currently being performed will provide more information of the safety and immunogenicity of Tdap during pregnancy[460,461]. Another possibility to increase the protection of neonates against pertussis is the administration of a pertussis dose at birth. Studies have shown that neonatal immunization with acellular pertussis vaccines can act as a basis for future immune response by priming T and B cells[462,463]. Nevertheless, vaccination at birth might result in interference with subsequent vaccinations (against other pathogens)[436]. Additional studies exploring this effect and the efficacy of vaccinating newborns against pertussis are currently underway[436]. Similar to the cocooning strategy, a disadvantage of neonatal vaccination and the accelerated programme is that it will leave the infant susceptible to pertussis for some weeks depending on how fast immunity an immune response will be induced.

Each of the above discussed strategies have their specific advantages and disadvantages but all can be effective in preventing infant pertussis cases. However, the most (cost–)effective way to reduce the pertussis burden would probably be to develop vaccines which induce long lasting immunity against infection and disease and thereby eliminating the need for toddler and adolescent booster doses.

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SUMMARY

A crowded vaccination schedule and restrained health–care budgets limit the uptake of new vaccines into the Dutch national immunization programs (NIP). Next to many other factors, cost-effectiveness considerations highly influence the decision whether to introduce vaccines into Dutch NIP.

The first part of this thesis focuses on the (cost-) effectiveness of pneumococcal vaccination. It is shown that there are large differences in the observed disease epidemiology after implementation of paediatric pneumococcal immunization programs between the USA and Europe. In Europe, less cases of pneumococcal disease were avoided in unvaccinated individuals (herd effects) than in the USA, while significant replacement was observed in Europe with strains not included in the vaccine. As a consequence, the 7-valent pneumococcal vaccine, which was previously used in the Dutch NIP, was less cost-effective as predicted beforehand. More valent pneumococcal vaccines are more likely to be considered cost-effective as more direct and herd effects and less serotype replacement effects are expected. These potential herd effects reduce the cost-effectiveness of elderly and adult (risk) groups vaccination in time. In particular, a modelling study showed that vaccinating risk groups in England was unlikely to be considered cost-effective in the base-case analysis unless the vaccine would also offer protection against non–bacteraemic pneumonia. Evidence on whether the latter occurs is awaited from a large Dutch clinical trial.

The second part of the thesis explores the impact of extending the childhood pertussis vaccination programme to adolescents and adults. Given the nature of the problem, the development of a complex population dynamical model was required. The developed dynamic model showed that the most (cost-) effective age for the introduction of an additional booster is around 12 years. Nevertheless, this strategy only offered limited indirect protection to the (partly) unvaccinated infants with potentially most serious disease which might be considered the primary aim of extended pertussis vaccination.

In conclusion, the dynamics of infectious diseases makes it challenging to predict the impact of new vaccination programs. Extending the vaccination programs against pneumococcal disease and pertussis offers the possibility to prevent morbidity and mortality and decrease the economic burden of disease for society.

SAMENVATTING

Omdat het Nederlandse Rijksvaccinatieprogramma al intensief is en de gezondheidszorg kampt met gelimiteerde budgetten, zijn de mogelijkheden voor opname van nieuwe vaccins in het Rijksvaccinatieprogramma beperkt. Naast vele andere factoren, hebben doelmatigheidsuitkomsten een groot effect op de beslissing om een vaccin op te nemen in het Rijksvaccinatieprogramma.

In het eerste gedeelte van dit proefschrift ligt de focus op de (kosten-) effectiviteit van pneumokokkenvaccinatie. Het blijkt dat er grote verschillen zijn in de geobserveerde epidemiologie na de introductie van het vaccin in Amerika en Europa. In Europa werden er minder pneumokokken gevallen voorkomen in ongevaccineerde individuen ('herd immunity') terwijl er meer ziekte werd waargenomen veroorzaakt door serotypen waartegen het vaccin geen bescherming biedt (serotypevervanging). Dit had tot gevolg dat de kosteneffectiviteit van het destijds gebruikte 7-valente pneumokokkenvaccin minder gunstig was dan eerder voorspeld. Meer valente pneumokokkenvaccins hebben een grotere kans om te worden beschouwd als kosteneffectief omdat deze waarschijnlijk meer directe en herd immunity effecten bieden terwijl de kans op serotypevervanging kleiner is. Als gevolg van deze potentiele herd immunity zal het vaccineren van andere (risico-) groepen potentieel minder gunstig worden. Zo blijkt uit een economisch model dat het vaccineren van risicogroepen in Engeland waarschijnlijk niet als kosteneffectief kan worden beschouwd tenzij het vaccin ook bescherming biedt tegen niet-invasieve pneumonie. Dit laatste wordt momenteel onderzocht in een grote Nederlandse klinische trial.

Het tweede gedeelte van dit proefschrift verkent de impact van de uitbreiding van het huidige pertussis vaccinatie programma naar adolescenten en volwassenen. Gegeven de complexiteit van de pertussis transmissie, was het nodig een dynamisch transmissie model te ontwikkelen. Dit model suggereert dat de meest kosteneffectieve leeftijd om een extra booster te introduceren rond de 12 jaar is. Het beoogde beschermende effect voor (gedeeltelijk) ongevaccineerde zuigelingen bleek echter minimaal te zijn.

Gezien de dynamiek van infectieziekten zijn soms complexe methoden nodig om de impact van nieuwe vaccinatieprogramma's te voorspellen. Het uitbreiden van het huidige pneumokokken– en pertussis vaccinatieprogramma biedt de mogelijkheid om de morbiditeit en mortaliteit te verminderen en de ziektegerelateerde kosten te verlagen.

LIST OF PUBLICATIONS

Publications supporting this thesis

Rozenbaum MH, Postma MJ. Response on "RE: Cost-effectiveness of pertussis booster vaccination in the Netherlands". *Vaccine* (2012), http://dx.doi.org/10.1016/j.vaccine.2012.11.082

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CURRICULUM VITAE

Mark Rozenbaum was born in Delft on January 17th 1983. After finishing high school at the Weazenburg in Leek, he started to study Biology at the University of Groningen in 2001. Mark obtained his master degree in Medical Biology with the study direction Management & Policy in 2007. Subsequently, he started his PhD program under supervision of Prof. dr. M.J. Postma at the department of PharmacoEpidemiology and PharmacoEconomics. His research focused on the costs and effectiveness of interventions (particularly immunization) to prevent infectious diseases such as *Streptococcus pneumoniae, Bordetella pertussis,* rotavirus, varicella, influenza, RSV, HPV and HIV. Also, he conducted research on various other topics of his interest (e.g., orphan drugs, discounting and pharmacogenetic and genomic screening programmes).

Next to his PhD program, Mark Rozenbaum has held several positions including a position (2009) as policy advisor at the Dutch Health Care Insurance Board (CVZ) where he was responsible for the assessment of pharmacoeconomic dossiers submitted by pharmaceutical companies and other parties in order to receive reimbursement in the Netherlands. In 2011 he worked as research fellow at the Health Protection Agency (London, UK) where he performed a cost-effectiveness analysis on risk group vaccination against pneumococcal disease. Also, he coordinated the course Pharmacy in Perspective at the University of Groningen.

During his PhD training he authored or co-authored more than 20 papers in both national and international journals, of which several were used by the Dutch, the Spanish, the Irish, and the UK's ministry of health in decision making processes. Also, he obtained several research grants and presented several podium and poster presentations at international conferences (e.g., ISPPD, ECHE, ISPOR) and. In 2009 as well as 2010 he received a SHARE 'PhD Top Publication Award' for three of his publications. One of these papers (BMJ 2010) was also awarded as best article of 2009 by the Dutch Society for Infectious Diseases (Nederlandse Vereniging voor Infectieziekten).

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